O-LINKED THIADIAZOLYL COMPOUNDS AS DNA POLYMERASE THETA INHIBITORS

BACKGROUND

Targeting DNA repair deficiencies has become a proven and effective strategy in cancer treatment. However, DNA repair deficient cancers often become dependent on backup DNA repair pathways, which present an "Achilles heel" that can be targeted to eliminate cancer cells, and is the basis of synthetic lethality. Synthetic lethality is exemplified by the success of poly (ADP-ribose) polymerase (PARP) inhibitors in treating BRCA-deficient breast and ovarian cancers (Audeh M. W., et al., Lancet (2010); 376 (9737): 245-51).

DNA damage repair processes are critical for genome maintenance and stability, among which, double strand breaks (DSBs) are predominantly repaired by the nonhomologous end joining (NHEJ) pathway in G1 phase of the cell cycle and by homologous recombination (HR) in S-G2 phases. A less addressed alternative end-joining (alt-EJ), also known as microhomology-mediated end-joining (MMEJ) pathway, is commonly considered as a "backup" DSB repair pathway when NHEJ or HR are compromised. Numerous genetic studies have highlighted a role for DNA polymerase theta (Polθ, encoded by *POLQ*) in stimulating MMEJ in higher organisms (Chan S. H., et al., PLoS Genet. (2010); 6: e1001005; Roerink S. F., et al., Genome research. (2014); 24: 954–962; Ceccaldi R., et. al., Nature (2015); 518: 258-62; and Mateos-Gomez P. A., et al., Nature (2015); 518: 254-57).

Polθ is distinct among human DNA polymerases, exhibiting not only a C-terminal DNA polymerase domain but also an N-terminal helicase domain separated by a long and lesser-conserved central domain of unknown function beyond Rad51 binding (Seki eta. Al, 2003, Shima et al 2003; Yousefzadeh and Wood 2013). The N-terminal ATPase/helicase domain belongs to the HELQ class of SF2 helicase super family. In homologous recombination deficient (HRD) cells, Polθ can carry out error-prone DNA synthesis at DNA damage sites through alt-EJ pathway. It has been shown that the helicase domain of Polθ causes suppression of HR pathway through disruption of Rad51 nucleoprotein complex formation involved in initiation of the HR-dependent DNA repair reactions following ionizing radiation. This anti-recombinase activity of Polθ promotes the alt-EJ pathway. In addition, the helicase domain of Polθ contributes to microhomology-mediated strand annealing (Chan SH et al., PLoS Genet. (2010); 6: e1001005; and Kawamura K et al., Int. J. Cancer (2004); 109: 9-16).

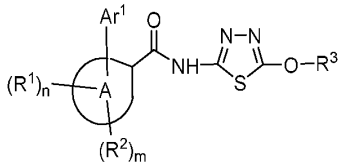
Polθ efficiently promotes end-joining in alt-EJ pathway by employing this annealing activity when ssDNA overhangs contain >2 bp of microhomology (Kent T., et al., Elife (2016); 5: e13740), and Kent T., et al., Nat. Struct. Mol. Biol. (2015); 22: 230–237). This reannealing activity is achieved through coupled actions of Rad51 interaction followed by ATPase-mediated displacement of Rad51 from DSB damage sites. Once annealed, the primer strand of DNA can be extended by the polymerase domain of Polθ.

The expression of Polθ is largely absent in normal cells but upregulated in breast, lung, and ovarian cancers (Ceccaldi R., et al., Nature (2015); 518, 258-62). Additionally, the increase of Polθ expression correlates with poor prognosis in breast cancer (Lemee F et al., Proc Natl Acad Sci USA. (2010) ;107: 13390-5). It has been shown that cancer cells with deficiency in HR, NHEJ or ATM are highly dependent on Polθ expression (Ceccaldi R., et al., Nature (2015); 518: 258-62, Mateos-Gomez PA et al., Nature (2015); 518: 254-57, and Wyatt D.W., et al., Mol. Cell (2016); 63: 662-73). Therefore, Polθ is an attractive target for novel synthetic lethal therapy in cancers containing DNA repair defects.

SUMMARY

Disclosed herein are certain thiadiazolyl derivatives that inhibit Polθ activity, in particular inhibit Polθ activity by inhibiting the ATP dependent helicase domain activity of Polθ. Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating and/or preventing diseases treatable by inhibition of Polθ such as cancer, including homologous recombination (HR) deficient cancers.

In one aspect, provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein ring A, Ar^1, R^1, R^2, R^3, and subscripts n and m have the meanings provided hereinbelow.

In related aspects, provided are pharmaceutical compositions comprising a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

In another aspect, provided is a method for treating and/or preventing a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof. In one embodiment, the patient is in recognized need of such treatment. In another embodiment, the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition. In yet another embodiment, the disease is a cancer.

In still another aspect, provided is a method for treating and/or preventing a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof. In one embodiment, the patient is in recognized need of such treatment. In another embodiment, the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition.

In another aspect, provided is a method for inhibiting DNA repair by Polθ in a cancer cell comprising contacting the cell with an effective amount of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof. In one embodiment, the cancer is HR deficient cancer.

In yet another aspect, provided is a method for treating and/or prevening a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutical composition.

In still another aspect, provided is a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof for use in a method of treatment.

In still another aspect, provided is a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof for inhibiting DNA repair by Polθ in a cell. In one embodiment, the cell is HR deficient cell.

In another aspect, provided is a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a disease in a patient, wherein the disease is characterized by overexpression of Polθ.

In yet another aspect, provided is a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein.

In still another aspect, provided is a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a HR deficient cancer in a patient.

In another aspect, provided is a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a cancer that is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy in a patient. Examples of cancers resistant to PARP-inhibitors include, but are not limited to, breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and neck cancer, pancreatic cancer, gastrointestinal cancer, and colorectal cancer.

In still another aspect, provided is the use of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of cancer, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein.

In still another aspect, provided is the use of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of a HR deficient cancer.

In still another aspect, provided is the use of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the

treatment of cancer that is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy in a patient.

In related aspects for the methods, uses and compositions above, the cancer is lymphoma, rhabdoid tumor, multiple myeloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, breast cancer, ovarian cancer, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer, and pancreatic cancer (data from large scale drop out screens in cancer cell lines indicate that some cell lines from the above cancers are dependent on polymerase theta for proliferation https://depmap.org/portal/).

In some embodiments, a HR-deficient cancer is breast cancer. Breast cancer includes, but is not limited to, lobular carcinoma *in situ* (LCIS), a ductal carcinoma *in situ* (DCIS), an invasive ductal carcinoma (IDC), inflammatory breast cancer, Paget disease of the nipple, Phyllodes tumor, Angiosarcoma, adenoid cystic carcinoma, low- grade adenosquamous carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, micropapillary carcinoma, mixed carcinoma, or another breast cancer, including but not limited to triple negative, HER positive, estrogen receptor positive, progesterone receptor positive, HER and estrogen receptor positive, HER and progesterone receptor positive, estrogen and progesterone receptor positive, and HER and estrogen and progesterone receptor positive. In other embodiments, HR-deficient cancer is ovarian cancer. Ovarian cancer includes, but is not limited to, epithelial ovarian carcinomas (EOC), maturing teratomas, dysgerminomas, endodermal sinus tumors, granulosa-theca tumors, Sertoli-Leydig cell tumors, and primary peritoneal arcinoma.

DETAILED DESCRIPTION

Before the present invention is further described, it is to be understood that the invention is not limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The singular forms “a,” “an,” and “the” as used herein and in the appended claims include plural referents unless the context clearly dictates otherwise. It is further noted that the

claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

When needed, any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkoxyalkyl means that an alkoxy group is attached to the parent molecule through an alkyl group.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

DEFINITIONS:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a saturated straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* C_{1-8} means one to eight carbons). Alkyl can include any number of carbons, such as C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{1-8}, C_{1-9}, C_{1-10}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

The term "alkylene" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the same atom or different atoms of the alkylene group. For instance, a straight chain alkylene can be the bivalent radical of $-(CH_2)_n-$, where n is 1, 2, 3, 4, 5 or 6. Representative alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, hexylene, and the like.

The term "alkoxy" refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O-. As for an alkyl group, alkoxy groups can have any suitable number of carbon atoms, such as C_{1-6}, and can be straight or branced. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc.

As used herein, the term “cyano,” by itself or as part of another substituent, refers to a moiety having the formula –CN, *i.e.*, a carbon atom triple-bonded to nitrogen atom.

The term "cycloalkyl" refers to a saturated or partially unsaturated hydrocarbon ring having the indicated number of ring atoms (*e.g.*, C_{3-6} cycloalkyl). Cycloalkyl can include any number of carbons, such as C_{3-6}, C_{4-6}, C_{5-6}, C_{3-8}, C_{4-8}, C_{5-8}, C_{6-8}, C_{3-9}, and C_{3-10}. Partially unsaturated cycloalkyl groups have one or more double or triple bonds in the ring, but cycloalkyl groups are not aromatic. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl.

The term "cycloalkyloxy" refers to a cycloalkyl group having an oxygen atom that connects the cycloalkyl group to the point of attachment: cycloalkyl-O-. The cycloalkyl group is as defined herein.

The terms "spirocyclyl" or "spirocycloalkyl" refer to a saturated or partially unsaturated bicyclic ring having 6 to 12 ring atoms, where the two rings are connected via a single carbon atom (also called the spiroatom). Partially unsaturated spirocycloalkyl groups have one or more double or triple bonds in the ring, but spirocycloalkyl groups are not aromatic. Representative examples include, but are not limited to, spiro[3.3]heptane, spiro[4.4]nonane, spiro[3.4]octane, and the like.

The term "bridged cycloalkyl" means a monocyclic 6- to 11-membered hydrocarbon radical in which two non-adjacent ring atoms are linked by a $(CH_2)_n$ group where n is 1 to 3 (also

referred to herein as the bridging group). Examples of bridged cycloalkyl include but are not limited to bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane. For brevity, the term is also meant to include bridged polycyclic hydrocarbon groups such as adamantane.

The term "heterocycloalkyl" refers to a saturated or partially unsatured monocyclic ring having the indicated number of ring vertices (e.g., a 3- to 7-membered ring) and having from one to five heteroatoms selected from N, O, and S as ring vertices. Partially unsaturated heterocycloalkyl groups have one or more double or triple bonds in the ring, but heterocycloalkyl group are not aromatic. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 7, 4 to 7, or 5 to 7 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. Non-limiting examples of heterocycloalkyl groups include pyrrolidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, quinuclidine, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom.

The term "bicyclic heterocycloalkyl" or "bicyclic heterocyclyl" refers to a saturated or partially unsaturated fused bicyclic ring having the indicated number of ring vertices (e.g., a 6- to 12-membered ring) and having from one to five heteroatoms selected from N, O, and S as ring vertices. Partially unsaturated bicyclic heterocycloalkyl groups have one or more double or triple bonds in the ring, but bicyclic heterocycloalkyl groups are not aromatic. Bicyclic heterocycloalkyl groups can include any number of ring atoms, such as, 6 to 8, 6 to 9, 6 to 10, 6 to 11, or 6 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. Non-limiting examples of bicyclic heterocycloalkyl groups include decahydro-1,5-naphthyridine, octahydropyrrolo[1,2-a]pyrazine, and the like.

The terms "bridged heterocyclyl" or "bridged heterocycloalkyl" refers to a heterocycloalkyl ring (having 5 to 8 ring vertices) in which two non-adjacent ring atoms are linked by a $(CRR')_n$ group where n is 1 to 3 and each R is independently H or methyl (also may be referred to herein as “bridging” group). Bridged heterocyclyl groups have one to five heteroatoms selected from N, O, and S as ring vertices. The heteroatom ring vertices can be

in both the heterocycloalkyl ring portion as well as the bridging group. When in the bridging group, the heteroatom replaces a CRR' group. Examples include, but are not limited to, 2-azabicyclo[2.2.2]octane, quinuclidine, 7-oxabicyclo[2.2.1]heptane, and the like.

The terms "spiroheterocyclyl" or "spiroheterocycloalkyl" refer to a saturated or partially unsaturated bicyclic ring having 6 to 12 ring atoms, where the two rings are connected via a single carbon atom (also called the spiroatom). Spiroheterocyclyl groups have from one to five heteroatoms selected from N, O, and S as ring vertices, and the nitrogen atom(s) are optionally quaternized. Partially unsaturated spiroheterocycloalkyl groups have one or more double or triple bonds in the ring, but spiroheterocycloalkyl groups are not aromatic. Representative examples include, but are not limited to, 4-oxaspiro[2.4]heptane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.4]octane, 2-azaspiro[3.5]-nonane, 2,7-diazaspiro[4.4]nonane, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

The term "haloalkyl" refers to alkyl, as defined above, where some or all of the hydrogen atoms are replaced with halogen atoms. As for alkyl group, haloalkyl groups can have any suitable number of carbon atoms, such as C_{1-6}. For example, the term "C_{1-4} haloalkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "haloalkoxy" refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for an alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as C_{1-6}, and can be straight or branced, and are substituted with 1, 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2,-trifluoroethoxy, perfluoroethoxy, etc.

The term "hydroxyalkyl" refers to an alkyl group where one of the hydrogen atoms is substituted with a hydroxy (–OH) group. As for an alkyl group, hydroxyalkyl groups can have any suitable number of carbon atoms, such as C_{1-6}, and can be straight or branced. Hydroxyalkyl groups include, for example, hydroxymethyl, 1-hydroxylethyl, 2-hydroxyethyl, 2-hydroxylpropan-2-yl, etc.

The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl.

The term "heteroaryl" refers to a 5- to 10-membered aromatic ring (or fused ring system) that contains from one to five heteroatoms selected from N, O, and S. Heteroaryl groups can include any number of ring atoms, such as, 5 to 6, 5 to 8, 6 to 8, 6 to 9, 9 to 10, 9, 10 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occuring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine,

glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. For the purposes of the present disclosure, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. All potential physical forms are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers); the racemates, diastereomers, and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. When a stereochemical depiction is shown, it is meant to refer the compound in which one of the

isomers is present and substantially free of the other isomer. 'Substantially free of' another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in an amount of at least 99%.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. Unnatural proportions of an isotope may be defined as ranging from the amount found in nature to an amount consisting of 100% of the atom in question. For example, the compounds may incorporate radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C), or non-radioactive isotopes, such as deuterium (^{2}H) or carbon-13 (^{13}C). Such isotopic variations can provide additional utilities to those described elsewhere within this application. For instance, isotopic variants of the compounds of the invention may find additional utility, including but not limited to, as diagnostic and/or imaging reagents, or as cytotoxic/radiotoxic therapeutic agents. Additionally, isotopic variants of the compounds of the invention can have altered pharmacokinetic and pharmacodynamic characteristics which can contribute to enhanced safety, tolerability or efficacy during treatment. All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

The terms "administration," "administer" and the like, as they apply to, for example, a subject, cell, tissue, organ, or biological fluid, refer to contact of, for example, an Polθ modulator, a pharmaceutical composition comprising same, or a diagnostic agent to the subject, cell, tissue, organ, or biological fluid. In the context of a cell, administration includes contact (e.g., in vitro or ex vivo) of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell.

The terms "treat," "treating," "treatment" and the like refer to a course of action (such as administering a Polθ modulator or a pharmaceutical composition comprising same) initiated after a disease, disorder or condition, or a symptom thereof, has been diagnosed, observed, and the like so as to eliminate, reduce, suppress, mitigate, or ameliorate, either temporarily or permanently, at least one of the underlying causes of a disease, disorder, or condition afflicting a subject, or at least one of the symptoms associated with a disease, disorder, condition afflicting a subject. Thus, treatment includes inhibiting (e.g., arresting the development or further development of the disease, disorder or condition or clinical symptoms association therewith) an active disease.

The term "in need of treatment" as used herein refers to a judgment made by a physician or other caregiver that a subject requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of the physician's or caregiver's expertise. For example, the patient has been diagonosed as having a disease linked to overexpression of Polθ or a homologous recombination (HR)-deficient cancer.

The terms "prevent," "preventing," "prevention" and the like refer to a course of action (such as administering an Polθ modulator or a pharmaceutical composition comprising same) initiated in a manner (e.g., prior to the onset of a disease, disorder, condition or symptom thereof) so as to prevent, suppress, inhibit or reduce, either temporarily or permanently, a subject's risk of developing a disease, disorder, condition or the like (as determined by, for example, the absence of clinical symptoms) or delaying the onset thereof, generally in the context of a subject predisposed to having a particular disease, disorder or condition.

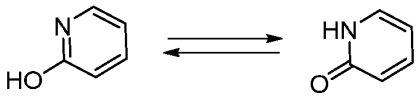
The term "in need of prevention" as used herein refers to a judgment made by a physician or other caregiver that a subject requires or will benefit from preventative care. This judgment is made based on a variety of factors that are in the realm of a physician's or caregiver's expertise.

The phrase "therapeutically effective amount" refers to the administration of an agent to a subject, either alone or as part of a pharmaceutical composition and either in a single dose or as part of a series of doses, in an amount capable of having any detectable, positive effect on any symptom, aspect, or characteristic of a disease, disorder or condition when administered to the subject. The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of an Polθ modulator (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been used.

The terms "modulate," "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of Polθ, either directly or indirectly. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules.

The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

Certain compounds of the present disclosure can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this disclosure. For example, certain hydroxy substituted compounds may exist as as tautomers as shown below:



"Pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

As used herein, a wavy line, "〰", that intersects a single, double or triple bond in any chemical structure depicted herein, represent the point attachment of the single, double, or triple bond to the remainder of the molecule. Additionally, a bond extending to the center of a ring (e.g., a phenyl ring) is meant to indicate attachment at any of the available ring vertices. One of skill in the art will understand that multiple substituents shown as being attached to a ring will occupy ring vertices that provide stable compounds and are otherwise sterically compatible.

"About, " as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that the numerical value encompasses ± 10%, preferably ± 5% of the recited numerical value.

"Disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder, " "syndrome, " and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

"Patient" is generally synonymous with the term "subject" and as used herein includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

"Inhibiting", "reducing," or any variation of these terms in relation of Polθ, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of Polθ activity compared to its normal activity.

The term "homologous recombination" refers to the cellular process of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA.

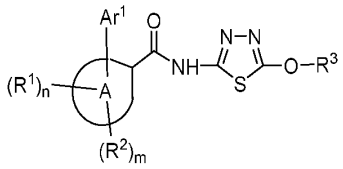
The term "homologous recombination (HR) deficient cancer" refers to a cancer that is characterized by a reduction or absence of a functional HR repair pathway. HR deficiency may arise from absence of one or more HR-assocated genes or presence of one or more mutations in one or more HR-assocated genes. Examples of HR-associated genes include BRCA1, BRCA2, RAD54, RAD51B, Ct1P (Choline Transporter-Like Protein), PALB2 (Partner and Localizer of BRCA2), XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2), RECQL4 (RecQ Protein-Like 4), BLM (Bloom syndrome, RecQ helicase-like), WRN (Werner syndrome , one or more HR-assocated genes) Nbs 1 (Nibrin), and genes encoding Fanconi anemia (FA) proteins or FA-like genes e.g, FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANJ (BRIP1), FANCL, FANCM, FANCN (RALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C, and XPF.

The term "Polθ overexpression" refers to the increased expression or activity of Polθ in a diseases cell e.g., cancerous cell, relative to expression or activity of Polθ in a normal cell (e.g., non-diseased cell of the same kind). The amount of Polθ can be at least 2-fold, at least

3-fold, at least 4- fold, at least 5- fold, at least 10-fold, or more relative to the Polθ expression in a normal cell. Examples of Polθ cancers include, but are not limited to, breast, ovarian, cervical, lung, colorectal, gastric, bladder and prostate cancers.

COMPOUNDS:

In some aspects, provided herein are compounds of Formula (I)



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 6- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1–$cyano, $–NO_2$, $–C(O)OR^a$, $–NR^aC(O)R^b$, $–X^1–C(O)NR^aR^b$, $–X^1–$OH, C_{3-6} cycloalkyl, $–X^1–O–$ C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $–X^1–NR^aR^b$, $–X^1–S(O)_2R^a$,$–X^1–S(O)_2NR^aR^b$, $X^1–X^{1a}–OR^a$, and a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and

$–X^1–$cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene,

X^{1a} is 3- to 6- membered heterocycloalkylene having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl, naphthyl, pyridin-2-one, and a 5- to 10-membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–C(O)_2R^c$, $–NR^cC(O)R^d$, $–O–C_{1-4}$ alkylene$–O–C_{1-4}$ alkyl , $–X^2$-$C(O)NR^cR^d$, $–X^2$-

$S(O)_2NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2–$cyano, $–O-X^2–$cyano, $–X^2–S(O)R^c$, $–X^2–S(O)_2R^c$, $–X^2–N(R^d)S(O)_2R^c$, $–P(O)R^cR^d$, -Y and $–X^2–OH$; or

two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered cycloalkyl or heterocycloalkyl, having 0 to 2 heteroatoms as ring vertices independently selected from N, O, and S, and which is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

wherein

each Y is independently selected from phenyl, benzyl, 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-5} cycloalkyl and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl, C_{6-11} bridged cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $-ONO_2$, 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$,$–X^3–$cyano, and oxo; and

R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-3} haloalkyl, C_{1-6} haloalkoxy, –O–C_{1-6} alkyl, cyano, –OH, –NR^eR^f,

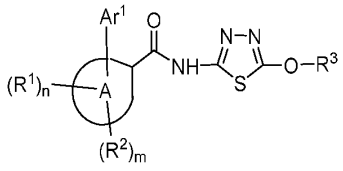
–$CONR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

each R^e and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl and -C_{1-3}alkylene-C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt thereof.

In some aspects, provided herein are compounds of Formula (I):



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, –X^1–O–C_{1-6} alkyl,

C_{1-6} haloalkoxy, –X^1–cyano, –NO_2, –$C(O)OR^a$, –$NR^aC(O)R^b$, –X^1–$C(O)NR^aR^b$, –X^1–OH, C_{3-6} cycloalkyl, –X^1–O– C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, –X^1–NR^aR^b, –X^1–$S(O)_2R^a$,–X^1–$S(O)_2NR^aR^b$, X^1–X^{1a}–OR^a, and a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and

–X^1–cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene,

X^{1a} is 3- to 6- membered heterocycloalkylene having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl, naphthyl, pyridin-2-one, and a 5- to 10-membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-X^2-O-C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $-C(O)R^c$, $-C(O)_2R^c$, $-NR^cC(O)R^d$, $-O-C_{1-4}$ alkylene$-O-C_{1-4}$ alkyl , $-X^2$-$C(O)NR^cR^d$, $-X^2$-$S(O)_2NR^cR^d$, $-X^2-NR^cR^d$, $-C(O)NR^cR^d$, $-X^2-$cyano, $-O$-X^2-cyano, $-X^2-S(O)R^c$, $-X^2-S(O)_2R^c$, $-X^2-N(R^d)S(O)_2R^c$, $-P(O)R^cR^d$, -Y and $-X^2-OH$; or

two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered cycloalkyl or heterocycloalkyl, having 0 to 2 heteroatoms as ring vertices independently selected from N, O, and S, and which is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

wherein

each Y is independently selected from phenyl, benzyl, 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-5} cycloalkyl and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl, C_{6-11} bridged cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $-ONO_2$, 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$,$–X^3–$cyano, and oxo; and

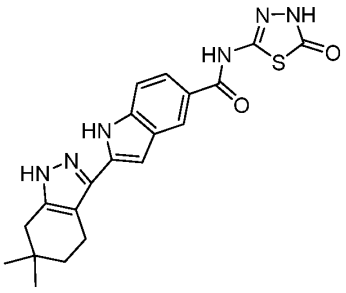
R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-3} haloalkyl, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, –OH, $–NR^eR^f$, $–CONR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

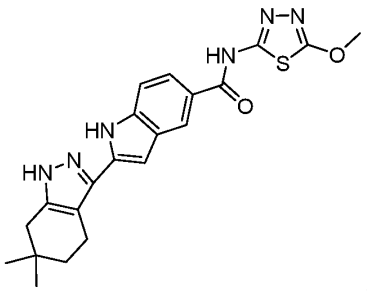
each R^e and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl and $-C_{1-3}$alkylene-C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt thereof;

provided that the compound of Formula I is other than



or



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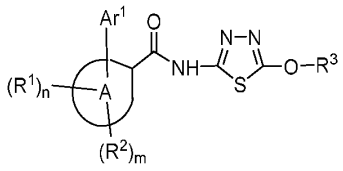
In some aspects, provided herein are compounds of Formula (I)



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1–$cyano, $–NO_2$, $–C(O)OR^a$, $–NR^aC(O)R^b$, $–X^1–C(O)NR^aR^b$, $–X^1–$OH, C_{3-6} cycloalkyl, $–X^1–O–$ C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $–X^1–NR^aR^b$, $–X^1–S(O)_2R^a$,$–X^1–S(O)_2NR^aR^b$, $X^1–X^{1a}–OR^a$, and a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and

$–X^1–$cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene,

X^{1a} is 3- to 6- membered heterocycloalkylene having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl, naphthyl, pyridin-2-one, and a 5- to 10-membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–C(O)_2R^c$, $–NR^cC(O)R^d$, $–O–C_{1-4}$ alkylene$–O–C_{1-4}$ alkyl , $–X^2$-$C(O)NR^cR^d$, $–X^2$-$S(O)_2NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2–$cyano, $–O$-$X^2–$cyano, $–X^2–S(O)R^c$, $–X^2–S(O)_2R^c$, $–X^2–N(R^d)S(O)_2R^c$, $–P(O)R^cR^d$, -Y and $–X^2–OH$; or

two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered cycloalkyl or heterocycloalkyl, having 0 to 2 heteroatoms as ring vertices independently selected from N, O, and S, and which is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

wherein

each Y is independently selected from phenyl, benzyl, 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-5} cycloalkyl and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl, C_{6-11} bridged cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $-ONO_2$, 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$, $–X^3–$cyano, and oxo; and

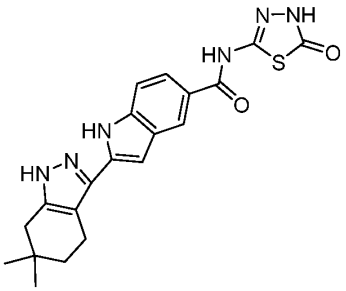
R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-3} haloalkyl, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, $–OH$, $–NR^eR^f$, $–CONR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

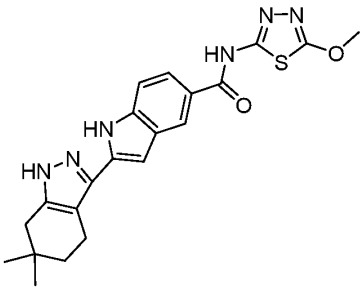
each R^e and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl and $-C_{1-3}$alkylene-C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds of Formula I are other than

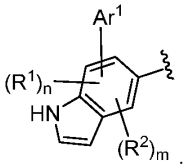


N-(4,5-dihydro-5-oxo-1,3,4-thiadiazol-2-yl)-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1*H*-indazol-3-yl)- 1*H*-Indole-5-carboxamide (CAS No. 1309787-94-7); or



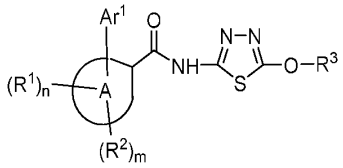
N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2-(4,5,6,7-tetrahydro-6,6-dimethyl-1H-indazol-3-yl)-1H-Indole-5-carboxamide (CAS No. 1309795-15-0).

In some embodiments, the compounds of Formula I are other than those where ring A is



In some embodiments, the compounds of Formula I are other than those where ring A is indole.

In some aspects, provided herein are compounds of Formula (I)



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1$–cyano, $–C(O)OR^a$, $–NR^aC(O)R^b$, $–X^1–C(O)NR^aR^b$, $–X^1$–OH, C_{3-6} cycloalkyl, $–X^1–O–$ C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $–X^1–NR^aR^b$, $–X^1–S(O)_2R^a$,$–X^1–S(O)_2NR^aR^b$, and $X^1–X^{1a}–OR^a$;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and $–X^1$–cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene,

X^{1a} is 3- to 6- membered heterocycloalkylene having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–NR^cC(O)R^d$, $–NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2$–cyano, $–X^2–S(O)R^c$ and $–X^2$–OH; or

two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered heterocycloalkyl having 1 to 2 heteroatoms as ring vertices independently selected from N, O, and S, wherein

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$, $–X^3–$cyano, and oxo; and

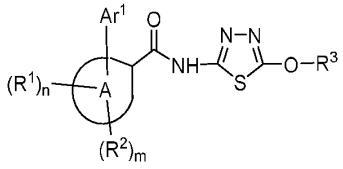
R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, $–OH$, $–NR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

each R^e and R^f is independently selected from H and C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

In some aspects, provided herein are compounds of Formula (I)



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1–$cyano, $–C(O)OR^a$, $–NR^aC(O)R^b$, $–X^1–C(O)NR^aR^b$, $–X^1–OH$, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $–X^1–NR^aR^b$, $–X^1–S(O)_2R^a$, and $–X^1–S(O)_2NR^aR^b$;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and $–X^1–$cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene, and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–NR^cC(O)R^d$, $–NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2–$cyano, and $–X^2–OH$, wherein

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$, $–X^3–$cyano, and oxo; and

R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, $–OH$, $–NR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

each R^e and R^f is independently selected from H and C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, ring A in Formula (I) is phenyl, pyridinyl, pyridazinyl, imidazolyl, pyrazolyl, triazolyl, imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

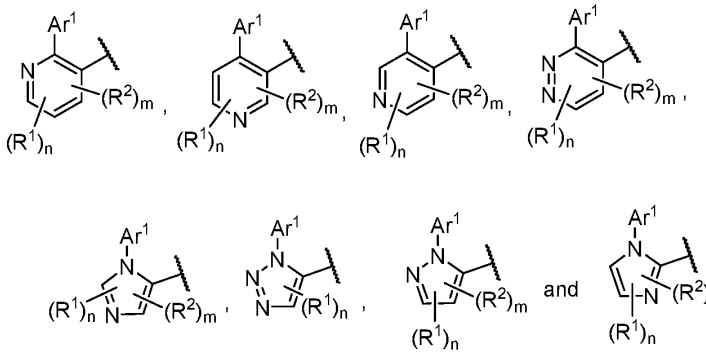
In some embodiments, ring A in Formula (I) is a nine or ten membered heteroaryl ring. In some embodiments, ring A in Formula (I) is a nine membered heteroaryl ring. In some embodiments, ring A in Formula (I) is a ten membered heteroaryl ring.

In some embodiments, ring A in Formula (I) is imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

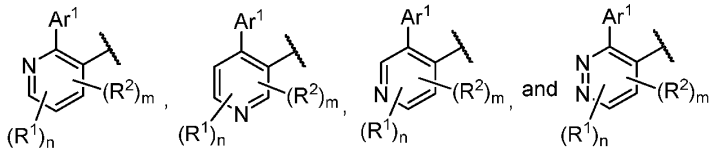
In some embodiments, ring A in Formula (I) is a five or six membered heteroaryl ring. In some embodiments, ring A in Formula (I) is a five membered heteroaryl ring. In some embodiments, ring A in Formula (I) is a six membered heteroaryl ring.

In some embodiments, ring A in Formula (I) is pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, or triazolyl.

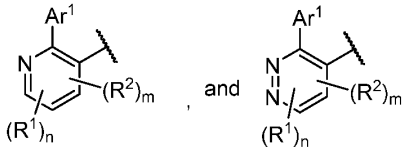
In some embodiments, ring A together with Ar^1, R^1, and R^2 in Formula (I) is selected from the group consisting of:



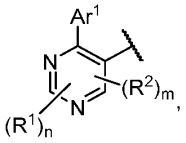
In some embodiments, ring A together with Ar^1, R^1, and R^2 in Formula (I) is selected from the group consisting of:



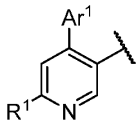
In some embodiments, ring A together with Ar^1, R^1, and R^2 in Formula (I) is selected from the group consisting of:



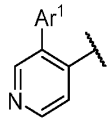
In some embodiments, ring A together with Ar^1, R^1, and R^2 in Formula (I) is selected from the group consisting of:



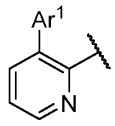
In some embodiments, ring A together with Ar^1 and R^1 in Formula (I) is:



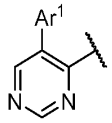
In some embodiments, ring A together with Ar^1 in Formula (I) is:



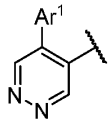
In some embodiments, ring A together with Ar^1 in Formula (I) is:



In some embodiments, ring A together with Ar^1 in Formula (I) is:



In some embodiments, ring A together with Ar^1 in Formula (I) is:



In some embodiments, ring A in Formula (I) is not pyrimidine.

In some embodiments, ring A in Formula (I) is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, and imidazo[1,2-a]pyridinyl, 1,2,3-triazole, pyrazolyl, isoxazolyl, imidazo[1,5-a]pyridinyl

In some embodiments, ring A in Formula (I) is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, and imidazo[1,2-a]pyridinyl.

In some embodiments, ring A in Formula (I) is phenyl.

In some embodiments, ring A in Formula (I) is pyridinyl.

In some embodiments, Ar^1 is attached to ring A in the ortho position relative to the amide substituent.

In some embodiments, when ring A is pyridyl, the N atom of pyridyl is oxidized to form the N-oxide.

In some embodiments, n in Formula (I) and subembodiments thereof is 1. In some embodiments, n in Formula (I) and subembodiments thereof is 0.

In some embodiments, n is 1 in Formula (I) and subembodiments thereof n is 1 and R^1 is a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S. In some embodiments, n is 1 in Formula (I) and subembodiments thereof n is 1 and R^1 is a 6-membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S. In some embodiments, n is 1 in Formula (I) and subembodiments thereof n is 1 and R^1 is a 5-membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S. In some embodiments, n is 1 in Formula (I) and subembodiments thereof n is 1 and R^1 is a 4-membered

heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S. In some embodiments, n is 1 in Formula (I) and subembodiments thereof n is 1 and R^1 is selected from the group consisting of azetinidinyl, pyrrolidinyl, pyrazolidinyl, piperidinyl, and piperazinyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof n is 1 and R^1 is azetinidinyl.

In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1–$cyano, $–X^1–$OH, C_{3-6} cycloalkyl, and $–X^1–NR^aR^b$. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of C_{1-6} alkyl, halo, $–X^1–$cyano, and C_{1-6} haloalkyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1–$OH, and $–X^1–NR^aR^b$. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of–$X^1–O–$ C_{3-6} cycloalkyl, and $X^1–X^{1a}–OR^a$. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of C_{1-6} alkyl, halo, $–X^1–$cyano, and C_{1-6} haloalkyl, $–X^1–O–$ C_{3-6} cycloalkyl, and $X^1–X^{1a}–OR^a$. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of C_{1-6} alkyl, halo, $–X^1–$cyano, and C_{1-6} haloalkyl, and $–X^1–O–$ C_{3-6} cycloalkyl.

In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of C_{1-6} alkyl and $–X^1–$OH.

In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of methyl and hydroxymethyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is selected from the group consisting of ethyl and hydroxyethyl.

[0001] In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is methyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is ethyl or propyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is O-cyclopropyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is O-cyclopropyl. In some embodiments, n is 1 in Formula (I) and subembodiments thereof and R^1 is -CH_2-O-cyclopropyl.

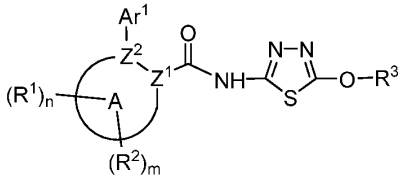
In some embodiments, m is 1 in Formula (I) and R^2 is C_{1-6} alkyl, halo, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy. In some embodiments, m is 1 in Formula (I) and R^2 is C_{1-6} alkyl, halo, and C_{1-6} haloalkyl.

In some embodiments, m in Formula (I) and subembodiments thereof is 0. In some embodiments, m in Formula (I) and subembodiments thereof is 1.

In some embodiments, each X^1 in Formula (I) and subembodiments thereof is a bond. In some embodiments, each X^1 in Formula (I) and subembodiments thereof is C_{1-4} alkylene. In some embodiments, each X^1 in Formula (I) and subembodiments thereof is C_{1-2} alkylene. In some embodiments, each X^1 in Formula (I) and subembodiments thereof is methylene.

In some embodiments, each R^a and R^b in Formula (I) and subembodiments thereof is hydrogen. In some embodiments, each R^a is hydrogen and each R^b in Formula (I) and subembodiments thereof is C_{1-4} alkyl or C_{1-4} haloalkyl. In some embodiments, each R^a and R^b in Formula (I) and subembodiments thereof is C_{1-4} alkyl. In some embodiments, each R^a and R^b in Formula (I) and subembodiments thereof is C_{1-2} alkyl. In some embodiments, each R^a and R^b in Formula (I) and subembodiments thereof is methyl. In some embodiments, each R^a and R^b in Formula (I) and subembodiments thereof is C_{1-4} haloalkyl. In some embodiments, each R^a and R^b in Formula (I) and subembodiments thereof is C_{1-2} haloalkyl.

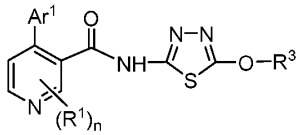
In some embodiments, the compound has the Formula (Iaa):



(Iaa),

or a pharmaceutically acceptable salt thereof, wherein Z^1 and Z^2 are ring vertices of ring A linked by a single or a double bond, and each of Z^1 and Z^2 are carbon atoms.

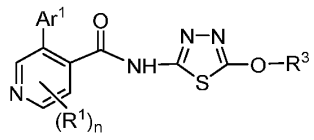
In some embodiments, the compound has the Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof.

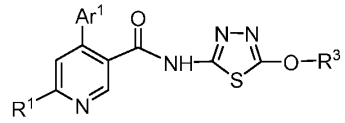
In some embodiments, the compound has the Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof.

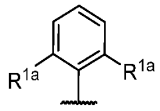
In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is selected from the group consisting of phenyl, pyridinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, pyridazyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, and tetrazolo[1,5-a]pyridinyl, each of which is substituted with 0 to 4 R^{1a}

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is selected from the group consisting of phenyl, pyridinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, and pyridazyl each of which is substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is selected from the group consisting of 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, benzo[c]isothiazolyl, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, tetrazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyridinyl, each of which is substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is phenyl substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is



In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is pyridinyl substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is naphthyl substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is pyridin-2-one substituted with 0 to 4 R^{1a}.

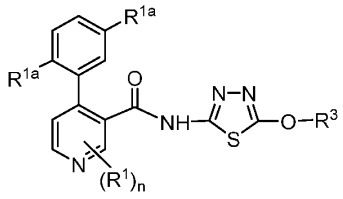
In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is naphthyl substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is pyridin-2-one substituted with 0 to 4 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is substituted with 0 to 3 R^{1a}.

In some embodiments, Ar^1 in Formula (I), (Ia), (Ib), and (Ic) is substituted with 0 to 2 R^{1a}.

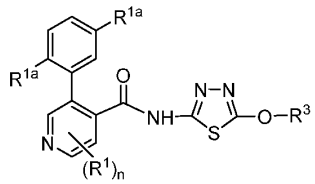
In some embodiments, the compound has the Formula (Ia1):



(Ia1),

or a pharmaceutically acceptable salt thereof.

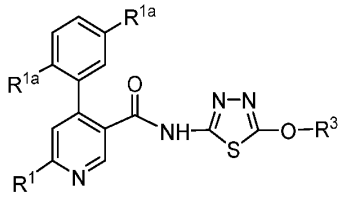
In some embodiments, the compound has the Formula (Ib1):



(Ib1),

or a pharmaceutically acceptable salt thereof.

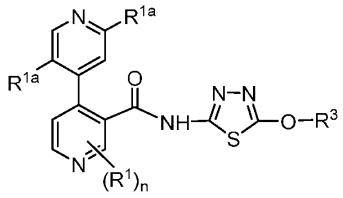
In some embodiments, the compound has the Formula (Ic1):



(Ic1),

or a pharmaceutically acceptable salt thereof.

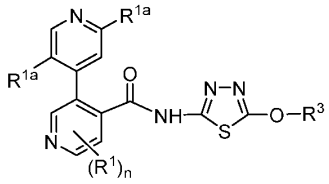
In some embodiments, the compound has the Formula (Ia2):



(Ia2),

or a pharmaceutically acceptable salt thereof.

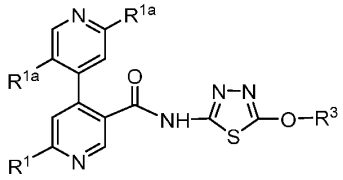
In some embodiments, the compound has the Formula (Ib2):



(Ib2),

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the Formula (Ic2):



(Ic2),

or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, $–NR^aR^b$, $–X^2–$cyano, and $–X^2–OH$. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, –

X^2–O–C_{1-6} alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, –NR^aR^b, –X^2–cyano, –X^2–OH, and –X^2–$S(O)R^c$.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, –O–C_{1-6} alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, –NR^aR^b, and –X^2–OH. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, –X^2–O–C_{1-6} alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, –NR^aR^b, –X^2–cyano, –X^2–OH, and –$S(O)R^c$.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, cyclopropyl, $–NH_2$, hydroxymethyl, and 1-hydroxyethyl. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, cyclopropyl, $–NH_2$, hydroxymethyl, 1-hydroxyethyl and $-S(=O)CH_3$. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, and difluoromethoxy. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from ethyl, fluoro, chloro, difluoromethyl, and ethoxy. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, and difluoromethoxy. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected methyl, ethyl, fluoro, cyclopropyl, $–NH_2$, hydroxymethyl, and 1-hydroxyethyl.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from C_{1-6} alkyl, halo, –O–C_{1-6} alkyl, $–C(O)_2R^c$, -C_{1-4} alkoxy-C_{1-4} alkoxy, –X^2-$C(O)NR^cR^d$, –X^2-$S(O)_2NR^cR^d$, –O-X^2–cyano, –X^2–$S(O)_2R^c$, and –X^2–$N(R^d)S(O)_2R^c$. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from $–C(O)_2R^c$, -C_{1-4} alkoxy-C_{1-4} alkoxy, –X^2-$C(O)NR^cR^d$, –X^2-$S(O)_2NR^cR^d$, –O-X^2–cyano, –X^2–$S(O)_2R^c$, and –X^2–$N(R^d)S(O)_2R^c$.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof, wherein at least one R^{1a} is Y and Y is selected from phenyl, benzyl, 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring

members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof, wherein at leaste one R^{1a} is Y and Y is phenyl or benzyl; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof, wherein at least one R^{1a} is Y and Y is 4- to 6-membered heterocycloalkyl or 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof, wherein at least one R^{1a} is Y and Y is 4- to 6-membered heterocycloalkyl, wherein each heterocycloalkyl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl. In some embodiments, the 4- to 6-membered heterocycloalkyl is selected from the group consisting of piperidinyl, morpholinyl, and tetrahydropyranyl.

In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof, wherein at least one R^{1a} is Y and Y is 5- or 6-membered heteroaryl, wherein each heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof, wherein at least one R^{1a} is Y and Y is 5- membered heteroaryl, wherein each heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl. In some embodiments, the 5- to 6- membered heteroaryl is pyrazolyl.

In some embodiments, two R^{1a} groups, in Formula (I) and subembodiments thereof, on adjacent ring vertices combine to form a 4 to 6 membered heterocycloalkyl having 1 to 2 heteroatoms as ring vertices independently selected from N, O, and S. In some embodiments, two R^{1a} groups, in Formula (I) and subembodiments thereof, on adjacent ring vertices combine to form a 5 membered heterocycloalkyl having 1 to 2 heteroatoms as ring vertices independently selected from N, O, and S. In some embodiments the heterocycloalkyl ring has 1 or 2 double bonds between ring members. In some embodiments the heterocycloalkyl

ring is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

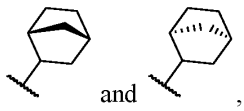
In some embodiments, two R^{1a} groups, in Formula (I) and subembodiments thereof, on adjacent ring vertices combine to form a 4 to 6 membered cycloalkyl. In some embodiments the cycloalkyl ring has 1 or 2 double bonds between ring members. In some embodiments the cycloalkyl ring is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl. In some embodiments, each R^{1a} in Formula (I) and subembodiments thereof is independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, and cyclopropyl.

In some embodiments, each X^2 in Formula (I) and subembodiments thereof is a bond. In some embodiments, each X^2 in Formula (I) and subembodiments thereof is C_{1-4} alkylene. In some embodiments, each X^2 in Formula (I) and subembodiments thereof is C_{1-2} alkylene. In some embodiments, each X^2 in Formula (I) and subembodiments thereof is methylene.

In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is hydrogen, C_{1-6} alkyl, C_{3-5} cycloalkyl and C_{1-6} haloalkyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is hydrogen. In some embodiments, each R^c is hydrogen and each R^d in Formula (I) and subembodiments thereof is C_{1-4} alkyl or C_{1-4} haloalkyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is C_{1-4} alkyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is C_{1-2} alkyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is methyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is C_{1-4} haloalkyl. In some embodiments, each R^c and R^d in Formula (I) and subembodiments thereof is C_{1-2} haloalkyl.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is C_{6-12} spirocyclyl or C_{3-6} cycloalkyl, each of which is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl , and is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of spiro[3.3]heptane, spiro[4.4]nonane, spiro[3.4]octane.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is C_{6-11} bridged cycloalkyl, each of which is substituted with 0 to 4 R^{3a}. In some embodiments, the C_{6-11} bridged cycloalkyl has the structure



each of which is substituted with 0 to 4 R^{3a}.

In some embodiments, R^3 is a 3- to 6-membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is a 5- membered heterocycloalkyl substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is a 6- membered heterocycloalkyl substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, 2-oxopiperazinyl, 2- tetrahydropyranyl, 3,6-dihydro-2H-pyranyl, 2-oxo-1,2-dihydropyridinyl, thiomorpholinyl, and 1,1-dioxothiomorpholinyl each of which is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of tetrahydropyran, oxetanyl, tetrahydrofuranyl, and tetrahydrothiopyranyl, each of which is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is tetrahydrothiopyranyl substituted with 2 oxo groups.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is a 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of 6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl and 2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl and is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of 6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl, benzo[d][1,3]dioxol-4-yl, (3,4-dihydro-2H-1,4-benzoxazin-8-yl), [5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl] and 2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl, and is substituted with 0 to 4 R^{3a}.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is a 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from

N, O, and S, and is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of 2-azabicyclo[2.2.2]octane, quinuclidine, and 7-oxabicyclo[2.2.1]heptane, and is substituted with 0 to 4 R^{3a}.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is a 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of 4-oxaspiro[2.4]heptane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.4]octane, 2-azaspiro[3.5]-nonane, and 2,7-diazaspiro[4.4]nonane, and is substituted with 0 to 4 R^{3a}.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is substituted with 0 to 2 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is substituted with 1 R^{3a}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is substituted with 2 R^{3a}. In some embodiments, each R^{3a} in Formula (I) and subembodiments thereof is selected from the group consisting of $C_{1\text{-}6}$ alkyl, halo, $–X^3–O–C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkoxy, $–X^3–OH$, $-ONO_2$, 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S and oxo. In some embodiments, each R^{3a} in Formula (I) and subembodiments thereof is selected from the group consisting of $C_{1\text{-}6}$ alkyl, halo, $–X^3–O–C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkoxy, $–X^3–OH$, and oxo. In some embodiments, each R^{3a} in Formula (I) and subembodiments thereof is selected from the group consisting of $C_{1\text{-}6}$ alkyl, halo, $–X^3–OH$, and oxo. In some embodiments, each R^{3a} in Formula (I) and subembodiments thereof is selected from the group consisting of methyl, –OH, and oxo. In some embodiments, at least one R^{3a} in Formula (I) and subembodiments thereof is selected from the group consisting of a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S and oxo. In some embodiments, at least one R^{3a} in Formula (I) and subembodiments thereof is selected from the group consisting of tetrahydropyranyl and oxetanyl.

In some embodiments, R^3 is in Formula (I) and subembodiments thereof hydrogen.

In some embodiments, R^3 is in Formula (I) and subembodiments thereof $C_{1\text{-}6}$ alkyl or $C_{2\text{-}6}$ alkynyl, and is substituted with 0 to 4 R^{3b}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is selected from the group consisting of 2-propynyl, ethyl, methyl, 2,2,-dimethylpropyl, isobutyl, isopropyl, and n-propyl, and is substituted with 0 to 4 R^{3b}.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is methyl and is substituted with 0 to 3 R^{3b}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is methyl.

In some embodiments, R^3 in Formula (I) and subembodiments thereof is C_{1-6} alkyl or C_{2-6} alkynyl and is substituted with 0 to 3 R^{3b}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is C_{1-6} alkyl or C_{2-6} alkynyl and is substituted with 0 to 2 R^{3b}. In some embodiments, R^3 in Formula (I) and subembodiments thereof is C_{1-6} alkyl or C_{2-6} alkynyl and is substituted with 1 R^{3b}.

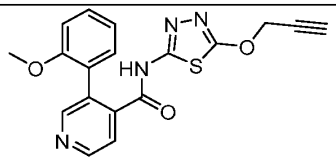
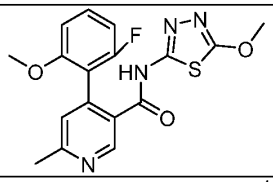
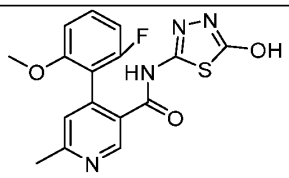
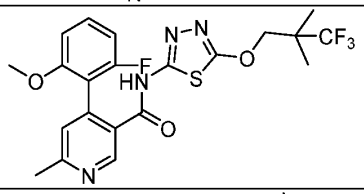
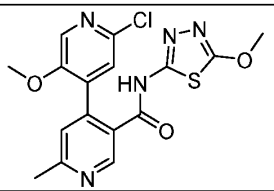
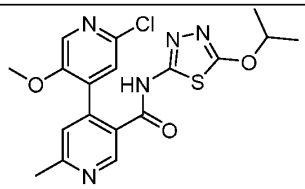
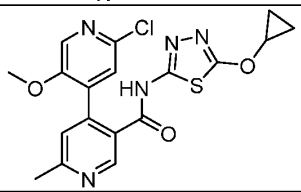
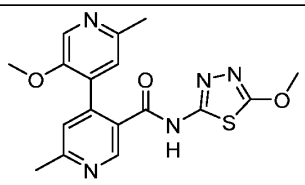
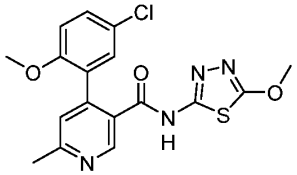
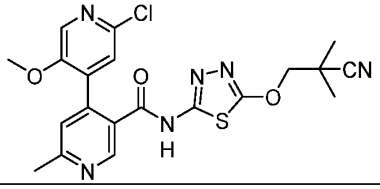
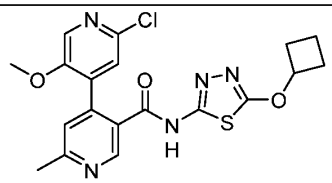
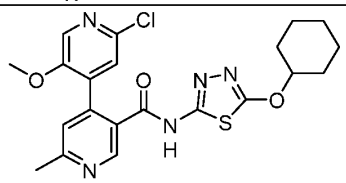
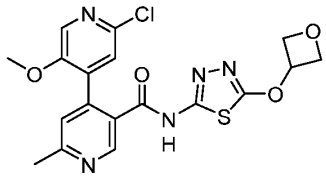
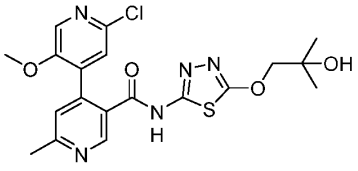
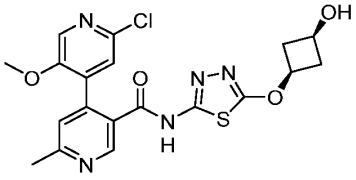
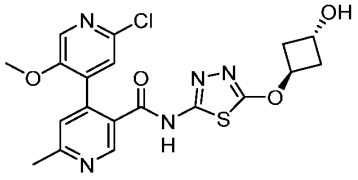
In some embodiments, each R^{3b} in Formula (I) and subembodiments thereof is selected from the group consisting of halo, C_{1-3} haloalkyl, –O–C_{1-6} alkyl, cyano,–OH, and –$CONR^eR^f$. In some embodiments, each R^{3b} in Formula (I) and subembodiments thereof is selected from the group consisting of halo, –O–C_{1-6} alkyl, cyano, and –OH. In some embodiments, each R^{3b} in Formula (I) and subembodiments thereof is selected from the group consisting of fluoro, methoxy, cyano, and –OH. In some embodiments, each R^{3b} in Formula (I) and subembodiments thereof is selected from the group consisting of –O–C_{1-6} alkyl, cyano, and –OH. In some embodiments, each R^{3b} in Formula (I) and subembodiments thereof is selected from the group consisting of methoxy, cyano, and –OH.

In some embodiments, each X^3 in Formula (I) and subembodiments thereof is a bond. In some embodiments, each X^3 in Formula (I) and subembodiments thereof is C_{1-4} alkylene. In some embodiments, each X^3 in Formula (I) and subembodiments thereof is C_{1-2} alkylene. In some embodiments, each X^3 in Formula (I) and subembodiments thereof is methylene.

In some embodiments, each R^e and R^f in Formula (I) and subembodiments thereof is hydrogen. In some embodiments, each R^e is hydrogen and each R^f in Formula (I) and subembodiments thereof is C_{1-4} alkyl or C_{1-4} haloalkyl. In some embodiments, each R^e and R^f in Formula (I) and subembodiments thereof is C_{1-4} alkyl. In some embodiments, each R^e and R^f in Formula (I) and subembodiments thereof is C_{1-2} alkyl. In some embodiments, each R^e and R^f in Formula (I) and subembodiments thereof is methyl. In some embodiments, each R^e and R^f in Formula (I) and subembodiments thereof is C_{1-4} haloalkyl. In some embodiments, each R^e and R^f in Formula (I) and subembodiments thereof is C_{1-2} haloalkyl.

Representative compounds of Formula (I) are listed in Table 1 below:

Table 1

Cpd #	Structure	Cpd #	Structure
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	

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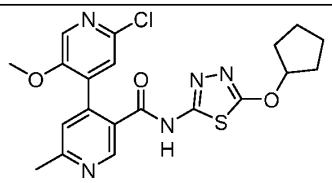
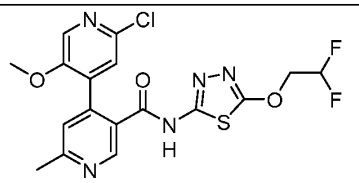
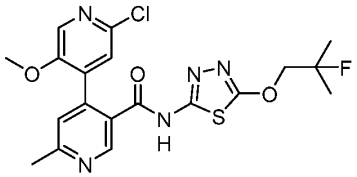
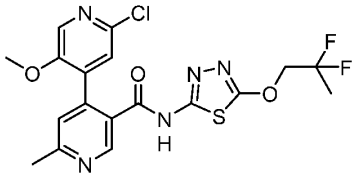
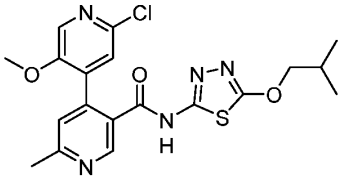
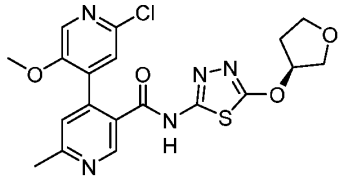
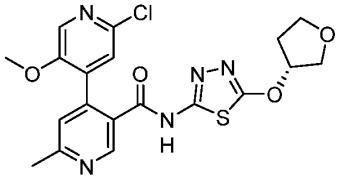
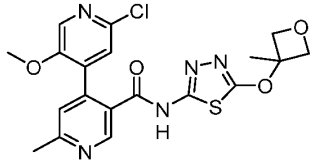
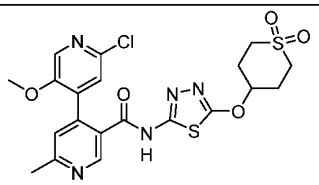
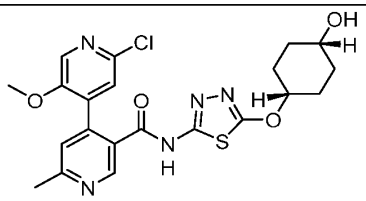
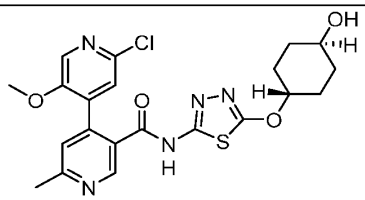
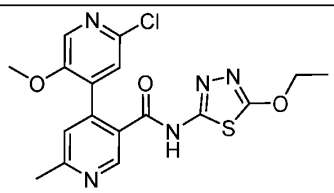
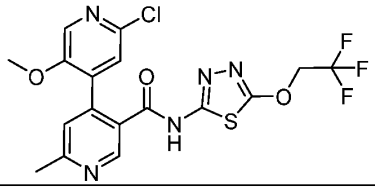
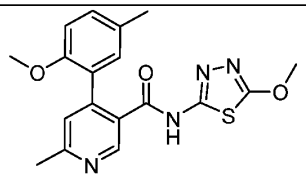
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	

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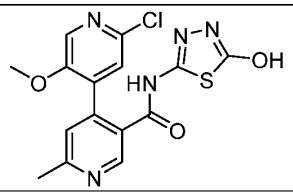
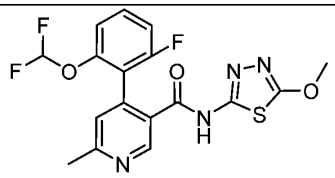
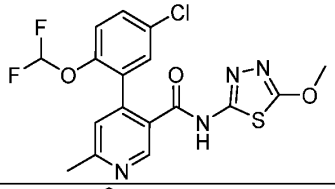
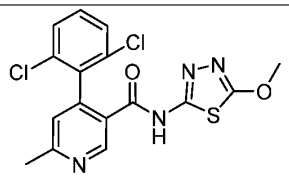
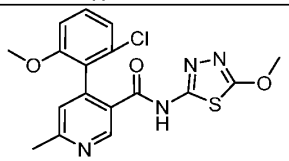
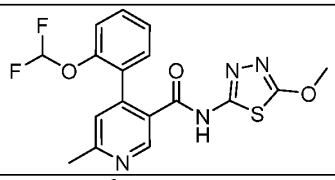
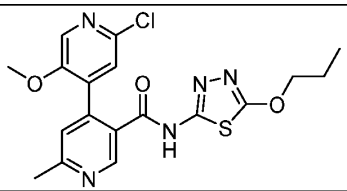
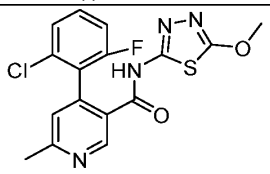
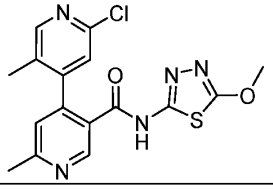
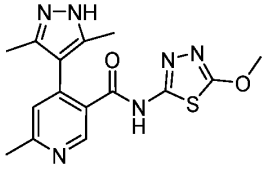
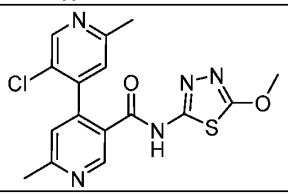
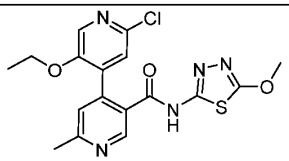
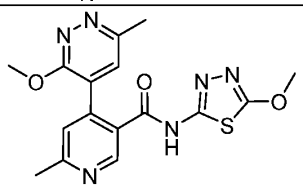
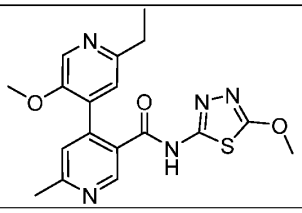
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	
43		44	

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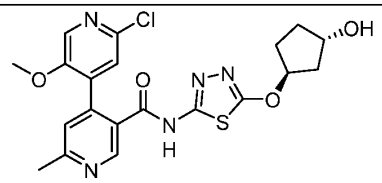
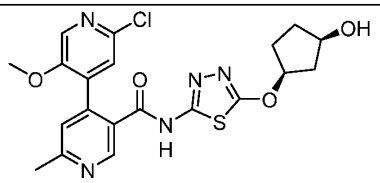
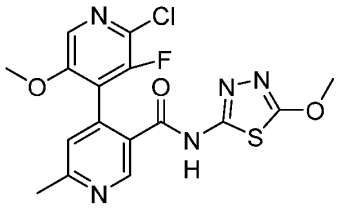
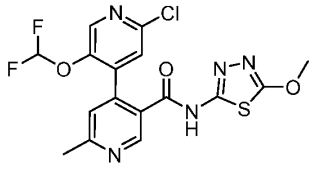
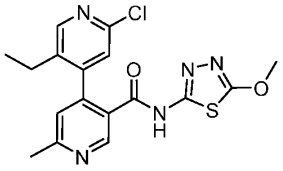
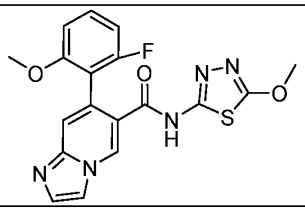
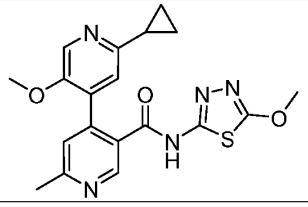
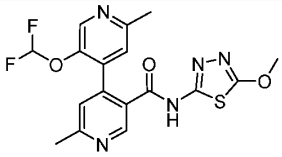
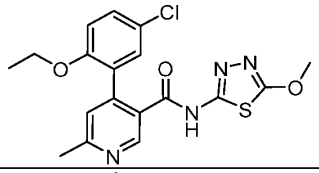
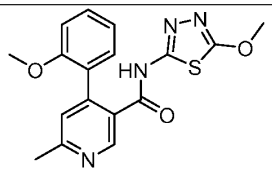
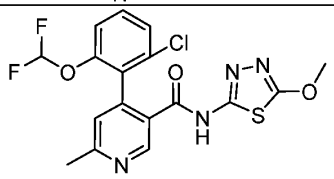
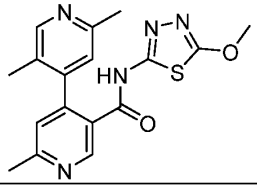
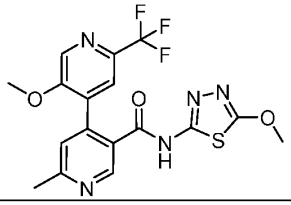
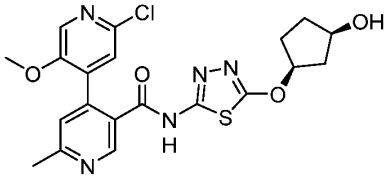
45		46	
47		48	
49		50	
51		52	
53		54	
55		56	
57		58	

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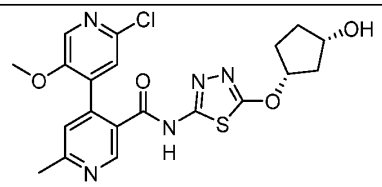
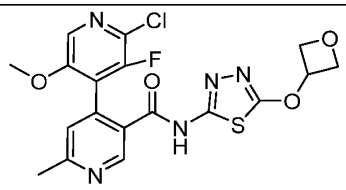
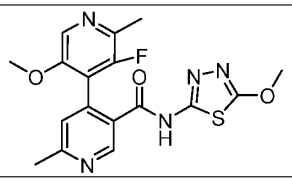
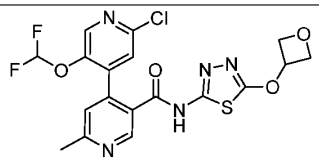
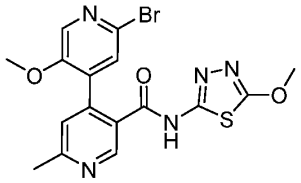
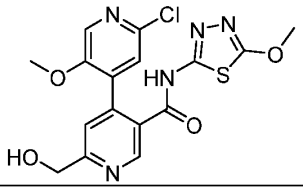
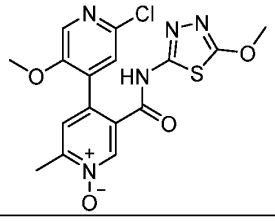
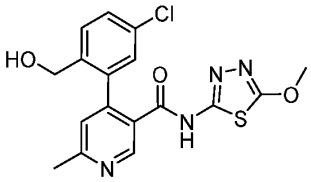
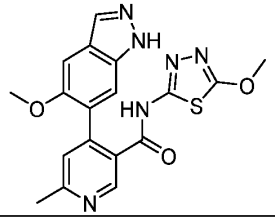
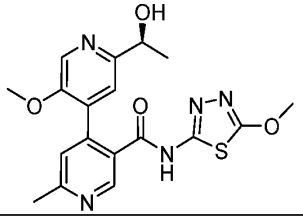
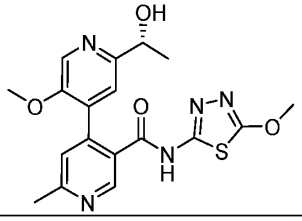
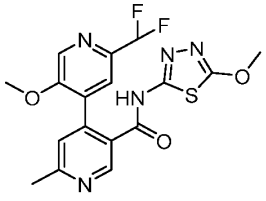
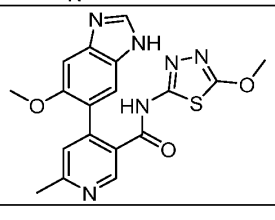
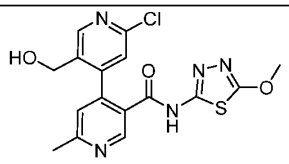
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	

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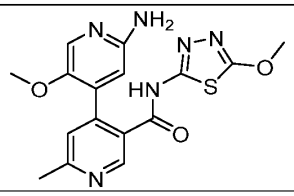
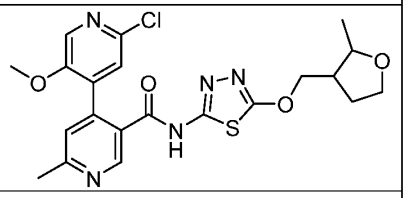
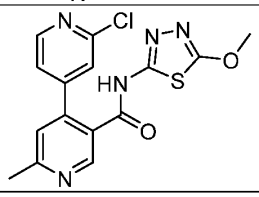
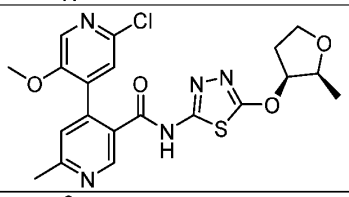
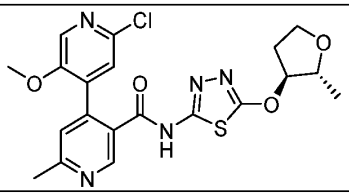
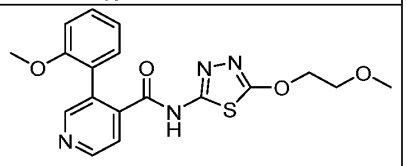
73		74	
75		76	
77		78	

Additional representative compounds of Formula (I) are listed in Table 2 below:

Table 2.

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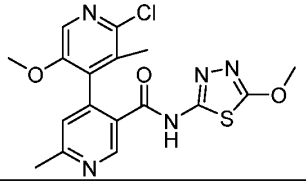
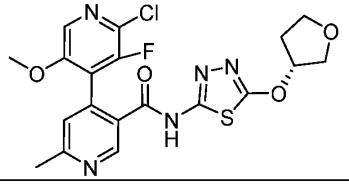
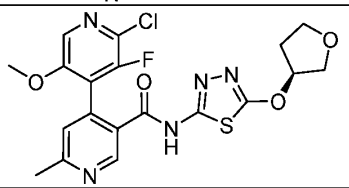
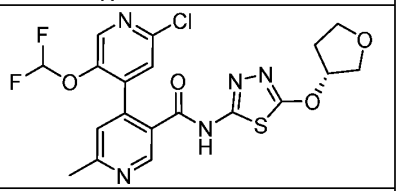
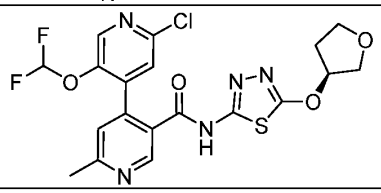
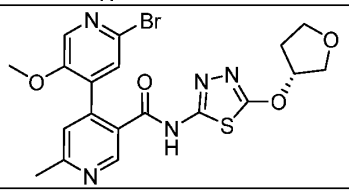
79		80	
81		82	
83		84	

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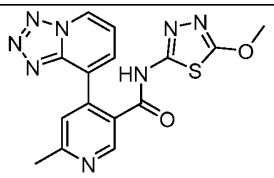
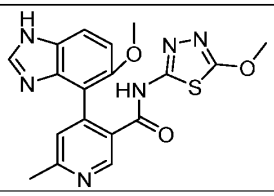
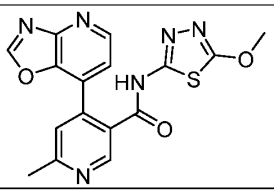
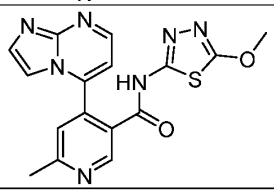
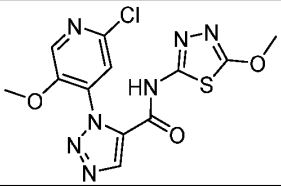
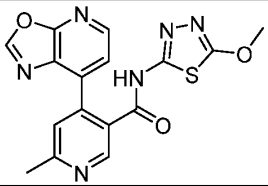
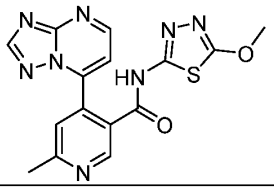
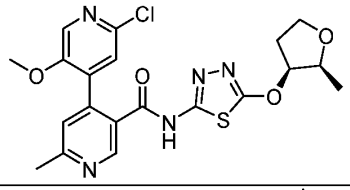
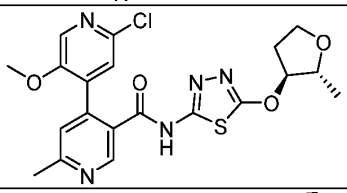
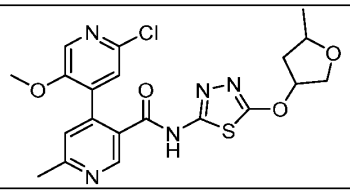
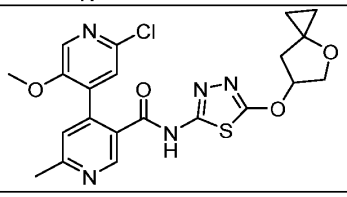
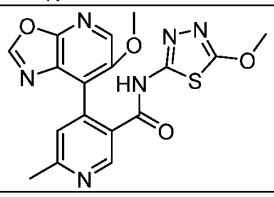
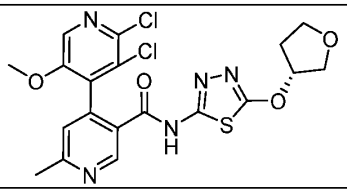
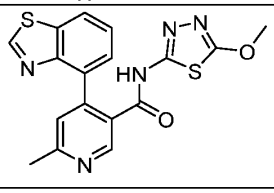
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	

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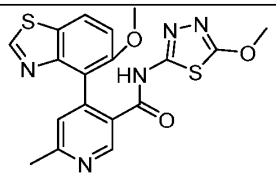
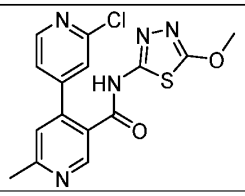
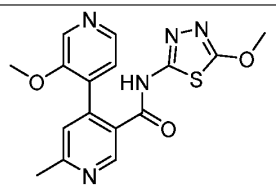
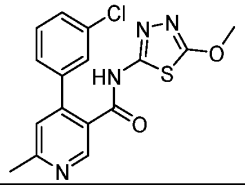
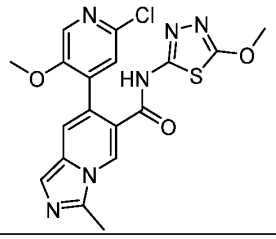
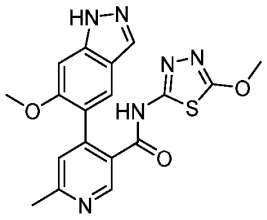
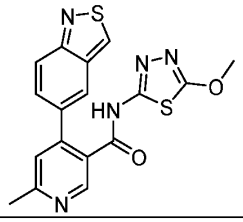
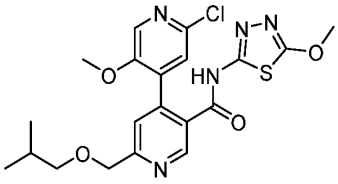
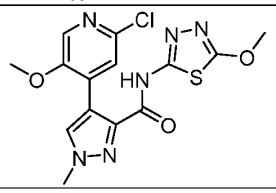
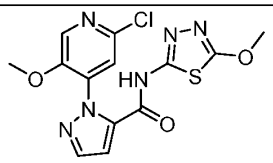
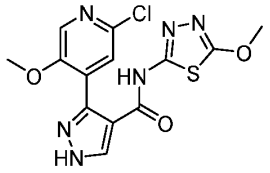
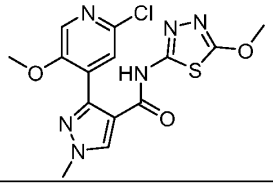
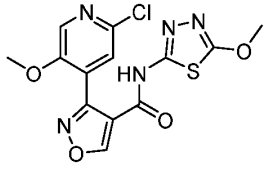
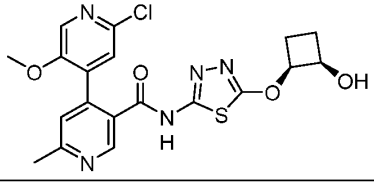
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	
111		112	

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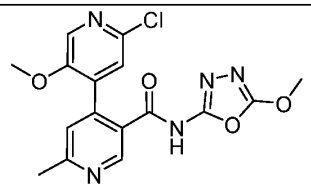
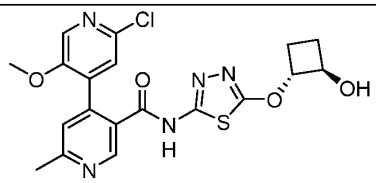
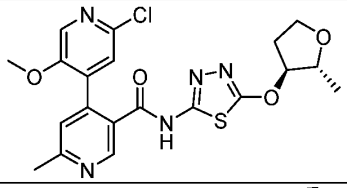
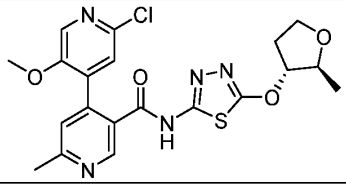
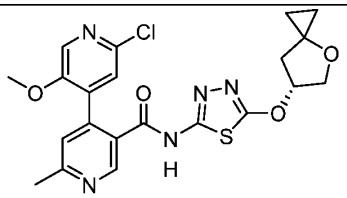
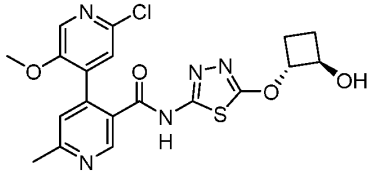
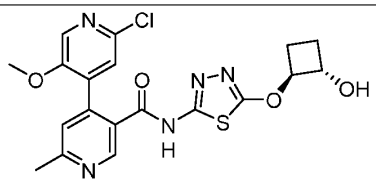
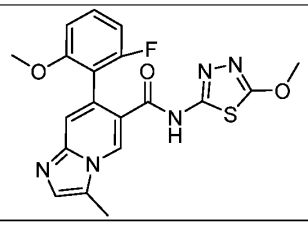
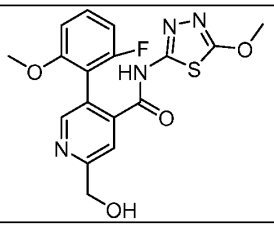
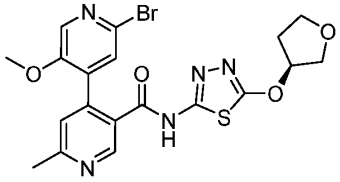
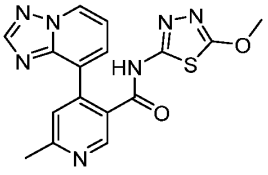
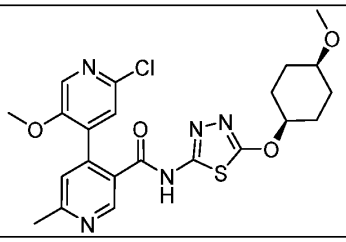
113		114	 racemate
115		116	
117		118	
119		120	
121		122	
123		124	

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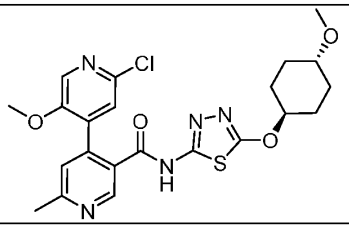
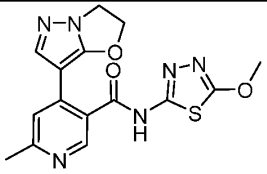
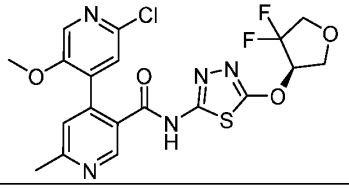
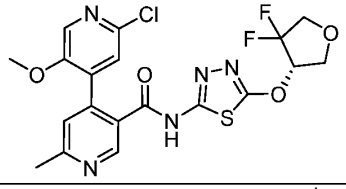
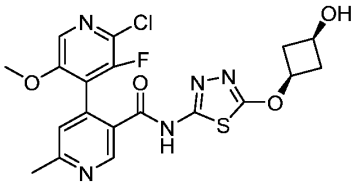
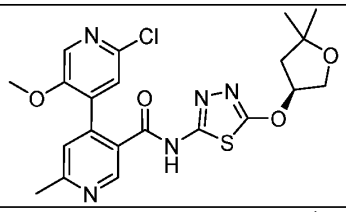
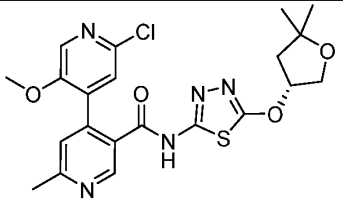
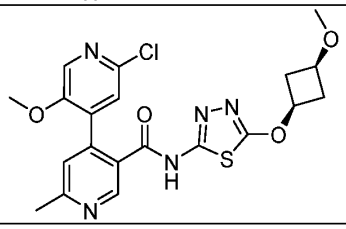
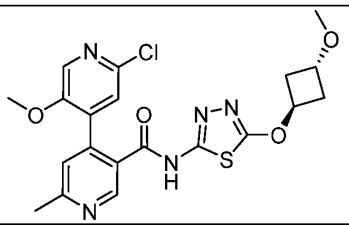
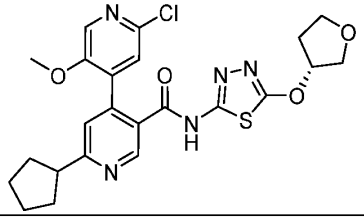
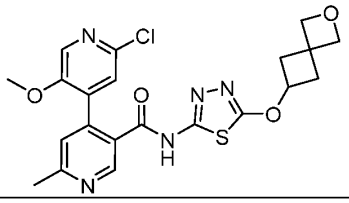
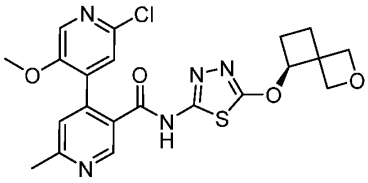
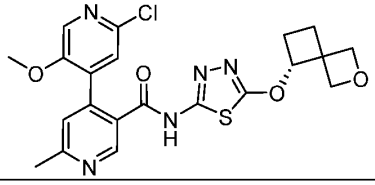
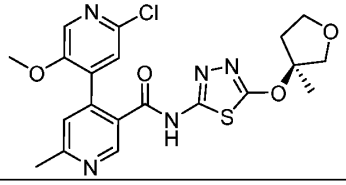
125		126	
127		128	
129		130	
131		132	
133		134	
135		136	
137		138	

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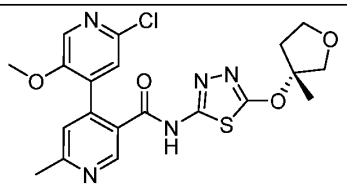
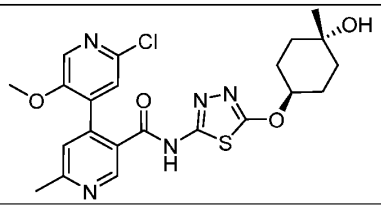
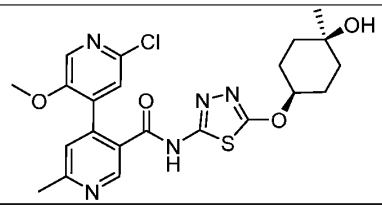
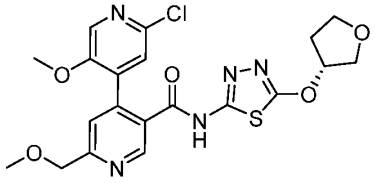
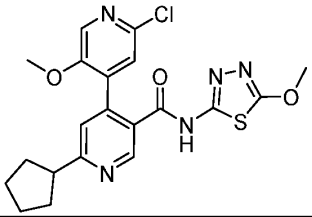
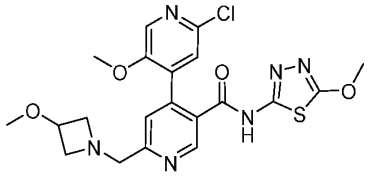
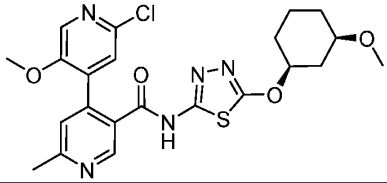
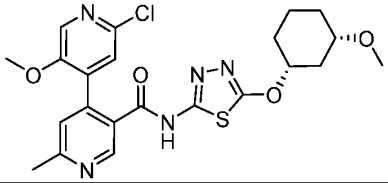
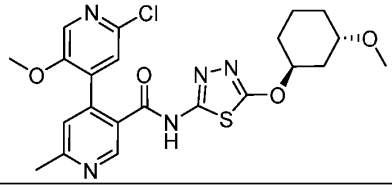
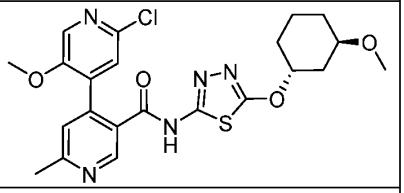
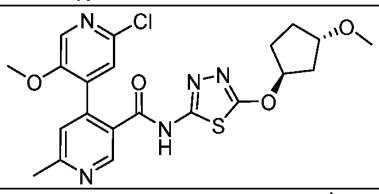
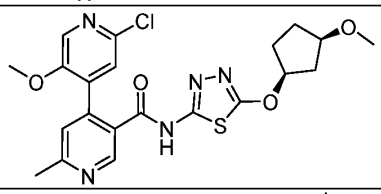
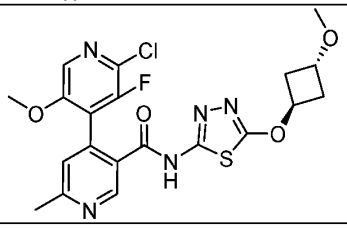
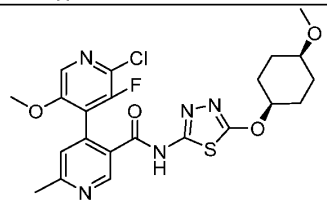
139		140	
141		142	
143		144	
145		146	
147		148	
149		150	
151		152	

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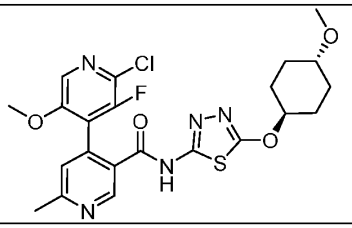
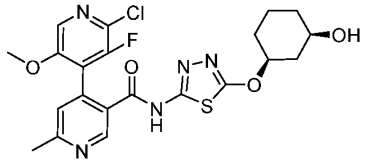
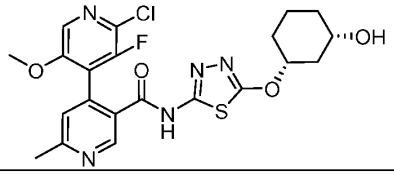
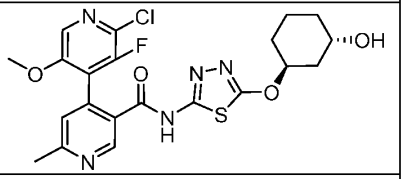
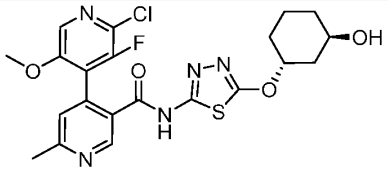
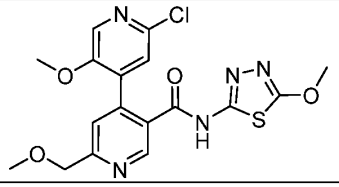
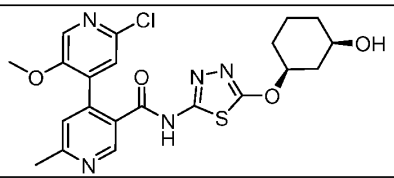
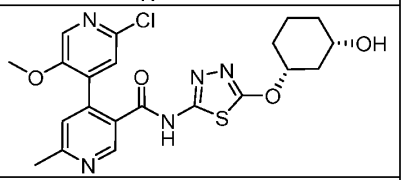
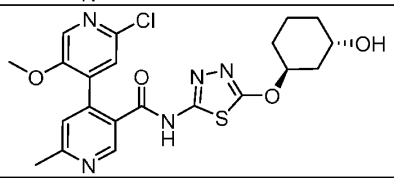
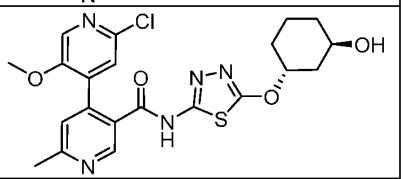
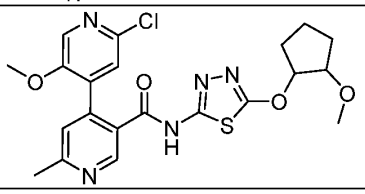
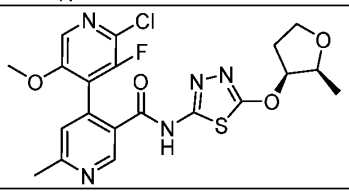
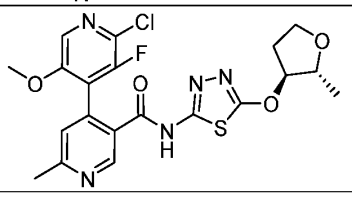
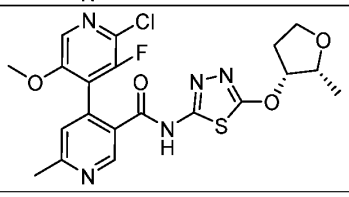
153		154	
155		156	
157		158	
159		160	
161		162	
163		164	
165		166	

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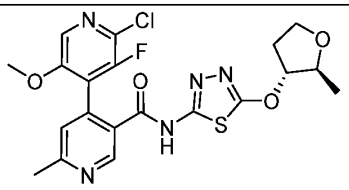
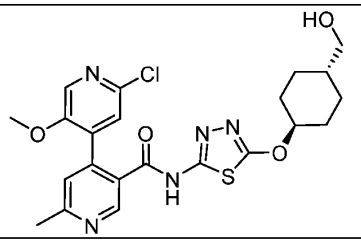
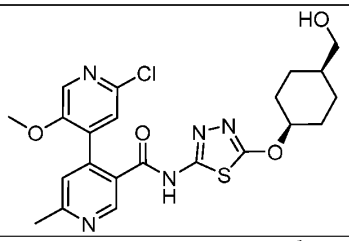
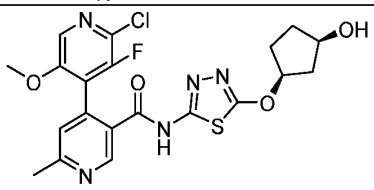
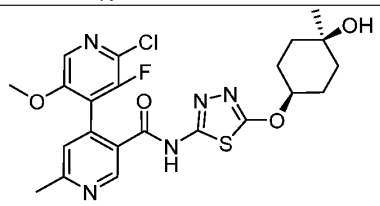
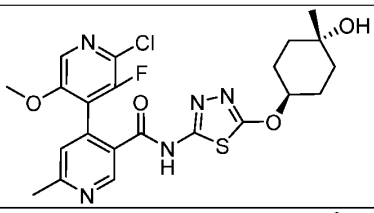
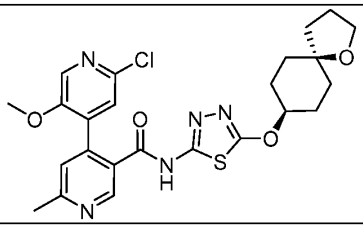
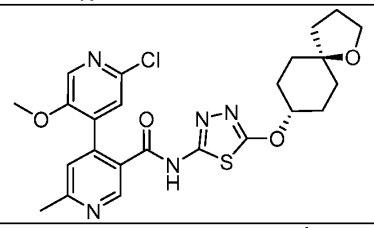
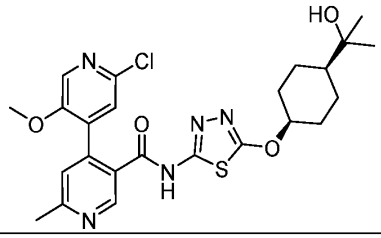
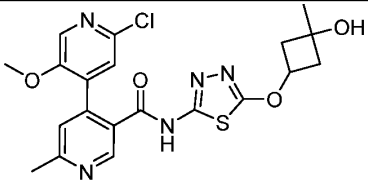
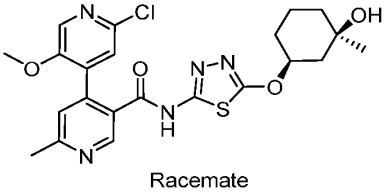
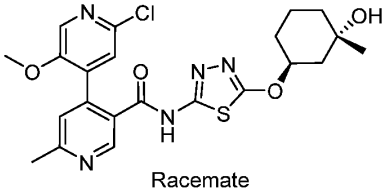
167		168	
169		170	
171		172	
173		174	
175		176	
177	 Racemate	178	 Racemate

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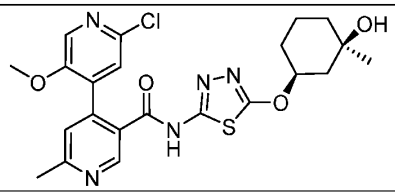
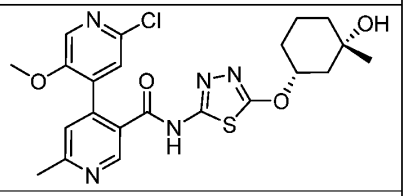
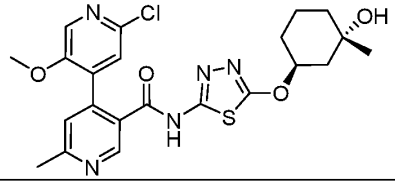
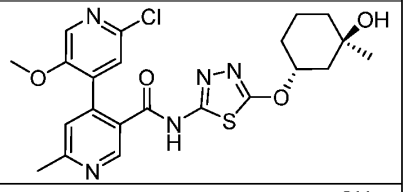
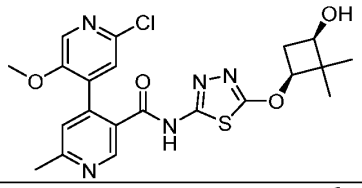
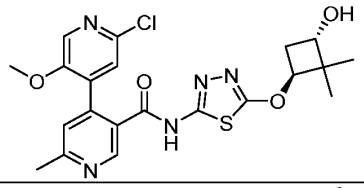
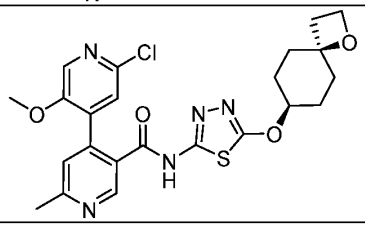
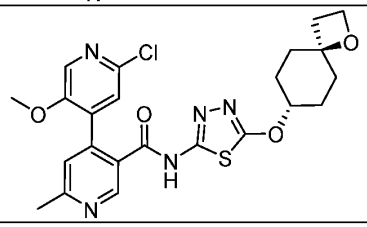
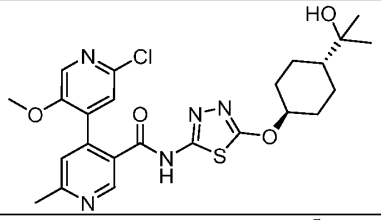
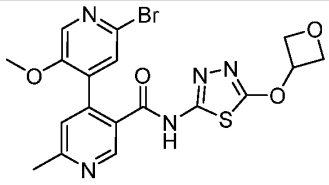
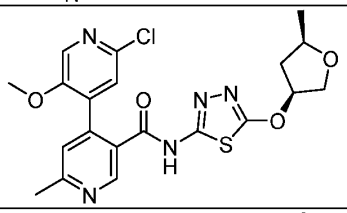
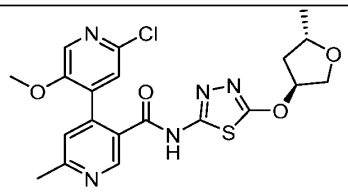
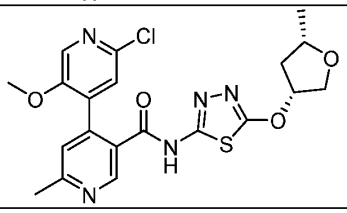
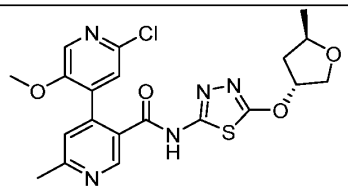
179		180	
181		182	
183		184	
185		186	
187		188	
189		190	
191		192	

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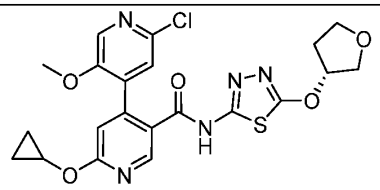
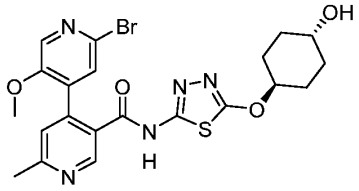
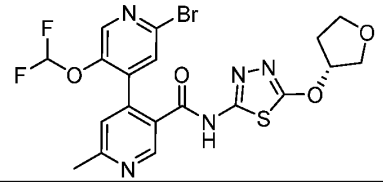
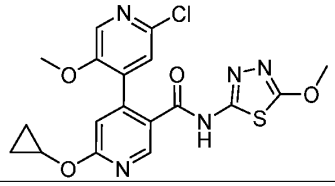
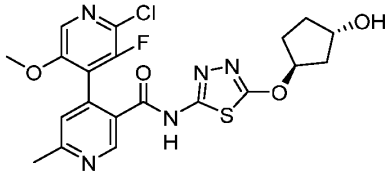
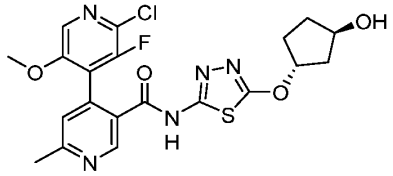
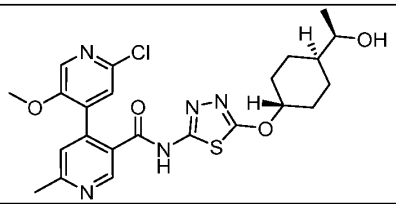
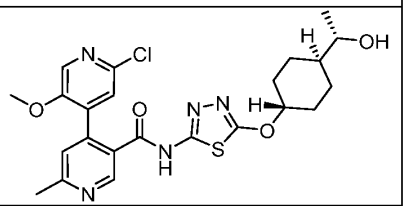
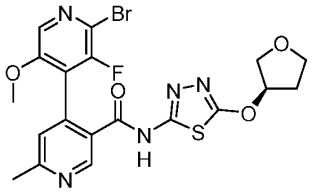
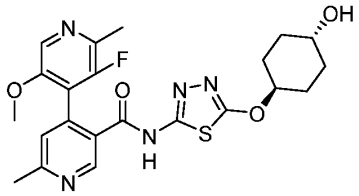
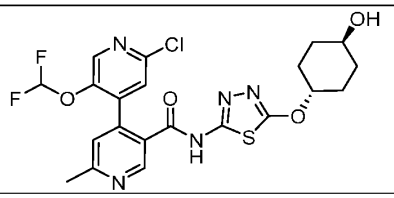
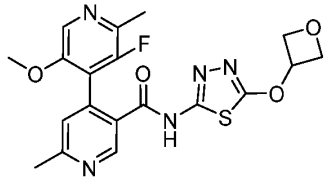
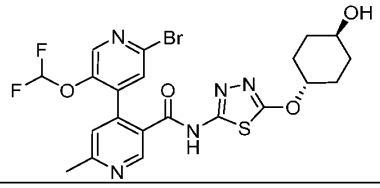
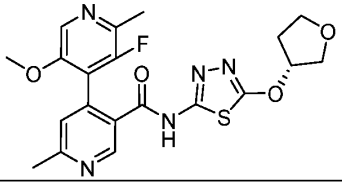
193		194	
195		196	
197		198	
199		200	
201		202	
203		204	
205		206	

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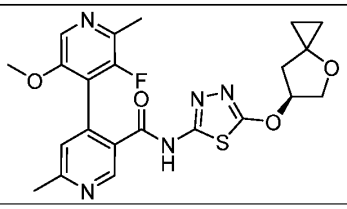
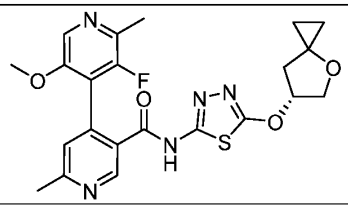
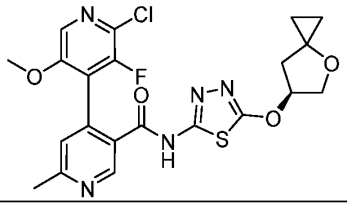
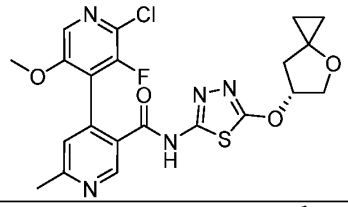
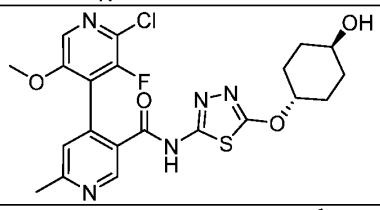
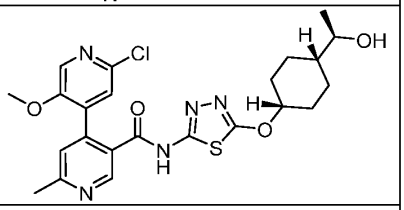
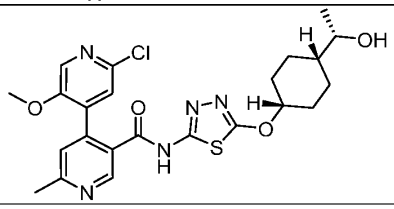
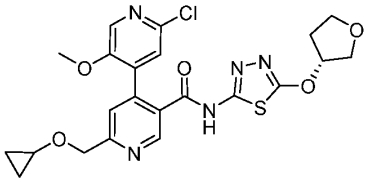
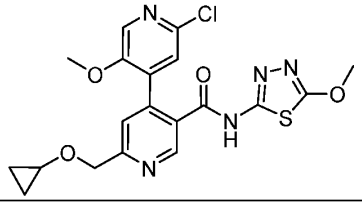
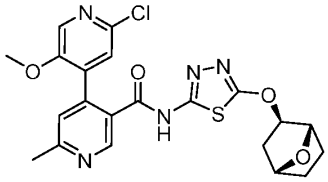
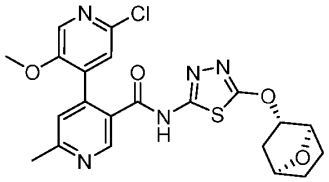
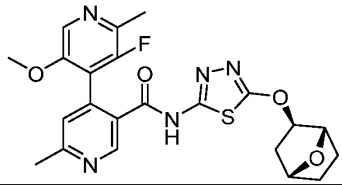
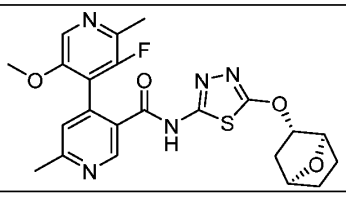
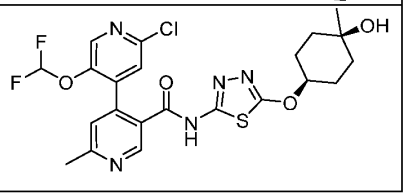
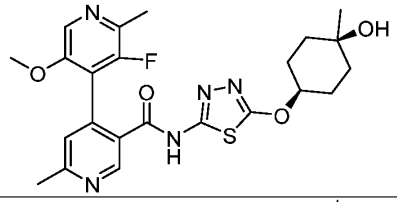
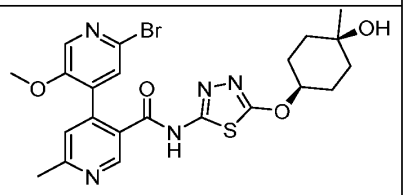
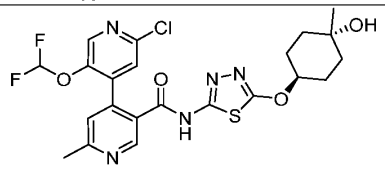
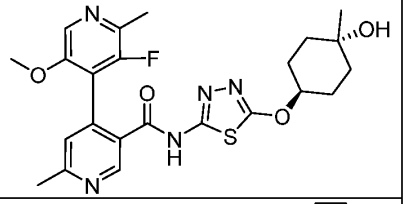
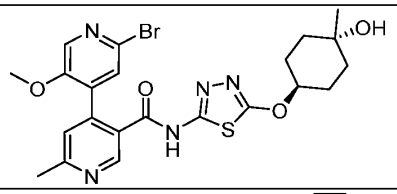
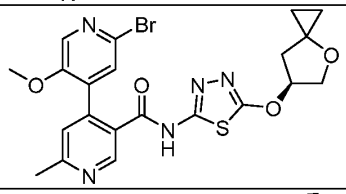
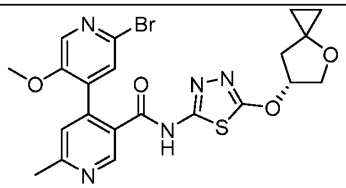
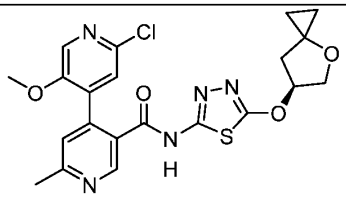
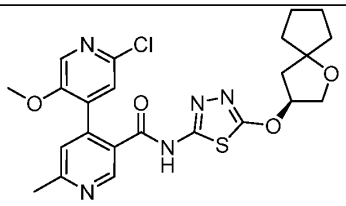
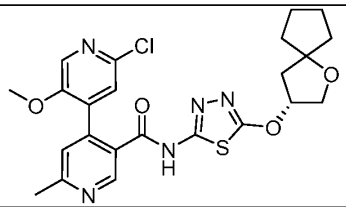
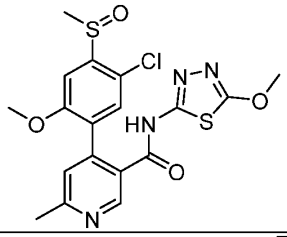
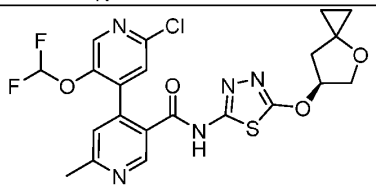
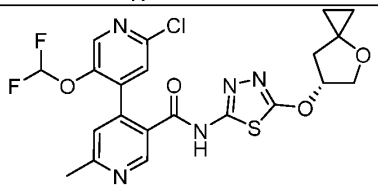
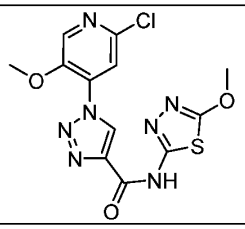
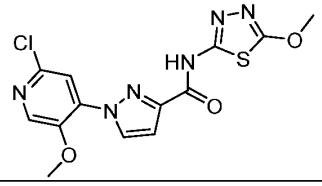
207		208	
209		210	
211		212	
213		214	
215		216	
217		218	
219		220	

Cpd #	Structure	Cpd #	Structure
221		222	
223		224	
225		226	
227		228	
229		230	
231		232	
233		234	

Cpd #	Structure	Cpd #	Structure
235			

Additional representative compounds of Formula (I) are listed in Table 3 below:

Table 3.

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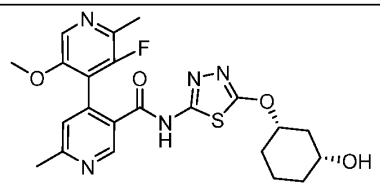
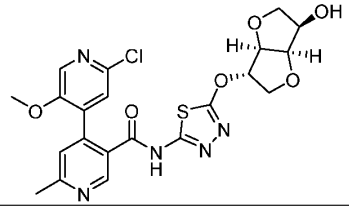
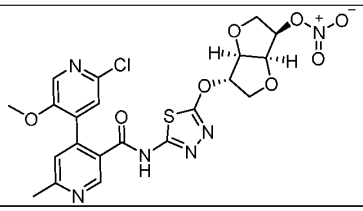
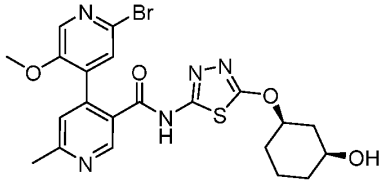
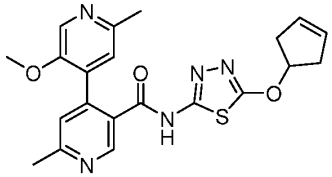
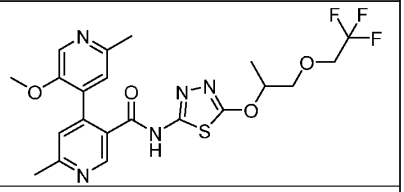
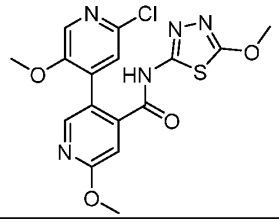
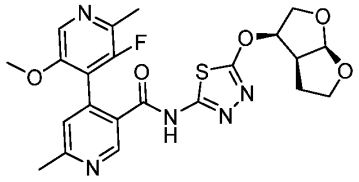
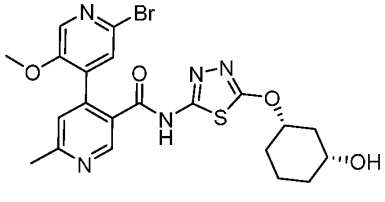
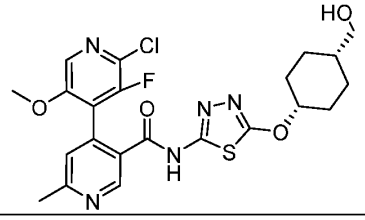
236		237	
238		239	
240		241	
242		243	
244		245	

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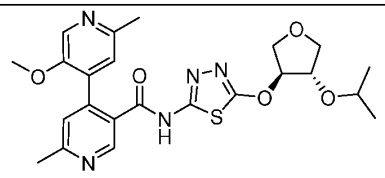
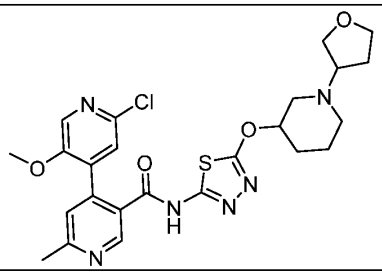
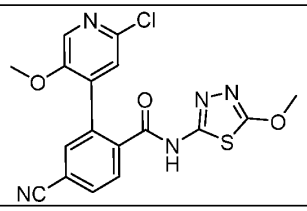
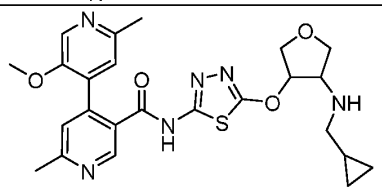
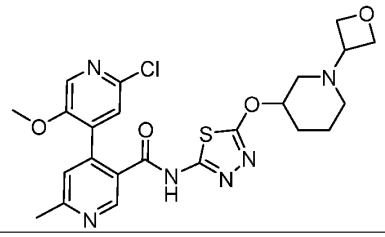
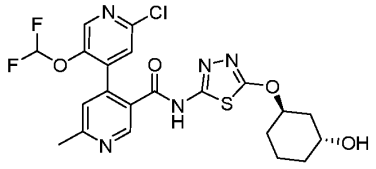
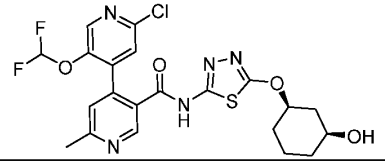
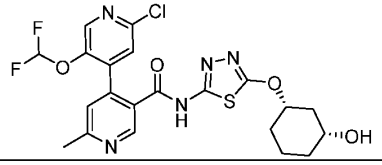
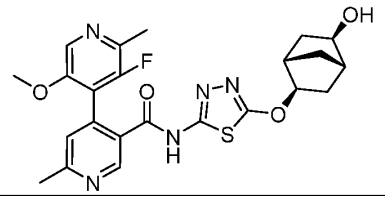
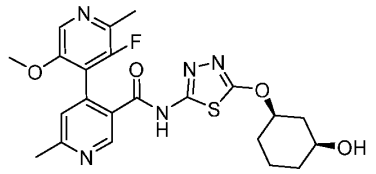
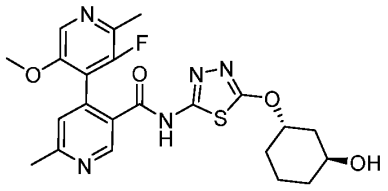
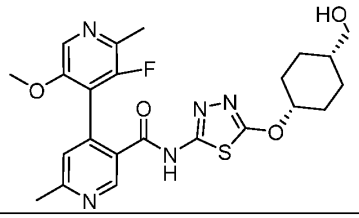
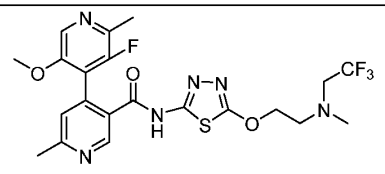
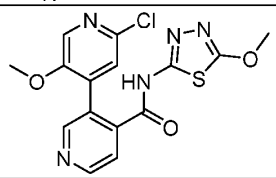
246		247	
248		249	
250		251	
252		253	
254		255	
256		257	
258		259	

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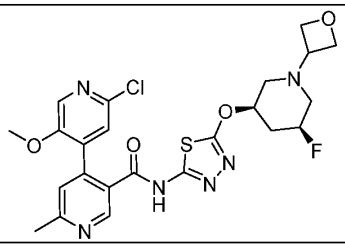
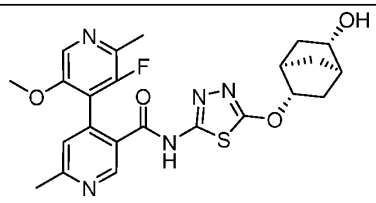
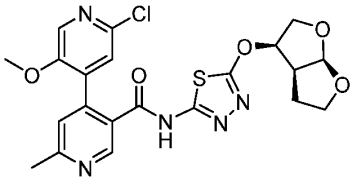
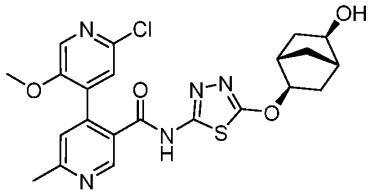
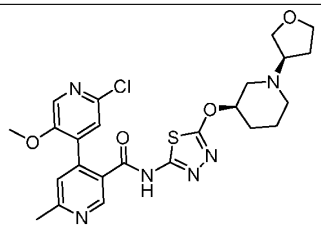
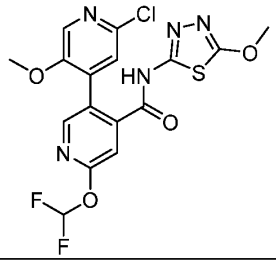
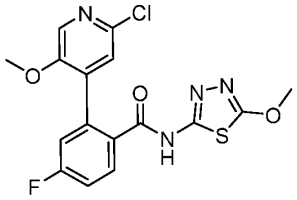
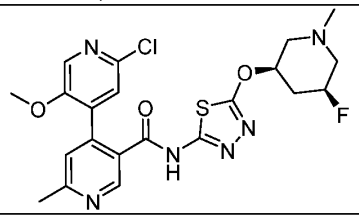
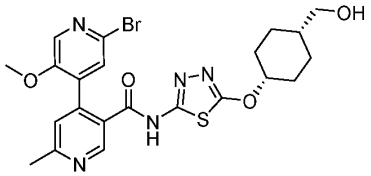
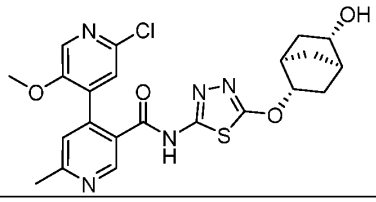
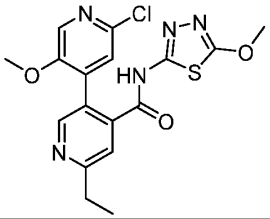
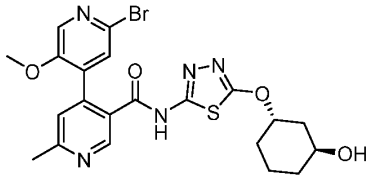
260		261	
262		263	
264		265	
266		267	
268		269	
270		271	

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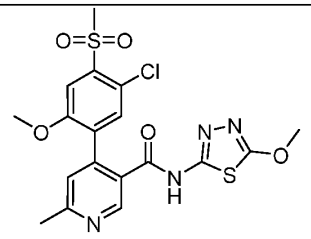
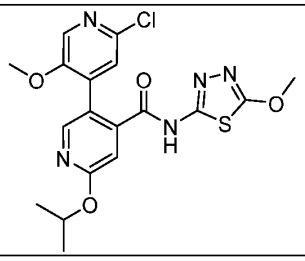
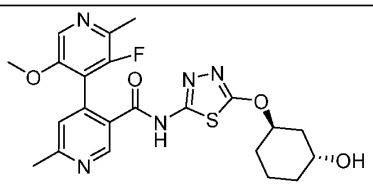
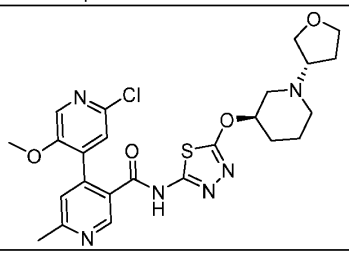
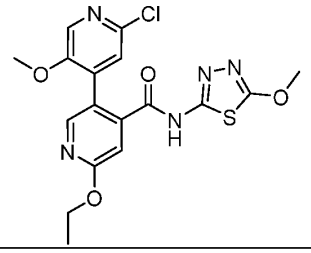
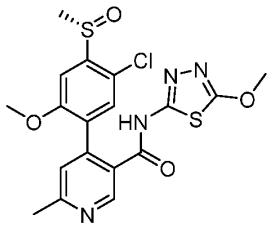
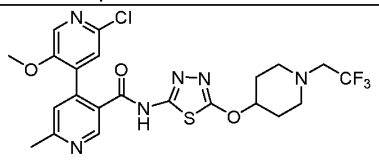
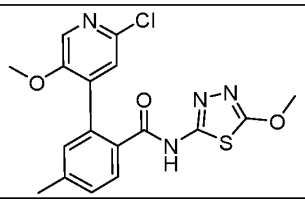
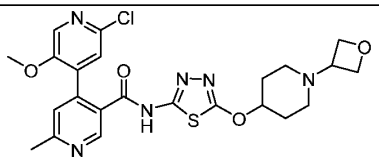
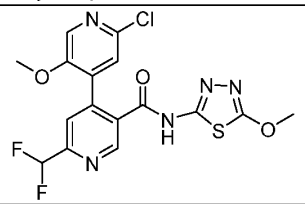
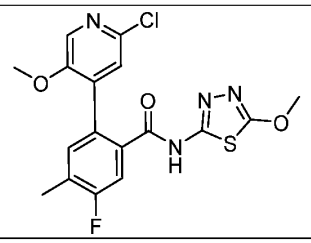
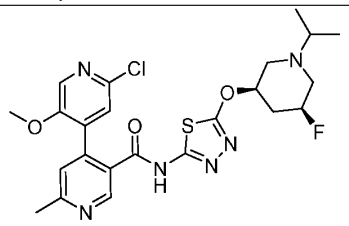
272		273	
274		275	
276		277	
278		279	
280		281	
282		283	

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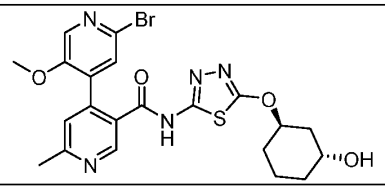
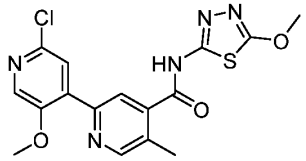
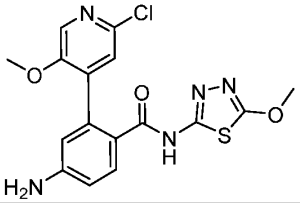
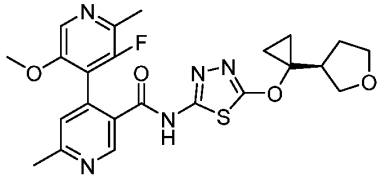
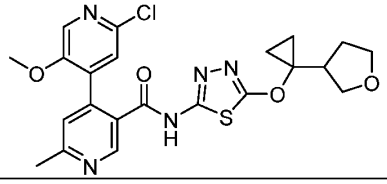
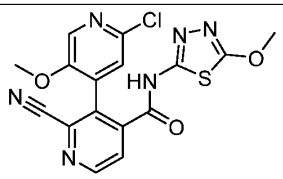
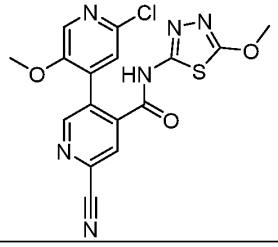
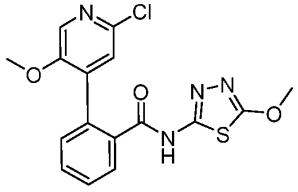
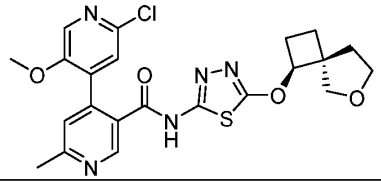
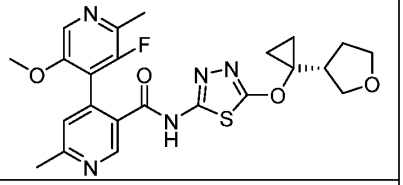
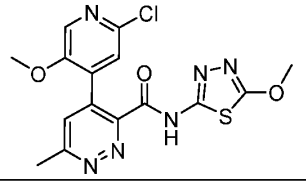
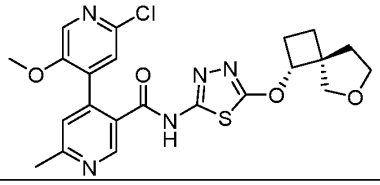
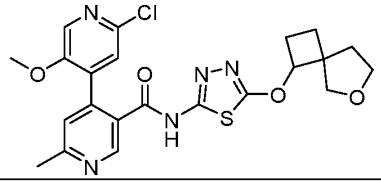
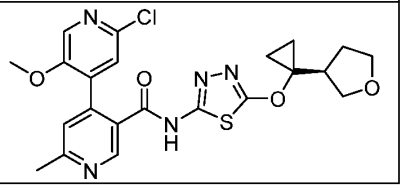
284		285	
286		287	
288		289	
290		291	
292		293	
294		295	
296		297	

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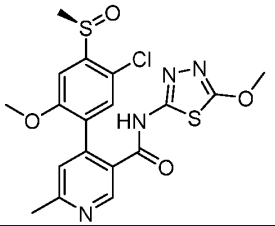
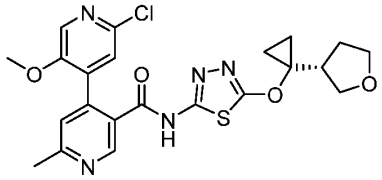
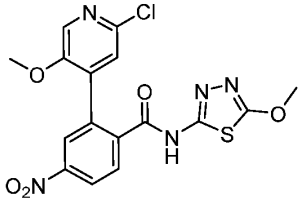
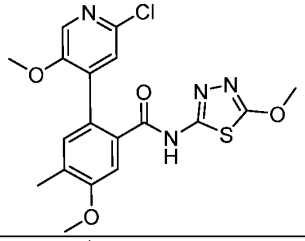
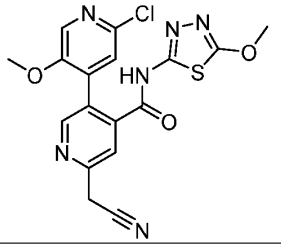
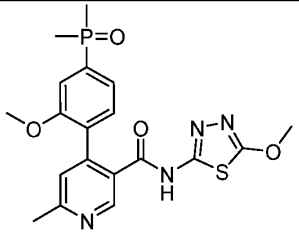
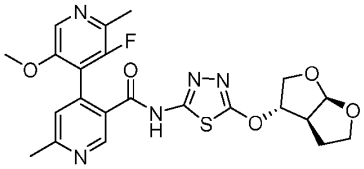
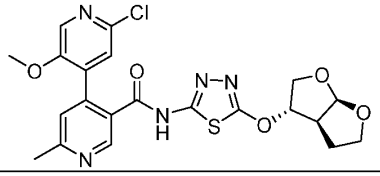
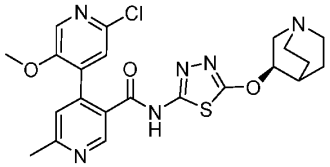
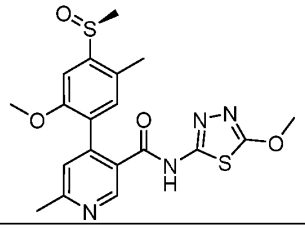
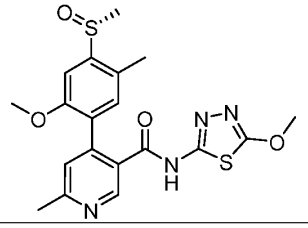
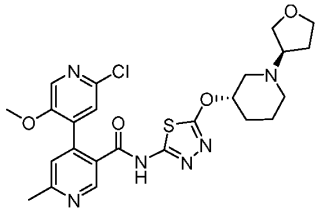
298		299	
300		301	
302		303	
304		305	
306		307	
308		309	

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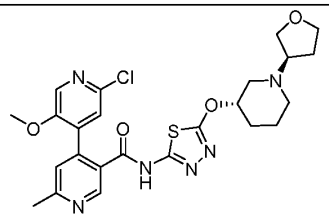
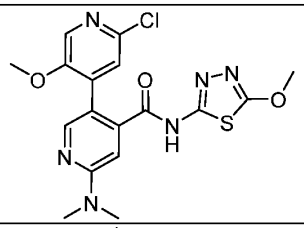
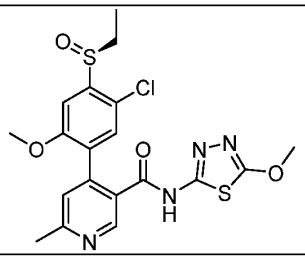
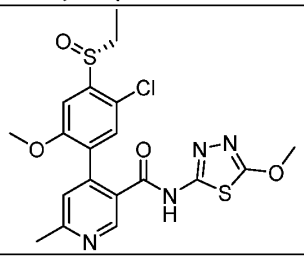
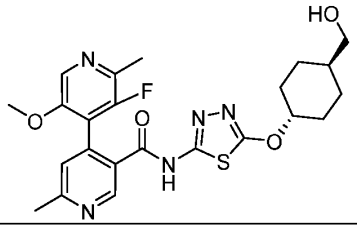
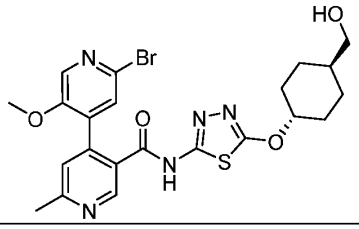
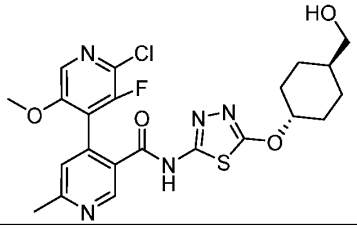
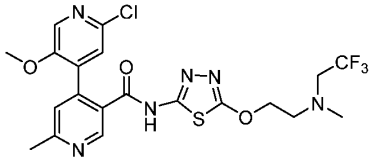
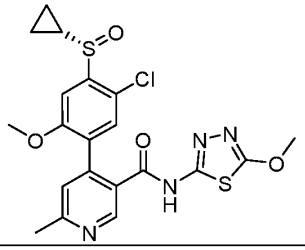
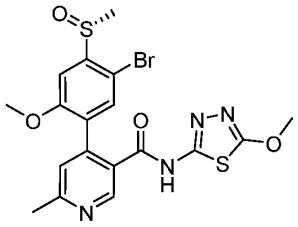
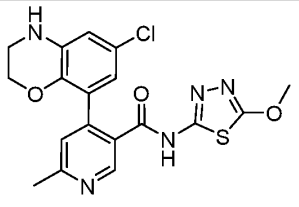
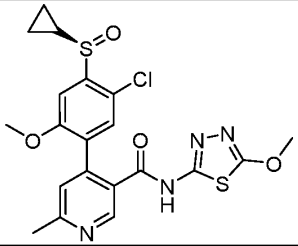
310		311	
312		313	
314		315	
316		317	
318		319	
320		321	

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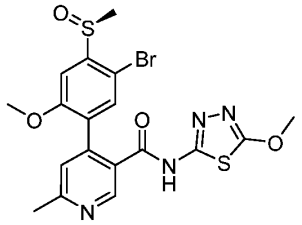
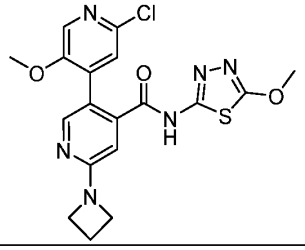
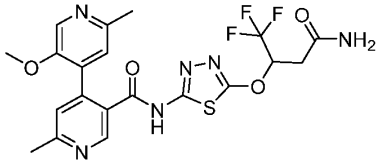
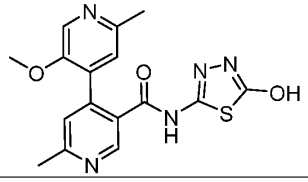
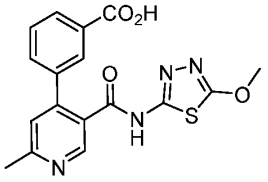
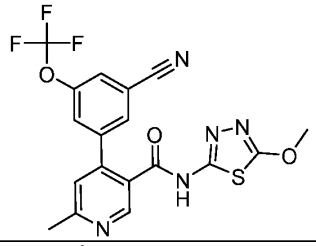
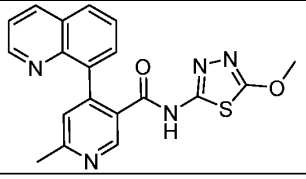
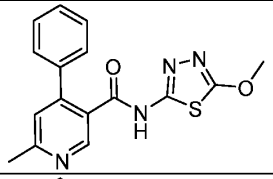
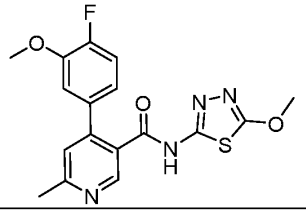
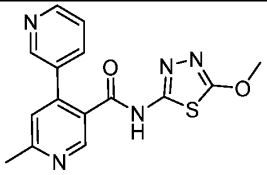
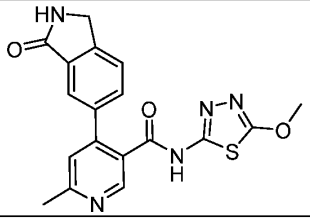
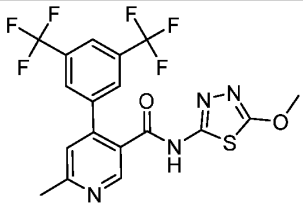
322		323	
324		325	
326		327	
328		329	
330		331	
332		333	

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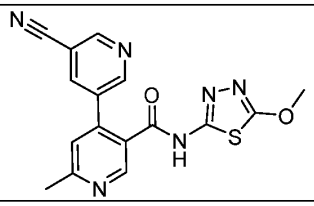
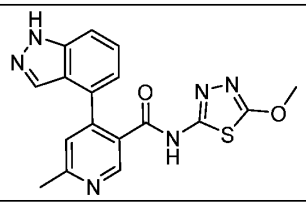
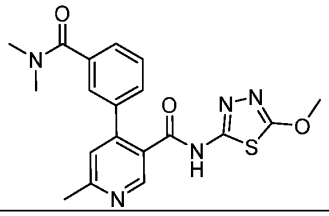
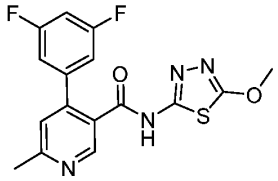
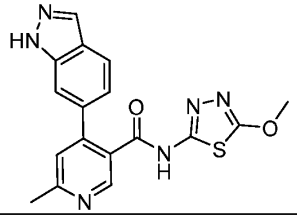
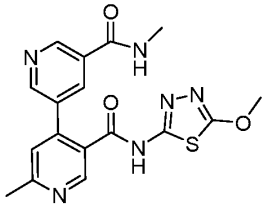
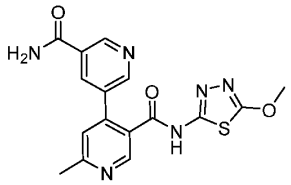
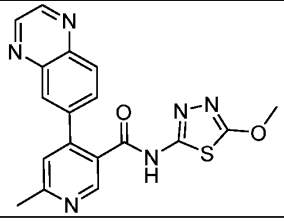
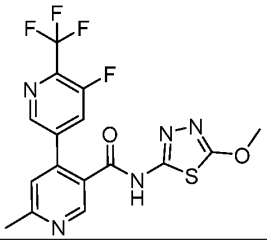
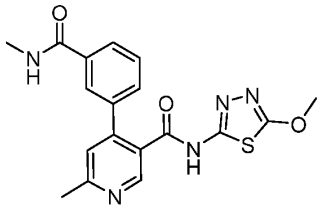
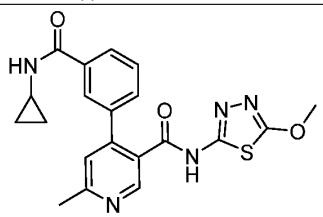
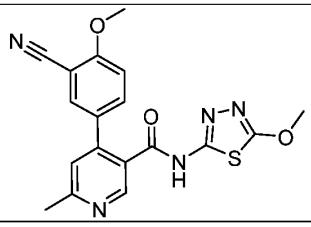
334		335	
336		337	
338		339	
340		341	
342		343	
344		345	

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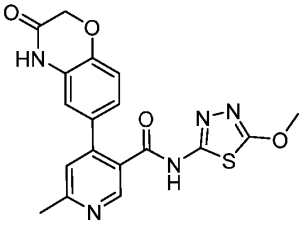
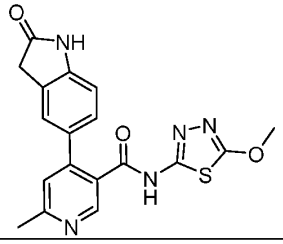
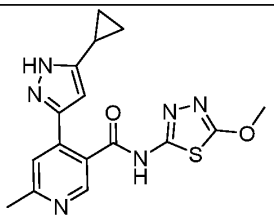
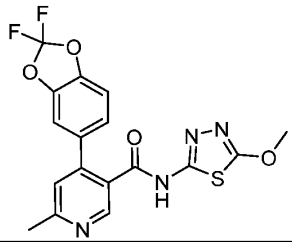
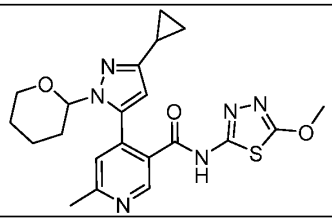
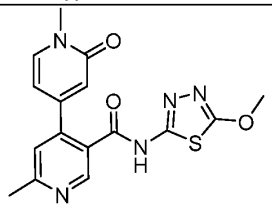
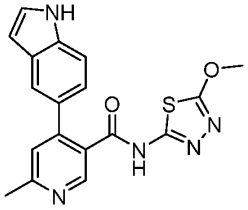
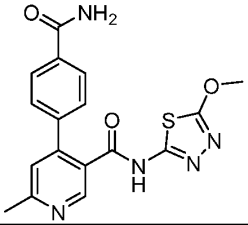
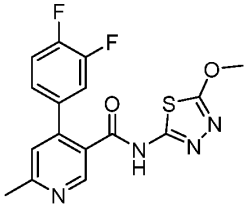
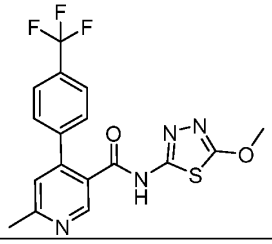
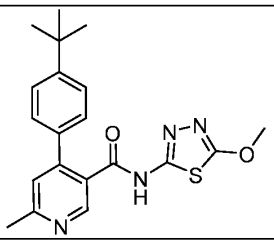
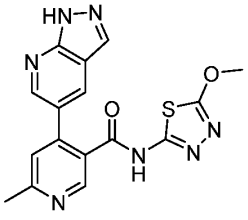
346		347	
348		349	
350		351	
352		353	
354		355	
356		357	

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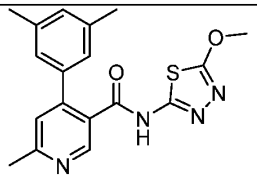
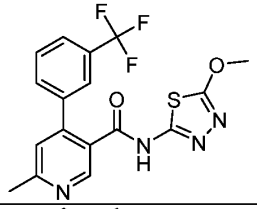
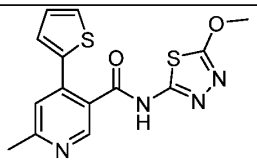
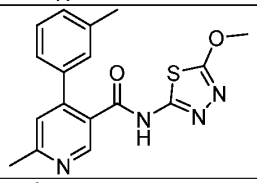
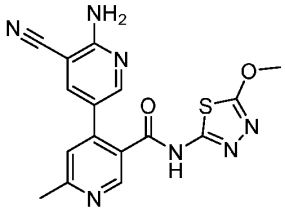
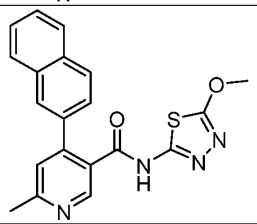
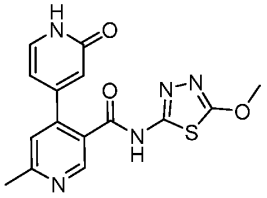
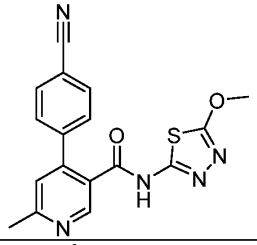
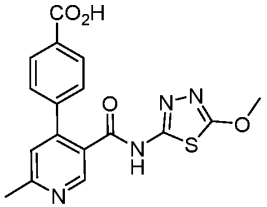
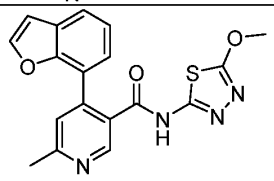
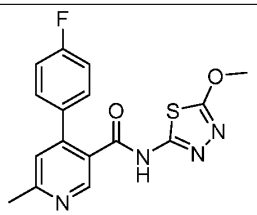
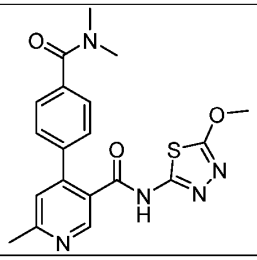
358		359	
360		361	
362		363	
364		365	
366		367	
368		369	

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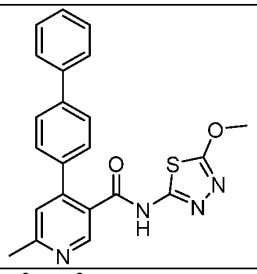
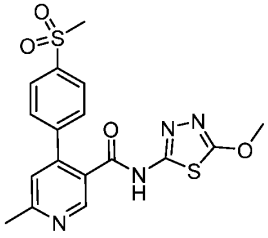
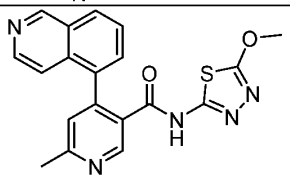
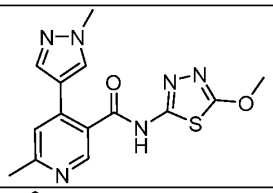
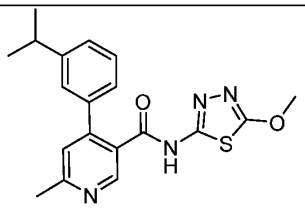
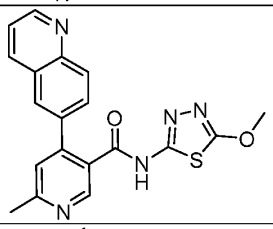
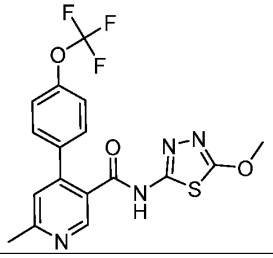
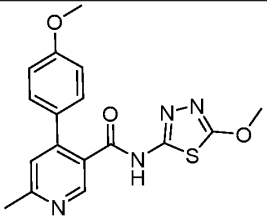
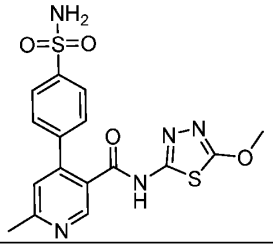
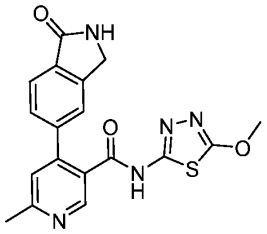
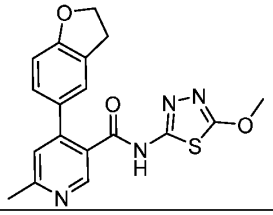
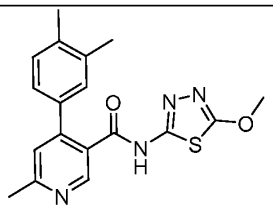
370		371	
372		373	
374		375	
376		377	
378		379	
380		381	

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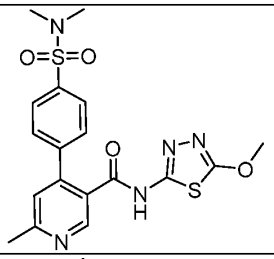
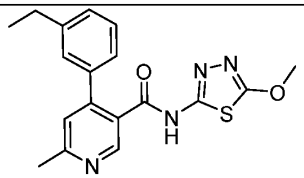
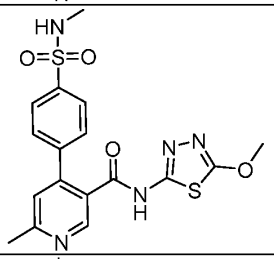
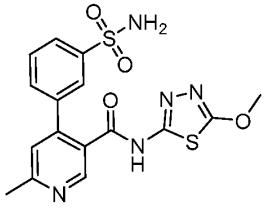
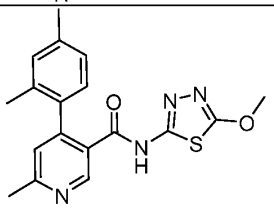
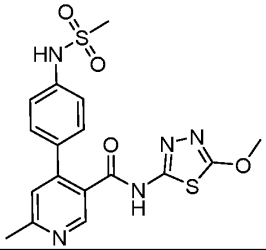
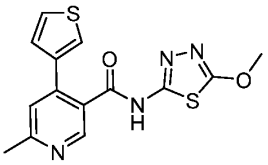
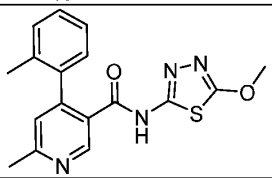
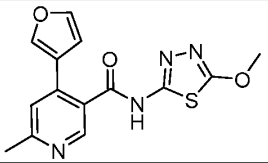
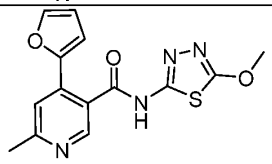
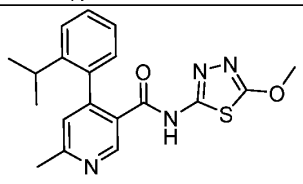
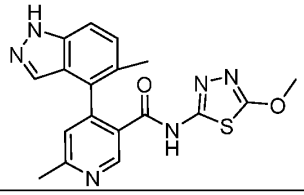
382		383	
384		385	
386		387	
388		389	
390		391	
392		393	

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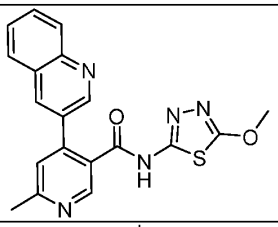
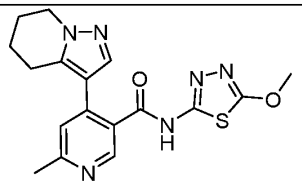
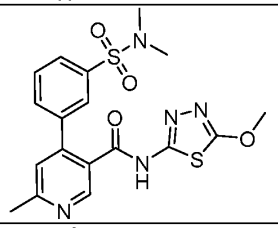
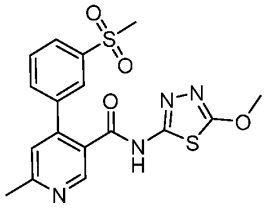
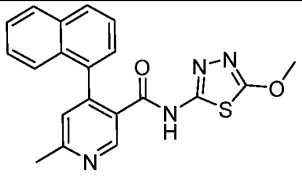
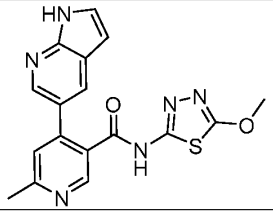
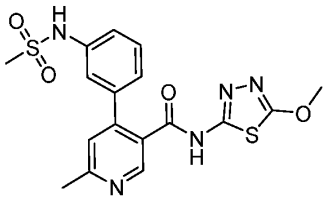
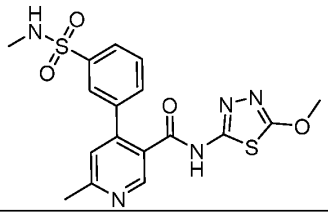
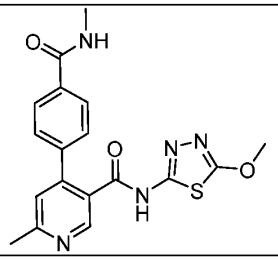
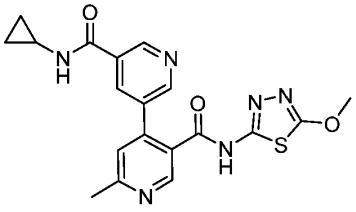
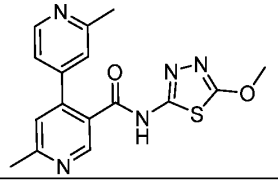
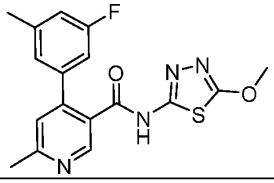
394		395	
396		397	
398		399	
400		401	
402		403	
404		405	

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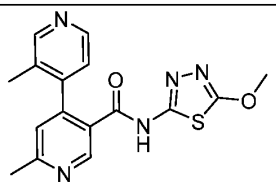
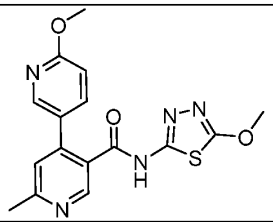
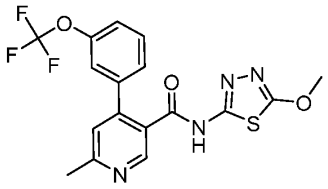
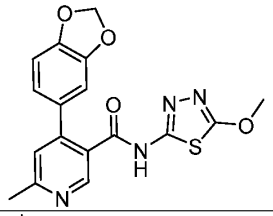
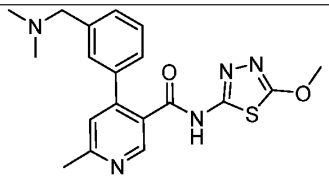
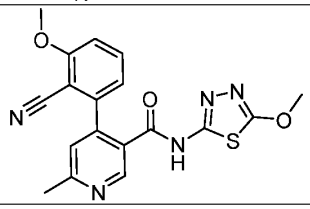
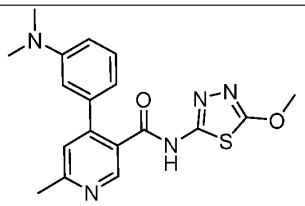
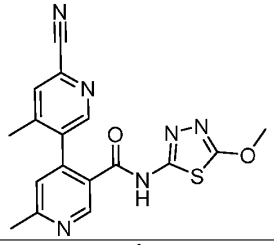
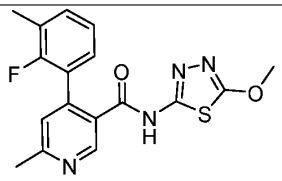
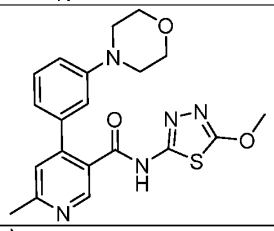
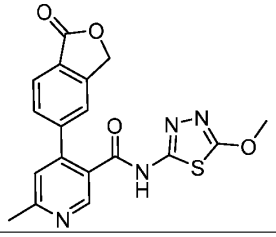
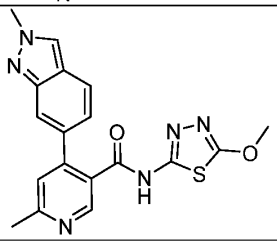
406		407	
408		409	
410		411	
412		413	
414		415	
416		417	

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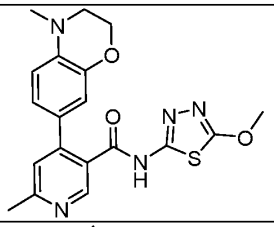
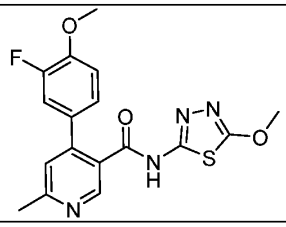
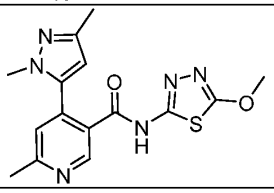
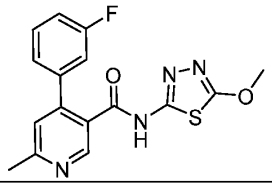
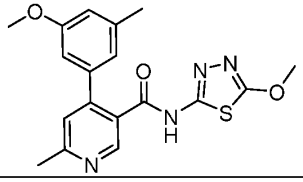
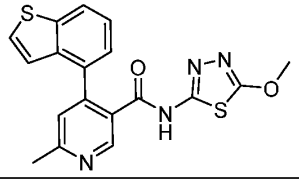
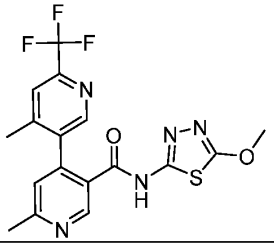
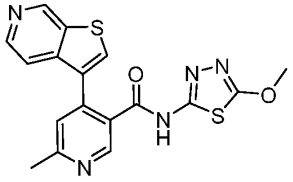
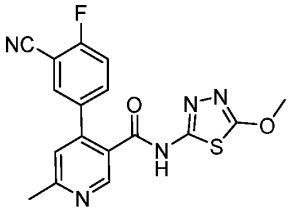
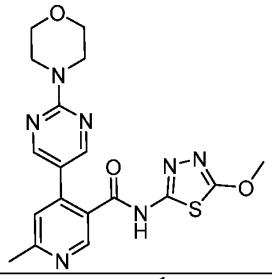
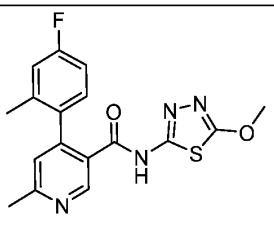
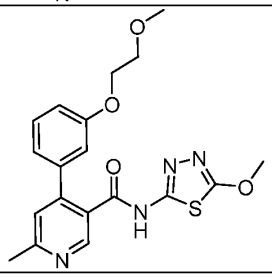
418		419	
420		421	
422		423	
424		425	
426		427	
428		429	

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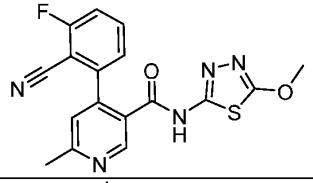
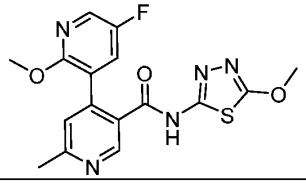
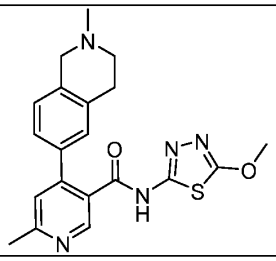
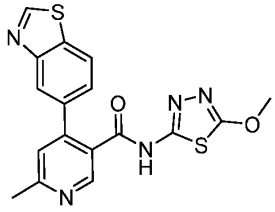
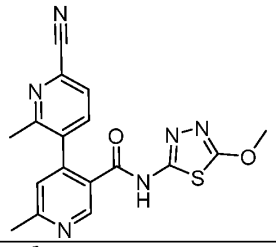
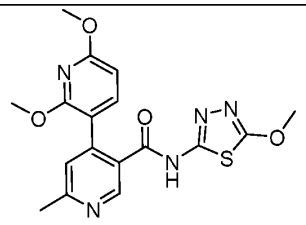
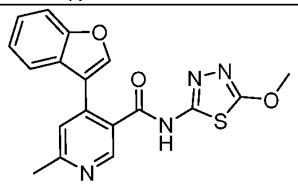
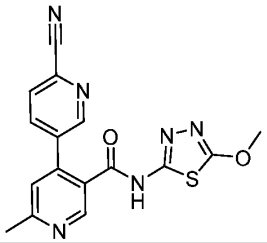
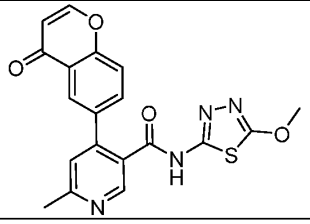
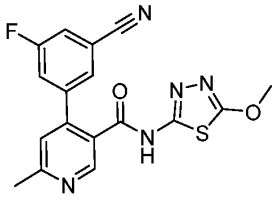
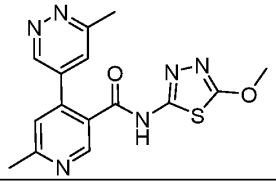
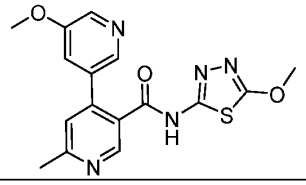
430		431	
432		433	
434		435	
436		437	
438		439	
440		441	

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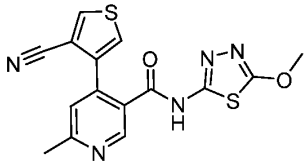
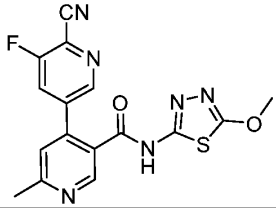
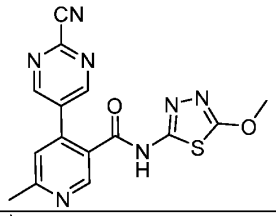
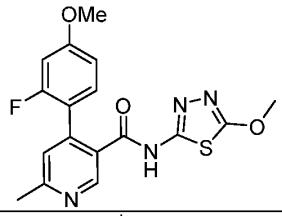
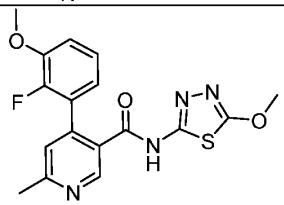
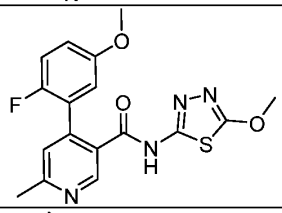
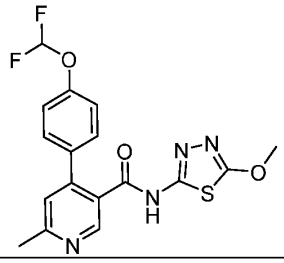
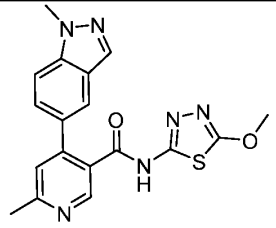
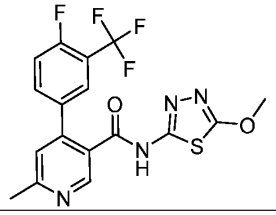
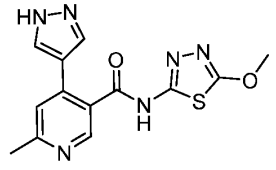
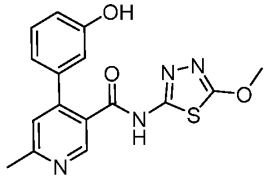
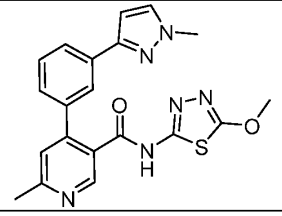
442		443	
444		445	
446		447	
448		449	
450		451	
452		453	

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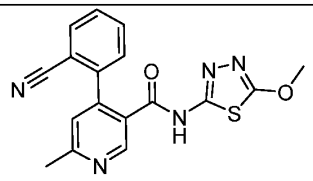
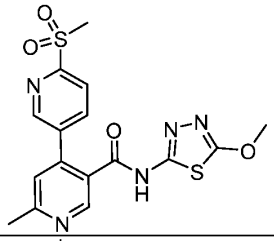
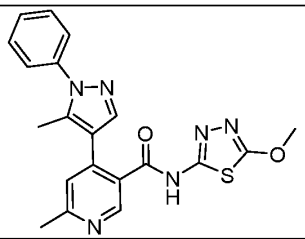
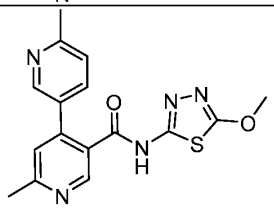
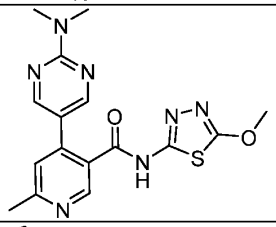
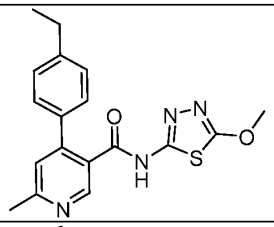
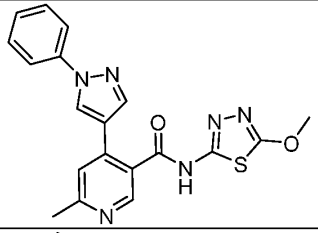
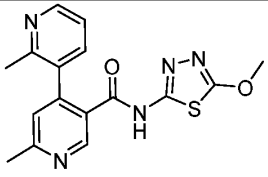
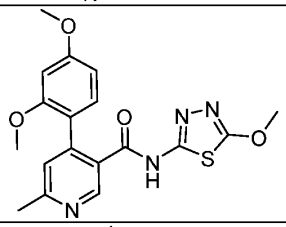
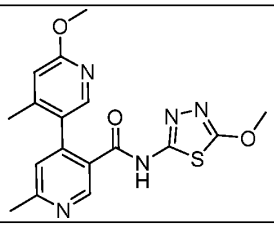
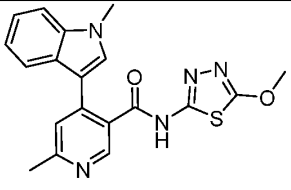
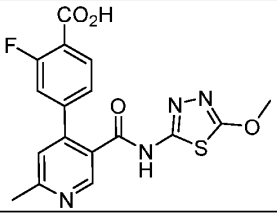
454		455	
456		457	
458		459	
460		461	
462		463	
464		465	

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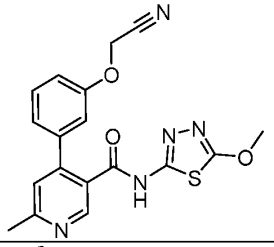
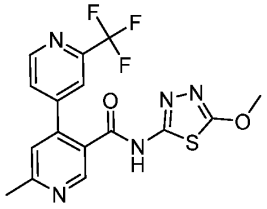
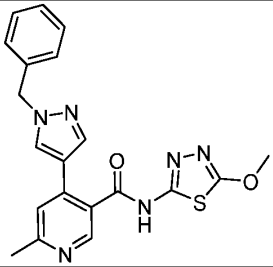
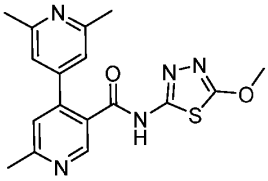
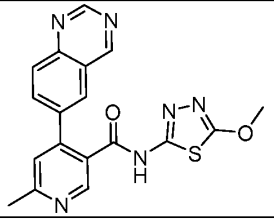
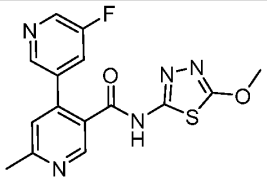
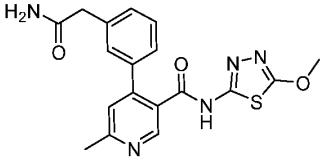
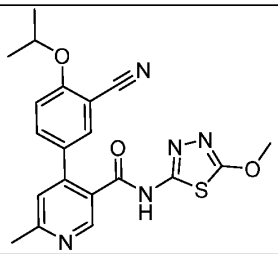
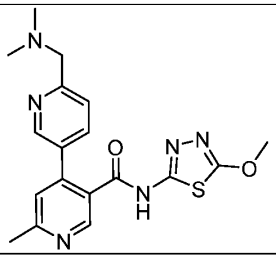
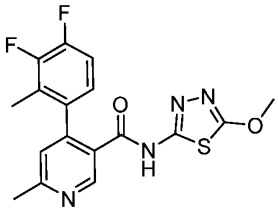
466		467	
468		469	
470		471	
472		473	
474		475	

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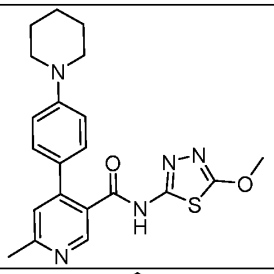
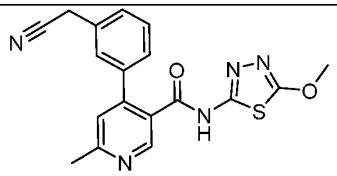
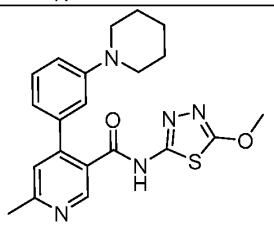
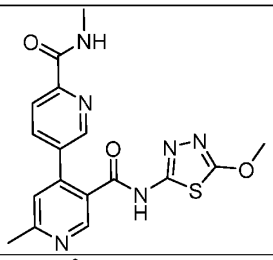
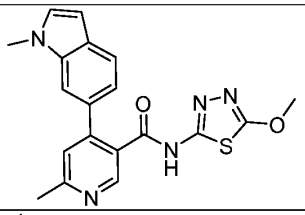
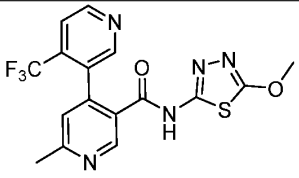
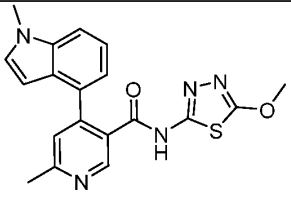
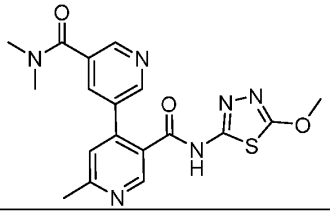
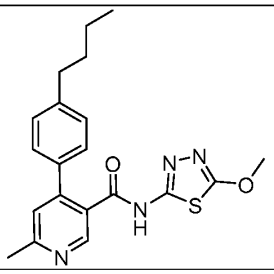
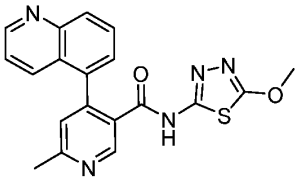
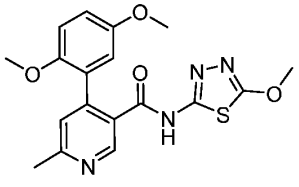
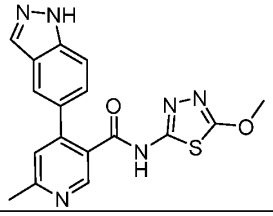
476		477	
478		479	
480		481	
482		483	
484		485	
486		487	

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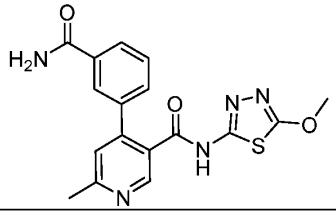
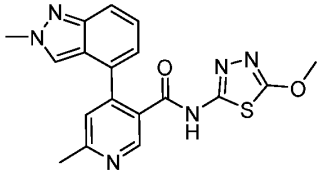
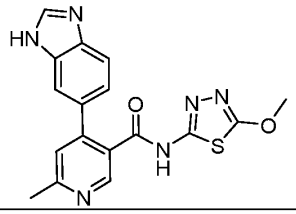
488		489	
490			

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 1, Table 2 or the Examples.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 1, Table 2, Table 3, or the Examples.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 1, Table 2, or Table 3.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 1 or Table 2.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 1.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 2.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound from Table 3.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound selected from examples 86, 87, 89, 90, 96, 97, 106, 108, 111, and 113.

In some embodiments, the compounds or pharmaceutically acceptable salts thereof is a compound selected from examples 79 to 85, 88, 91 to 93, 100 to 105, 109, 112, 114 to 119, 122, 124 to 143, and 145 to 233.

The compounds disclosed herein can be prepared as described in the examples section, below. For those compounds without detailed synthetic write-ups, it is understood that these compounds can be prepared following the general procedures described herein.

Assay

The ability of compounds of the disclosure to inhibit Polθ can be measured as described in the biological assay below.

Pharmaceutical Composition

The compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof provided herein may be in the form of compositions suitable for administration to a subject. In general, such compositions are pharmaceutical compositions comprising a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients. In certain embodiments, the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is present in a therapeutically effective amount. The pharmaceutical compositions may be used in all the methods disclosed herein; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic methods and uses described herein.

The pharmaceutical compositions can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. Furthermore, the pharmaceutical compositions may be used in combination with other therapeutically active agents or compounds as described herein in order to treat the diseases, disorders and conditions contemplated by the present disclosure.

The pharmaceutical compositions containing the active ingredient (e.g., a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs.

Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets, capsules, and the like. These excipients can include diluents, granulating agents, disintegrating agents, binding agents, and lubricating agents.

The tablets, capsules and the like suitable for oral administration may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can include suspending agents, dispersing agents and wetting agents. The aqueous suspensions may also contain one or more preservatives.

Oily suspensions may be formulated by suspending the active ingredient in an oil. Suitable oils are known in the art. The oily suspensions may contain additional agents such as a thickening agent or a sweetening agent.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

The pharmaceutical compositions may also be in the form of oil-in-water emulsions. Suitable emulsifying agents are known in the art.

The pharmaceutical compositions typically comprise a therapeutically effective amount of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients include, but are not limited to, antioxidants, preservatives, emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. Those skilled in the art will readily recognize a variety of exipients that can be used in the pharmaceutical compositions and dosage forms contemplated herein.

Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of

the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. The suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, which are known in the art.

A compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof may also be administered in the form of suppositories for rectal administration or sprays for nasal or inhalation use. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are known in the art.

All the compounds and pharmaceutical compositions provided herein can be used in all the methods provided herein. For eample, the compounds and pharmaceutical compositions provided herein can be used in all the methods for treatment and/or prevention of all diseases or disorders provided herein. Thus, the compounds and pharmaceutical compositions provided herein are for use as a medicament.

Routes of Administration

Compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof and compositions containing the same may be administered in any appropriate manner. Suitable routes of administration include oral, parenteral (e.g., intramuscular, intravenous, subcutaneous (e.g., injection or implant), intraperitoneal, intracisternal, intraarticular, intraperitoneal, intracerebral (intraparenchymal) and intracerebroventricular), nasal, vaginal, sublingual, intraocular, rectal, topical (e.g., transdermal), buccal and inhalation. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to administer the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof over a defined period of time. Particular embodiments of the present invention contemplate oral administration.

Combination Therapy

The present invention contemplates the use of compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof in combination with one or more active therapeutic agents (e.g., chemotherapeutic agents) or other prophylactic or therapeutic modalities (e.g., radiation). In such combination therapy, the various active agents frequently have different, complementary mechanisms of action. Such combination therapy may be especially advantageous by allowing a dose reduction of one or more of the agents, thereby reducing or eliminating the adverse effects associated with one or more of the agents. Furthermore, such combination therapy may have a synergistic therapeutic or prophylactic effect on the underlying disease, disorder, or condition.

As used herein, "combination" is meant to include therapies that can be administered separately, for example, formulated separately for separate administration (e.g., as may be provided in a kit), and therapies that can be administered together in a single formulation (i.e., a "co-formulation").

In certain embodiments, the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof are administered or applied sequentially, e.g., where one agent is administered prior to one or more other agents. In other embodiments, the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof are administered simultaneously, e.g., where two or more agents are administered at or about the same time; the two or more agents may be present in two or more separate formulations or combined into a single formulation (i.e., a co-formulation). Regardless of whether the two or more agents are administered sequentially or simultaneously, they are considered to be administered in combination for purposes of the present disclosure.

The compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof may be used in combination with at least one other (active) agent in any manner appropriate under the circumstances. In one embodiment, treatment with the at least one active agent and at least one compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is maintained over a period of time. In another embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), while treatment with the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is maintained at a constant dosing regimen. In a further embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), while treatment with a compound

of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is reduced (e.g., lower dose, less frequent dosing or shorter treatment regimen). In yet another embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), and treatment with the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is increased (e.g., higher dose, more frequent dosing or longer treatment regimen). In yet another embodiment, treatment with the at least one active agent is maintained and treatment with the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is reduced or discontinued (e.g., lower dose, less frequent dosing or shorter treatment regimen). In yet another embodiment, treatment with the at least one active agent and treatment with the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof are reduced or discontinued (e.g., lower dose, less frequent dosing or shorter treatment regimen).

The present disclosure provides methods for treating cancer with a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof and at least one additional therapeutic or diagnostic agent.

In some embodiments, the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is administered in combination with at least one additional therapeutic agent. In some embodiments, the additional therapeutic agent is a signal transduction inhibitor (STI) or chemotherapeutic agent.

In certain embodiments, the present disclosure provides methods for treating cancer comprising administration of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof described herein in combination with a signal transduction inhibitor (STI) to achieve additive or synergistic suppression of tumor growth. As used herein, the term “signal transduction inhibitor” refers to an agent that selectively inhibits one or more steps in a signaling pathway. Agents involved in immunomodulation can also be used in combination with one or more compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof described herein for the suppression of tumor growth in cancer patients.

In certain embodiments, the present disclosure provides methods for treating cancer comprising administration of a compound of Formula (I) or a subembodiment or a

pharmaceutically acceptable salt thereof described herein in combination with a chemotherapeutic agents.

Chemotherapeutic agents also include anti-hormonal agents that act to regulate or inhibit hormonal action on tumors such as anti-estrogens. In certain embodiments, combination therapy comprises administration of a hormone or related hormonal agent.

The present disclosure also contemplates the use of the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof described herein in combination with immune checkpoint inhibitors. The tremendous number of genetic and epigenetic alterations that are characteristic of all cancers provides a diverse set of antigens that the immune system can use to distinguish tumor cells from their normal counterparts. In the case of T cells, the ultimate amplitude (e.g., levels of cytokine production or proliferation) and quality (e.g., the type of immune response generated, such as the pattern of cytokine production) of the response, which is initiated through antigen recognition by the T-cell receptor (TCR), is regulated by a balance between co-stimulatory and inhibitory signals (immune checkpoints). Under normal physiological conditions, immune checkpoints are crucial for the prevention of autoimmunity (i.e., the maintenance of self-tolerance) and also for the protection of tissues from damage when the immune system is responding to pathogenic infection. The expression of immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism. Examples of immune checkpoint inhibitors include but are not limited to CTLA-4, PD-1, PD-L1, BTLA, TIM3, LAG3, OX40, 41BB, VISTA, CD96, TGFβ, CD73, CD39, A2AR, A2BR, IDO1, TDO2, Arginase, B7-H3, B7-H4. Cell-based modulators of anti-cancer immunity are also contemplated. Examples of such modulators include but are not limited to chimeric antigen receptor T-cells, tumor infiltrating T-cells and dendritic-cells.

The present disclosure encompasses pharmaceutically acceptable salts, acids or derivatives of any of the above.

Dosing

The compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof provided herein may be administered to a subject in an amount that is dependent upon, for example, the goal of administration (e.g., the degree of resolution desired); the age, weight, sex, and health and physical condition of the subject to which the formulation is

being administered; the route of administration; and the nature of the disease, disorder, condition or symptom thereof. The dosing regimen may also take into consideration the existence, nature, and extent of any adverse effects associated with the agent(s) being administered. Effective dosage amounts and dosage regimens can readily be determined from, for example, safety and dose-escalation trials, in vivo studies (e.g., animal models), and other methods known to the skilled artisan.

In general, dosing parameters dictate that the dosage amount be less than an amount that could be irreversibly toxic to the subject (the maximum tolerated dose (MTD)) and not less than an amount required to produce a measurable effect on the subject. Such amounts are determined by, for example, the pharmacokinetic and pharmacodynamic parameters associated with ADME, taking into consideration the route of administration and other factors.

An effective dose (ED) is the dose or amount of an agent that produces a therapeutic response or desired effect in some fraction of the subjects taking it. The "median effective dose" or ED_{50} of an agent is the dose or amount of an agent that produces a therapeutic response or desired effect in 50% of the population to which it is administered. Although the ED_{50} is commonly used as a measure of reasonable expectance of an agent's effect, it is not necessarily the dose that a clinician might deem appropriate taking into consideration all relevant factors. Thus, in some situations the effective amount is more than the calculated ED_{50}, in other situations the effective amount is less than the calculated ED_{50}, and in still other situations the effective amount is the same as the calculated ED_{50}.

In addition, an effective dose of a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof, as provided herein, may be an amount that, when administered in one or more doses to a subject, produces a desired result relative to a healthy subject. For example, for a subject experiencing a particular disorder, an effective dose may be one that improves a diagnostic parameter, measure, marker and the like of that disorder by at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more than 90%, where 100% is defined as the diagnostic parameter, measure, marker and the like exhibited by a normal subject.

In certain embodiments, the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof disclosed herein may be administered (e.g., orally) at

dosage levels of about 0.01 mg/kg to about 50 mg/kg, or about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

For administration of an oral agent, the compositions can be provided in the form of tablets, capsules and the like containing from 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 3.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient.

In certain embodiments, the dosage of the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof is contained in a "unit dosage form". The phrase "unit dosage form" refers to physically discrete units, each unit containing a predetermined amount of the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof, either alone or in combination with one or more additional agents, sufficient to produce the desired effect. It will be appreciated that the parameters of a unit dosage form will depend on the particular agent and the effect to be achieved.

Kits

The present invention also contemplates kits comprising a compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof. The kits are generally in the form of a physical structure housing various components, as described below, and may be utilized, for example, in practicing the methods described above.

A kit can include one or more of the compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof disclosed herein (provided in, e.g., a sterile container), which may be in the form of a pharmaceutical composition suitable for administration to a subject. The compound of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof can be provided in a form that is ready for use (e.g., a tablet or capsule) or in a form requiring, for example, reconstitution or dilution (e.g., a powder) prior to administration. When the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof are in a form that needs to be reconstituted or diluted by a user, the kit may also include diluents (e.g., sterile water), buffers, pharmaceutically acceptable excipients, and the like, packaged with or separately from the compounds of Formula (I) or a subembodiment or a pharmaceutically acceptable salt thereof. When combination therapy is contemplated, the kit may contain the several agents separately or they may already be combined in the kit. Each component of the kit may be enclosed

within an individual container, and all of the various containers may be within a single package. A kit of the present invention may be designed for conditions necessary to properly maintain the components housed therein (e.g., refrigeration or freezing).

A kit may contain a label or packaging insert including identifying information for the components therein and instructions for their use (e.g., dosing parameters, clinical pharmacology of the active ingredient(s), including mechanism of action, pharmacokinetics and pharmacodynamics, adverse effects, contraindications, etc.). Labels or inserts can include manufacturer information such as lot numbers and expiration dates. The label or packaging insert may be, e.g., integrated into the physical structure housing the components, contained separately within the physical structure, or affixed to a component of the kit (e.g., an ampule, tube or vial).

Labels or inserts can additionally include, or be incorporated into, a computer readable medium, such as a disk (e.g., hard disk, card, memory disk), optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/optical storage media, FLASH media or memory-type cards. In some embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided.

Examples

The following examples and references (intermediates) are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention, nor are they intended to represent that the experiments below were performed or that they are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate data and the like of a nature described therein. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.), but some experimental errors and deviations should be accounted for.

Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius (°C), and pressure is at or near atmospheric. Standard abbreviations are used, including the following: THF=

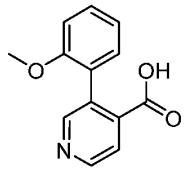
tetrahydrofuran; DIEA = diisopropylethylamine; EtOAc = ethyl acetate; NMP = N-methylpyridine, TFA = trifluoroacetic acid; DCM = dichloromethane; Cs_2CO_3= cesium carbonate; XPhos Pd G3 = 2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)(2-(2′-amino-1,1′-biphenyl))palladium-(II) methanesulfonate; LiCl = lithium chloride; $POCl_3$ = phosphoryl chloride; PE = petroleum ether; DMSO = dimethylsulfoxide; HCl = hydrochloric acid; Na_2SO_4 = sodium sulfate; DMF = dimethylformamide; NaOH = sodium hydroxide; K_2CO_3 = potassium carbonate; MeCN= acetonitrile; BOC= tert-butoxycarbonyl; MTBE = methyl tert-butyl ether; MeOH = methanol; $NaHCO_3$ = sodium bicarbonate; $NaBH_3CN$ = sodium cyanoborohydride; EtOH = ethanol; PCl_5= phosphorus pentachloride; NH_4OAc = ammonium acetate; Et_2O = ether; HOAc = acetic acid; Ac_2O = acetic anhydride; *i*-PrOH = isopropanol; NCS = N-chlorosuccinimide; K_3PO_4 = potassium phosphate; Pd(dtbpf)Cl_2 =1,1′-Bis(di-tert-butylphosphino)ferrocene)dichloro-palladium(II); $Zn(CN)_2$ = Zinc cyanide; $Pd(PPh_3)_4$ =tetrakis(triphenylphosphine)palladium(0); Et_3N = triethylamine; CuCN = copper cyanide; *t*-BuONO = tert-butyl nitrite; HATU = 1-(bis(dimethylamino)methylene)-1H-1,2,3-triazolo(4,5-b)pyridinium 3-oxid hexafluorophosphate; DBU= 1,8-diazabicyclo(5.4.0)undec-7-ene; $LiAlH_4$ = lithium aluminium hydride; NH_3 = ammonia; H_2SO_4 = sulfuric acid; H_2O_2 = hydrogen peroxide; EDCI = N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride; HOBT = 1-hydroxybenzotriazole hydrate; DHP = dihydropyran; TsOH = p-Toluenesulfonic acid; FA = formic acid; TCFH = N,N,N,N'-tetramethylchloroformamidinium hexafluorophosphate; NMI = N-methylimidazole; Pd(dppf)Cl_2 = (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II); Pd(dppf)Cl_2-DCM = (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II), complex with dichloromethane.

When the absolute or relative stereochemistry of one or more examples is not determined, the text of the Example indicates the same. The reported charaterizations in these examples and the tables of compounds arbitrarily assign absolute stereochemistry. It is understood that routine work well within the skill of the ordinary artisan can confirm the absolute stereochemistry for each relevant example disclosed herein.

Synthetic Examples

Intermediate A

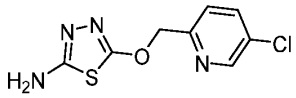
3-(2-methoxyphenyl) pyridine-4-carboxylic acid



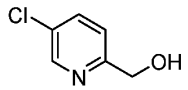
To a solution of 3-bromopyridine-4-carboxylic acid (2.0 g, 9.9 mmol) in dioxane (10 mL) and water (10 mL) was added 2-methoxyphenylboronic acid (2.3 g, 14.9 mmol), Na_2CO_3 (1.1 g, 9.9 mmol) and $Pd(PPh_3)_4$ (1.1 g, 0.99 mmol) at room temperature under nitrogen. The mixture was stirred at 100 °C overnight. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The aqueous layer was acidified to pH 6 with HCl (1 M). A solid formed and mixture was filtered to afford 3-(2-methoxyphenyl) pyridine-4-carboxylic acid as a white solid, which was used to next step without further purification.

Intermediate B

5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine

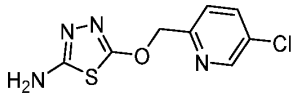


Step 1. Preparation of (5-chloropyridin-2-yl)methanol



To a solution of methyl 5-chloropicolinate (95 g, 554 mmol) in MeOH (950 mL) was added $NaBH_4$ (42.0 g, 1.11 mol) in portions at 0 °C. Then the mixture was stirred at rt for 2 h. The mixture was poured into H_2O. Mixture was cooled to 0 °C and 6 N HCl was added until pH of solution was 1 ~ 2. The temperature of the solution was 0 - 10 °C. Then the mixture was concentrated under reduce pressure to remove MeOH. 6 N NaOH was added until the pH of the solution was 8 ~ 10. The mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure to afford the title compound (158 g) as a yellow oil, which was used in the next step without further purification.

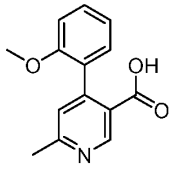
Step 2. Preparation of 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



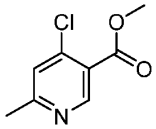
To a solution of NaH (65.7 g, 1.64 mol, 60.0% purity) in THF (1.20 L) was added a solution of (5-chloropyridin-2-yl)methanol (158 g, 1.10 mol) in THF (400 mL) at 5 °C dropwise. The mixture was stirred at 5 °C for 1 h. Then 2-amino-5-bromo-1,3,4-thiadiazole (237 g, 1.31 mol) was added in portions at 5 °C. The mixture was stirred at 5 °C for 4 h. The mixture was poured into H_2O and extracted with EtOAc (4x). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was diluted with MeOH and slurry was stirred at 25 °C for 0.5 h. The solids were collected and diluted with MeOH. The slurry was stirred at 80 °C for 2 h. The solids were collected to afford 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (57.6 g, 21% yield) as a grey solid.

Intermediate C

4-(2-methoxyphenyl)-6-methylnicotinic acid

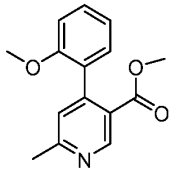


Step 1 methyl 4-chloro-6-methylnicotinate



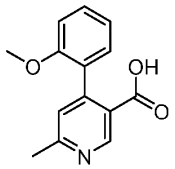
To a stirred solution of 4-chloro-6-methylnicotinic acid (5.0 g, 29.1 mmol) in dichloromethane (100 mL) was added methanol (10 mL) and (diazomethyl)trimethylsilane (29 mL, 58.3 mmol) dropwise at 0 °C. The resulting solution was stirred at room temperature for 16 hr. The organic solvent was removed under vacuum. The resulting residue was dissolved in dichloromethane (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 80.0 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 30 min to afford methyl 4-chloro-6-methylnicotinate (4.5 g, 81% yield) as a yellow oil. MS (ESI) calc'd for ($C_8H_8ClNO_2$) $(M+1)^+$, 186.0; found 186.0.

Step 2 methyl 4-(2-methoxyphenyl)-6-methylnicotinate



To a stirred solution of methyl 4-chloro-6-methylnicotinate (500.0 mg, 2.69 mmol) and 2-methoxyphenylboronic acid (819.0 mg, 5.39 mmol) in 1,4-Dioxane (1 mL) were sequentially added water (0.2 mL), (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (591.0 mg, 0.81 mmol) and potassium carbonate (1.1 g, 8.08 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The combined organic layers was diluted with ethyl acetate and the suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~35% ethyl acetate in petroleum ether within 30 min to afford methyl 4-(2-methoxyphenyl)-6-methylnicotinate (700.0 mg, 98%) as a yellow oil. MS (ESI) calc'd for ($C_{15}H_{15}NO3$) $(M+1)^+$, 258.1; found 258.0.

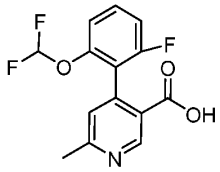
Step 3 4-(2-methoxyphenyl)-6-methylnicotinic acid



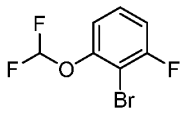
To a stirred solution of methyl 4-(2-methoxyphenyl)-6-methylnicotinate (400.0 mg, 1.56 mmol) in methanol (3 mL) were added water (3 mL) and sodium hydroxide (249.0 mg, 6.22 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 2 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid solution to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(2-methoxyphenyl)-6-methylnicotinic acid (342.0 mg, crude) as a yellow oil. MS (ESI) calc'd for ($C_{14}H_{13}NO_3$) $(M+1)^+$, 244.1; found 244.0.

Intermediate D

4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylnicotinic acid

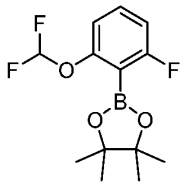


Step-1: 2-bromo-1-(difluoromethoxy)-3-fluorobenzene



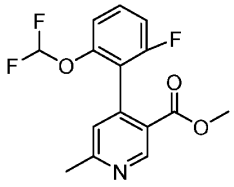
To a stirred solution of 2-bromo-3-fluorophenol (25.00 g, 130.89 mmol) in DMF (100.00 mL) and H_2O (10 mL) were added sodium 2-chloro-2,2-difluoroacetate (16.95 g, 130.89 mmol) in portions at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After cooled down to room temperature, the resulting mixture was diluted with water extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 0~10% ethyl acetate in petroleum ether to afford 2-bromo-1-(difluoromethoxy)-3-fluorobenzene (12.2 g, 34.8%) as a white oil. MS (ESI) calc'd for ($C_7H_4BrF_3O$) $(M+1)^+$, 240.9; found 241.0.

Step-2: 2-(2-(difluoromethoxy)-6-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a degassed solution of 2-bromo-1-(difluoromethoxy)-3-fluorobenzene (3.00 g, 12.44 mmol) in dioxane (15.00 mL) were added $Pd(dppf)Cl_2$ (0.91 g, 1.245 mmol), B_2Pin_2 (6.30 g, 24.89 mmol) and KOAc (2.44 g, 24.89 mmol). The resulting mixture was stirred at 90 °C overnight under nitrogen atmosphere. The solvent was removed under vacuum, the residue was purified by flash column chromatography with 0~10% ethyl acetate in petroleum ether to afford 2-(2-(difluoromethoxy)-6-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3 g, 46.01%) as a green solid.

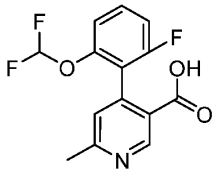
Step-3: methyl 4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylpyridine-3-carboxylate



To a degassed solution of 2-(2-(difluoromethoxy)-6-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.00 g, 10.41 mmol) in dioxane (15.00 mL) and water (3 mL) were added methyl 4-chloro-6-methylpyridine-3-carboxylate (1.93 g, 10.39 mmol), K_2CO_3 (4.32 g, 31.25

mmol) and $Pd(dppf)Cl_2$ (762.00 mg, 1.041 mmol). The resulting mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 0~50% ethyl acetate in petroleum ether to afford methyl 4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylpyridine-3-carboxylate (700 mg, 19%) as a yellow solid. MS (ESI) calc'd for ($C_{15}H_{12}F_3NO_3$) $(M+1)^+$, 312.1; found 312.0.

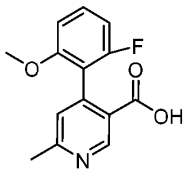
Step-4: 4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylpyridine-3-carboxylic acid



To a stirred solution of methyl 4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylpyridine-3-carboxylate (470.00 mg, 1.51 mmol) in THF (3.00 mL) and water (3 mL) was added $LiOH.H_2O$ (253.68 mg, 6.040 mmol). The resulting mixture was stirred at room temperature for 16 h. The organic solvent was removed under vacuum and then diluted with water. The solution was acidified by HCl (1 *N*) to pH ~6. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylpyridine-3-carboxylic acid (370 mg, 82.4%) as a white solid. MS (ESI) calc'd for ($C_{14}H_{10}F_3NO_3$) $(M+1)^+$, 298.1; found 298.0.

Intermediate E

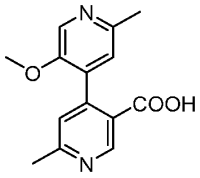
4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid



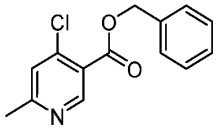
The title compound was prepared following the procedures for Intermediate C, Step 2 and 3 employing methyl 3-bromoisonicotinate and 2-fluoro-6-methoxyphenylboronic acid to afford 4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid as a white solid which was used without further purification.

Intermediate F

5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid

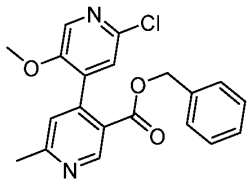


Step 1 benzyl 4-chloro-6-methylnicotinate



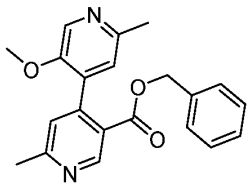
A mixture of 4-chloro-6-methylpyridine-3-carboxylic acid (10.00 g, 58.3 mmol) and Cs_2CO_3 (37.98 g, 116.6 mmol) in DMF (100 mL) was added benzyl bromide (14.95 g, 87.45 mmol). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~30% ethyl acetate in petroleum ether to afford benzyl 4-chloro-6-methylnicotinate (12.94 g, 84.8%) as a yellow oil. MS (ESI) calc'd for ($C_{14}H_{12}ClNO_2$) $(M+1)^+$, 262.0, found 262.1.

Step 2 benzyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



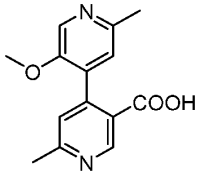
To a degassed mixture of methyl benzyl 4-chloro-6-methylpyridine-3-carboxylate (6.00 g, 22.926 mmol) and 2-chloro-5-methoxypyridin-4-ylboronic acid (4.30 g, 22.926 mmol) in 1,4-dioxane (50 mL) and H_2O (5 mL) were added K_2CO_3 (9.51 g, 0.069 mmol) and $Pd(DtBPF)Cl_2$ (1.49 g, 2.29 mmol). The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford benzyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (4 g, 47.3%) as a yellow oil. MS (ESI) calc'd for ($C_{20}H_{17}ClN_2O_3$) $(M+1)^+$, 369.1, found 369.0.

Step 3 benzyl 5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate



To a degassed mixture of benzyl 2-chloro-5-methoxy-6-methyl-(4,4-bipyridine)-3-carboxylate (4.00 g, 10.845 mmol) and K_2CO_3 (4.50 g, 33.0 mmol) in DME (30 mL) were added $Pd(dppf)Cl_2$ (0.79 g, 1.0 mmol) and trimethyl-1,3,5,2,4,6-trioxatriborinane (1.50 g, 12.0 mmol). The resulting mixture was stirred at 120 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase flash chromatography with 5~70% acetonitrile in water to afford benzyl 5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (2.8 g, 74.1%) as a yellow oil. MS (ESI) calc'd for ($C_{21}H_{20}N_2O_3$) $(M+1)^+$, 349.1, found 349.0.

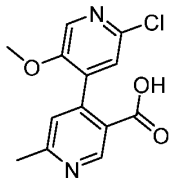
Step 4 5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid



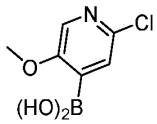
To a mixture of benzyl 5-methoxy-2,6-dimethyl-(4,4-bipyridine)-3-carboxylate (2.80 g, 8.037 mmol) in THF (20.00 mL) were added Pd/C (2.80 g, 10%). The resulting mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The resulting mixture was filtered. The filtrate was concentrated vacuum to afford 5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (2.5 g, curde) as a yellow solid, which was used for the next step directly without further purification. MS (ESI) calc'd for ($C_{14}H_{14}N_2O_3$) $(M+1)^+$, 259.1, found 259.0.

Intermediate G

2-chloro-5-methoxy-6-methyl-(4,4-bipyridine)-3-carboxylic acid

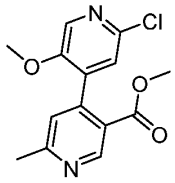


Step-1: 2-chloro-5-methoxypyridin-4-ylboronic acid



A stirred solution of 2-chloro-5-methoxypyridine (10.0 g, 69.65 mmol) in THF (500 mL) was added LDA (14.9 g, 139.30 mmol) dropwise at -78 °C under N_2 atmosphere. The resulting mixture was stirred at -78 °C for 2 h. Then Triisopropyl borate (26.2 g, 139.30 mmol) was added to the above mixture at -78 °C. The resulting mixture was stirred at -78 °C for 2 h. Then the resulting mixture was stirred at room temperature for 16 h. The resulting mixture was quenched with HCl (2 *N*) and stirred at room temperature for 30 min. The resulting mixture was extracted with ethyl acetate. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. 2-chloro-5-methoxypyridin-4-ylboronic acid (9 g, 68.9%) as a brown solid. MS (ESI) calc'd for ($C_6H_7BClNO_3$) $(M+1)^+$, 188.0; found 188.0.

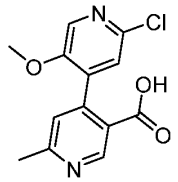
Step-2: methyl 2-chloro-5-methoxy-6-methyl-(4,4-bipyridine)-3-carboxylate



To a degassed solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (700 mg, 3.77 mmol) and 2-chloro-5-methoxypyridin-4-ylboronic acid (918 mg, 4.90 mmol) in dioxane (6 mL) and H_2O (2 mL) were added $Pd(dppf)Cl_2$ (275 mg, 0.37 mmol) and K_2CO_3 (1563 mg, 11.31 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 16 h under nitrogen atmosphere. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~60% ethyl acetate in petroleum ether to afford methyl 2-chloro-5-

methoxy-6-methyl-(4,4-bipyridine)-3-carboxylate (220 mg, 19.9%) as a white solid. MS (ESI) calc'd for ($C_{14}H_{13}ClN_2O_3$) $(M+1)^+$, 293.1; found 293.1.

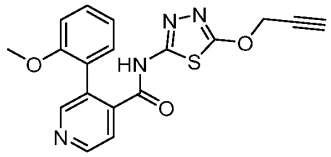
Step-3: 2-chloro-5-methoxy-6-methyl-(4,4-bipyridine)-3-carboxylic acid



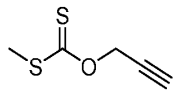
To a stirred solution of methyl 2-chloro-5-methoxy-6-methyl-(4,4-bipyridine)-3-carboxylate (220 mg, 0.75 mmol) in THF (2 mL) and water (2 mL) were added LiOH.H_2O (126 mg, 3.01 mmol). The resulting mixture was stirred at room temperature for 2 h. The mixture was acidified to pH 3 with citric acid. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2-chloro-5-methoxy-6-methyl-(4,4-bipyridine)-3-carboxylic acid (160 mg, 76.3%) as a white solid. MS (ESI) calc'd for ($C_{13}H_{11}ClN_2O_3$) $(M+1)^+$, 279.0; found, 279.0.

Example 1

3-(2-methoxyphenyl)-N-(5-(prop-2-yn-1-yloxy)-1,3,4-thiadiazol-2-yl)isonicotinamide



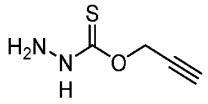
Step 1 S-methyl O-(prop-2-yn-1-yl) carbonodithioate



To a stirred solution of propargyl alcohol (15.00 g, 267.551 mmol, 1.00 equiv) in THF (200 mL) was added NaH (12.84 g, 321.062 mmol, 1.20 equiv, 60%) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0degrees C under nitrogen atmosphere. To the above mixture was added CS_2 (24.45 g, 0.321 mmol, 1.2 equiv) dropwise at 0 degrees C. The resulting mixture was stirred for additional 10 min at 0 degrees C followed by MeI (45.57 g, 0.321 mmol, 1.2 equiv). The resulting mixture was stirred for 10 min at 0 degrees C. The reaction was quenched by the addition 100mL of NH_4Cl (aq.) at

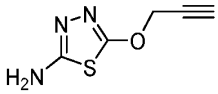
room temperature. The aqueous layer was extracted with EtOAc (2x2 100mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (20:1) to afford (methylsulfanyl)(prop-2-yn-1-yloxy)methanethione as a brown oil.

Step 2 O-(prop-2-yn-1-yl) hydrazinecarbothioate



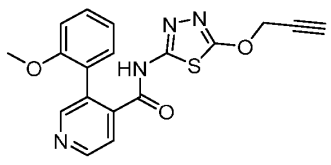
To a stirred solution/mixture of (methylsulfanyl)(prop-2-yn-1-yloxy)methanethione (25.00 g, 170.975 mmol, 1.00 equiv) in MeOH were added (methylsulfanyl)(prop-2-yn-1-yloxy)methanethione (25.00 g, 170.975 mmol, 1.00 equiv) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 30min at room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in (((prop-2-yn-1-yloxy)methanethioyl)amino)amine (23 g, 95.08%) as a brown oil.

Step 3 5-(prop-2-yn-1-yloxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of (((prop-2-yn-1-yloxy)methanethioyl)amino)amine (23.00 g, 176.692 mmol, 1.00 equiv) and TEA (35.76 g, 353.384 mmol, 2 equiv) in MeOH was added BrCN (22.46 g, 212.030 mmol, 1.2 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (2 x 100mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The product was precipitated by the addition of EtOAc. This resulted in 5-(prop-2-yn-1-yloxy)-1,3,4-thiadiazol-2-amine (7.8 g, 26.46%) as an off-white solid.

Step 4: 3-(2-methoxyphenyl)-N-(5-(prop-2-yn-1-yloxy)-1,3,4-thiadiazol-2-yl)isonicotinamide

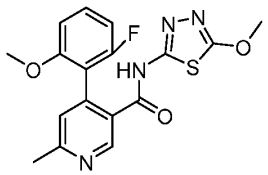


To a stirred solution of Intermediate A (5.00 g, 0.22 mmol, 1.00 equiv) and DIEA (8.45 g, 0.65 mmol, 3.00 equiv) in DMF (150 mL) was added HATU (9.94 mg, 0.26 mmol, 1.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added 5-(prop-2-yn-1-yloxy)-1,3,4-thiadiazol-2-amine(3.38 g, 0.22 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 2h at room temperature. The resulting mixture was diluted with water (450 mL). The aqueous layer was extracted with EtOAc (3x200 mL). The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (40:1). The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 50% gradient in 20 min; detector, UV 254 nm to afford 3-(2-methoxyphenyl)-N-(5-(prop-2-yn-1-yloxy)-1,3,4-thiadiazol-2-yl)isonicotinamide (5.01 g, 61.84%) as an orange solid.

LC-MS: *m/z* 367 $(M+H)^+$; H-NMR: ^{1}H NMR (300 MHz, Methanol-d4) δ8.68 -8.67 (d, 1H), 8.60 (s, 1H), 7.65 -7.64 (d, 1H), 7.42 - 7.36 (m, 2H), 7.11 - 7.08 (m, 1H), 6.99 - 6.96 (d, 1H), 5.09 (s, 2H), 3.60 (s, 3H), 3.11 (s, 1H) ppm.

Example 2

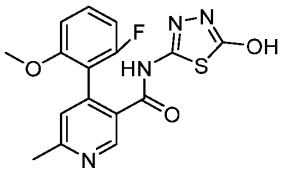
4-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide



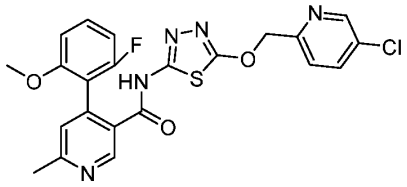
To a mixture of 5-methoxy-1,3,4-thiadiazol-2-amine (33.1 mg, 0.25 mmol) in acetonitrile (2 mL) were added Intermediate E (55.0 mg, 0.21 mmol) and NMI (36.3 mg, 0.44 mmol). A solution of TCFH (64.9 mg, 0.23 mmol) in acetonitrile (1 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The mixture was concentrated under vacuum. The residue was dissolved in DMF (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 20 g C18 column, eluted with 5~60% acetonitrile in water to afford 5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide (47.1 mg, 58%) as a white solid. MS (ESI) calc'd for $(C_{17}H_{15}FN_4O_3S)$ $(M+1)^+$, 375.1, found 375.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.80 (s, 1H), 7.40 – 7.36 (m, 1H), 7.34 – 7.28 (m, 1H), 6.95 – 6.86 (m, 2H), 4.06 (s, 3H), 3.58 (s, 3H), 2.56 (s, 3H).

Example 3

4-(2-fluoro-6-methoxyphenyl)-N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

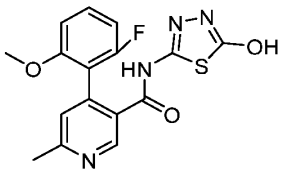


Step-1: N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide



To a mixture of Intermediate B (111.4 mg, 0.46 mmol) in acetonitrile (2 mL) were added Intermediate E (100.0 mg, 0.38 mmol) and NMI (66.0 mg, 0.80 mmol). A solution of TCFH (118.1 mg, 0.42 mmol) in acetonitrile (1 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The resulting mixture was concentrated under vacuum. The residue was dissolved in DMF (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 column, eluted with 15~60% acetonitrile in water within 30 min to afford N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide (170.0 mg, 91%) as a white solid. MS (ESI) calc'd for ($C_{22}H_{17}ClFN_5O_3S$) $(M+1)^+$, 486.1, found 486.0.

Step-2: 4-(2-fluoro-6-methoxyphenyl)-N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

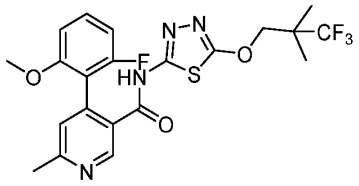


A mixture of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylpyridine-3-carboxamide (170.0 mg, 0.35 mmol) in concentrated HCl (3 mL) was stirred at room temperature for 2 hr before concentrated under vacuum. The residue was basified with $NH_3{\cdot}H_20$ to pH 9~10. The aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous

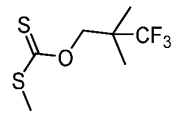
sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 × 150 mm 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10 B to 40 B in 8 min; 220 nm; RT: 7.23 min) to afford 4-(2-fluoro-6-methoxyphenyl)-N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (56.4 mg, 44%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{13}FN_4O_3S$) $(M+1)^+$, 361.1, found 361.0. ^1H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 2H), 8.75 (s, 1H), 7.46 – 7.32 (m, 1H), 7.30 (s, 1H), 6.95 – 6.82 (t, J = 8.0 Hz, 2H), 3.64 (s, 3H), 2.55 (s, 3H).

Example 4

4-(2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,3,4-thiadiazol-2-yl)pyridine-3-carboxamide

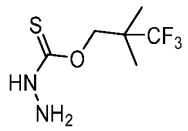


Step 1 (methylsulfanyl)(3,3,3-trifluoro-2,2-dimethylpropoxy)methanethione



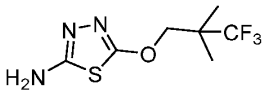
To a degassed solution of 3,3,3-trifluoro-2,2-dimethylpropan-1-ol (100.0 mg, 0.71 mmol) in dry Tetrahydrofuran (3 mL) was added NaH (34.0 mg, 1.41 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 1 h under nitrogen atmosphere. Then CS_2 (81.0 mg, 1.00 mmol) was added to the above mixture at 0 °C for 20 min. Then MeI (150.0 mg, 1.05 mmol) was added to the above mixture at 0 °C for 30 min. Then the mixture resulting was stirred at room temperature for 2 hr under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 30 min to afford (methylsulfanyl)(3,3,3-trifluoro-2,2-dimethylpropoxy)methanethione (160.0 mg, 97%) as a white solid. MS (ESI) calc'd for ($C_7H_{11}F_3N_2OS$) $(M+1)^+$, 234.0; found 234.0.

Step 2 (((3,3,3-trifluoro-2,2-dimethylpropoxy)methanethioyl)amino)amine



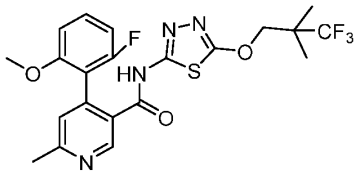
To a stirred solution of (methylsulfanyl)(3,3,3-trifluoro-2,2-dimethylpropoxy)methanethione (160.0 mg, 0.70 mmol) in MeOH (3 mL) was added $NH_2NH_2.H_2O$ (34.0 mg, 0.70 mmol) dropwise at 0 °C under nitrogen atmosphere. The mixture resulting was stirred at 0 °C for 1 hr under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to afford (((3,3,3-trifluoro-2,2-dimethylpropoxy)methanethioyl)amino)amine (150.0 mg, crude) as a yellow oil. MS (ESI) calc'd for ($C_6H_{11}F_3N_2OS$) $(M+1)^+$, 217.1; found 217.1.

Step 3 5-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of (((3,3,3-trifluoro-2,2-dimethylpropoxy)methanethioyl)amino)amine (150.0 mg, 0.70 mmol) in MeOH (3 mL) were added TEA (140.0 mg, 1.39 mmol) and BrCN (81.0 mg, 0.76 mmol) at 0 °C under nitrogen atmosphere. The mixture resulting was stirred at 0 °C for 1 hr under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 5-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,3,4-thiadiazol-2-amine (140.0 mg, crude) as a pink solid. MS (ESI) calc'd for ($C_7H_{10}F_3N_3OS$) $(M+1)^+$, 242.1; found 242.1.

Step 4 4-(2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,3,4-thiadiazol-2-yl)pyridine-3-carboxamide

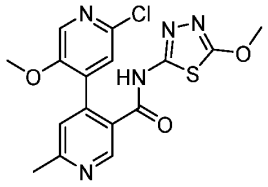


To a stirred solution of 5-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,3,4-thiadiazol-2-amine (50.0 mg, 0.21 mmol) and Intermediate E (54.0 mg, 0.21 mmol) in DMF (1 mL) were added NMI (68.0 mg, 0.83 mmol) and TCFH (87.0 mg, 0.31 mmol) at 25 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 1 hr under nitrogen atmosphere. The resulting mixture was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10 mmol/L

NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 57% B in 8 min, UV: 254 nm) to afford 4-(2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1,3,4-thiadiazol-2-yl)pyridine-3-carboxamide (23.2 mg, 23%) as a white solid. MS (ESI) calc'd for ($C_{21}H_{20}F_4N_4O_3S$) $(M+1)^+$, 485.1; found, 485.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.83 (s, 1H), 7.42 – 7.37 (m, 1H), 7.31 (d, J = 1.6 Hz, 1H), 6.93 – 6.87 (m, 2H), 4.45 (s, 2H), 3.58 (s, 3H), 2.57 (s, 3H), 1.22 (s, 6H).

Example 5

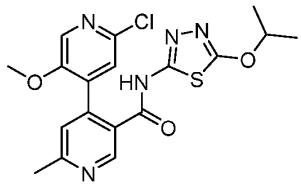
2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



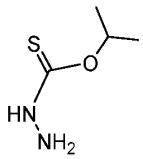
To a mixture of Intermediate G (50.0 mg, 0.17 mmol) in MeCN (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (28.2 mg, 0.21 mmol) and NMI (30.9 mg, 0.37 mmol). A solution of TCFH (55.3 mg, 0.19 mmol) in MeCN (1 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The resulting mixture was concentrated under vacuum. The residue was dissolved in DMF (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 column, eluted with 10~60% acetonitrile in water within 30 min to afford 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (34.7 mg, 33%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{14}ClN_5O_3S$) $(M+1)^+$, 392.0, found 392.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 4.08 (s, 3H), 3.63 (s, 3H), 2.59 (s, 3H).

Example 6

2'-chloro-N-(5-isopropoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

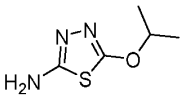


Step-1: ((isopropoxymethanethioyl)amino)amine



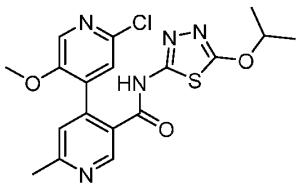
A mixture of isopropoxy(potassiosulfanyl)methanethione (1.0 g, 5.73 mmol) and Hydrazine (200.0 mg, 5.61 mmol) in MeOH (10 mL) was stirred at room temperature for 2 hr. The mixture was concentrated under vacuum to afford ((isopropoxymethanethioyl)amino)amine (800.0 mg, crude) as a yellow solid, which was used for the next step without further purification.

Step-2: 5-isopropoxy-1,3,4-thiadiazol-2-amine



To a mixture of ((isopropoxymethanethioyl)amino)amine (400.0 mg, 2.98 mmol), TEA (603.2 mg, 5.96 mmol) in MeOH (20 mL) was added BrCN (173.6 mg, 1.63 mmol). The resulting mixture was stirred at room temperature for 2 hr. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in DMF (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 column, eluted with 15~90% acetonitrile in water within 30 min to afford 5-isopropoxy-1,3,4-thiadiazol-2-amine (79.0 mg, 16%) as a white solid. MS (ESI) calc'd for ($C_5H_9N_3OS$) $(M+1)^+$, 160.0, found 160.0 .

Step-3: 2'-chloro-N-(5-isopropoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

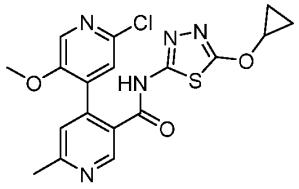


A mixture of Intermediate G (80.0 mg, 0.28 mmol) in MeCN (3 mL) were added 5-isopropoxy-1,3,4-thiadiazol-2-amine (59.4 mg, 0.37 mmol) and NMI (49.4 mg, 0.60 mmol). A solution of TCFH (88.6 mg, 0.31 mmol) in MeCN (1 mL) was added thereto dropwise under nitrogen. The resulting mixture was stirred at room temperature for 2 hr. The resulting mixture was concentrated under vacuum. The residue was dissolved in DMF (3 mL) and

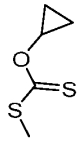
purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 column, eluted with 15~65% acetonitrile in water within 30 min to afford 2'-chloro-N-(5-isopropoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (29.4 mg, 23%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{18}ClN_5O_3S$) $(M+1)^+$, 420.0, found 420.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 5.17 – 5.05 (m, 1H), 3.63 (s, 3H), 2.58 (s, 3H), 1.37 (d, J = 6.0 Hz, 6H).

Example 7

2'-chloro-N-(5-cyclopropoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

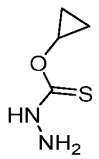


Step 1 cyclopropoxy(methylsulfanyl)methanethione



To a mixture of cyclopropanol (1.0 g, 17.21 mmol) in THF (20 mL) was added NaH (1.4 g, 34.40 mmol， 60%) in portions at 0 °C and stirred at 0 °C for 30 min. To the above mixture was added CS_2 (1.9 g, 25.82 mmol) at 0 °C and stirred at 0 °C for 30 min. Then MeI (3.7 g, 25.82 mmol) was added to the above mixture at 0 °C. The resulting solution was stirred at 0 °C for 30 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford cyclopropoxy(methylsulfanyl)methanethione (2.0 g, crude) as a yellow oil.

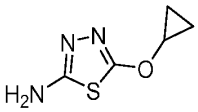
Step 2 N-amino-1-cyclopropoxymethanethioamide



To a mixture of cyclopropoxy(methylsulfanyl)methanethione (1.5 g, 10.11 mmol) in MeOH (10 mL) was added Hydrazine (389.1 mg, 12.14 mmol). The mixture was stirred at 25 °C for

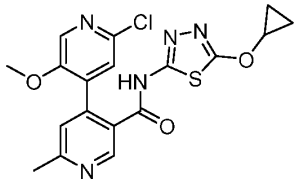
2 hr. The mixture was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum afford N-amino-1-cyclopropoxymethanethioamide (2.4 g, crude) as a yellow oil. MS (ESI) calc'd for ($C_4H_8N_2OS$) $(M-1)^+$, 133.0, found 133.0

Step 3 5-cyclopropoxy-1,3,4-thiadiazol-2-amine



To a mixture of N-amino-1-cyclopropoxymethanethioamide (1.5 g, 11.34 mmol), TEA (2.3 g, 22.69 mmol) in MeOH (10 mL) were added BrCN (1.3 g, 12.48 mmol), the resulting solution was stirred at 25 °C for 30 min. The mixture was quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford crude. The residue was dissolved in DMF (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 column, eluted with 15~90% acetonitrile in water within 30 min to afford 5-cyclopropoxy-1,3,4-thiadiazol-2-amine (400.0 mg, 22% over three steps) as a yellow solid. MS (ESI) calc'd for ($C_5H_7N_3OS$) $(M+1)^+$, 158.0, found 158.0.

Step 4 2'-chloro-N-(5-cyclopropoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

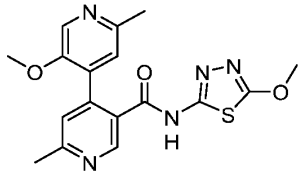


To a mixture of Intermediate G (100.0 mg, 0.35 mmol) in DMF (5 mL) were added 5-cyclopropoxy-1,3,4-thiadiazol-2-amine (84.6 mg, 0.53 mmol), HATU (204.6 mg, 0.53 mmol) and DIEA (139.1 mg, 1.07 mmol). The resulting solution was stirred at 25 °C for 2 hr. The resulting mixture was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30 mm X 150 mm, 5 um; Mobile Phase A: Water (10 MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 40% B in 8 min, 40% B to 95% B in 9 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 10 min; Wave Length: 254 nm; RT (min) :7.80) to afford 2'-chloro-N-(5-cyclopropoxy-1,3,4-thiadiazol-2-yl)-5-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (54.6 mg, 36%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{16}ClN_5O_3S$) $(M+1)^+$, 418.0, found 418.0. ^1H NMR (400

MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 4.39 – 4.29 (m, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 0.91 – 0.77 (m, 4H).

Example 8

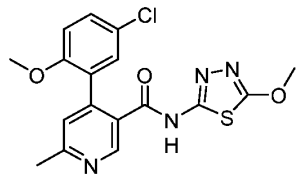
5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



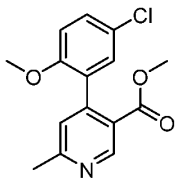
To a mixture of 5-methoxy-1,3,4-thiadiazol-2-amine (60.9 mg, 0.46 mmol) in DMF (1 mL) and acetonitrile (1 mL) were added Intermediate F (100.0 mg, 0.38 mmol), NMI (95.0 mg, 1.16 mmol). A solution of TCFH (163.0 mg, 0.58 mmol) in Acetonitrile (1 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The resulting solution was purified by Combi Flash (Biotage Isolera Prime) which applied to a 40g C18 column that was eluted with 5~30% acetonitrile in water within 30 min to afford 5'-methoxy-N-(5-methoxy-1,3,4-t hiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (124.0 mg, 85%) as a white solid. MS (ESI) calculated for ($C_{17}H_{17}N_5O_3S$) $(M+1)^+$, 372.1; found, 372.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.75 (s, 1H), 8.19 (s, 1H), 7.36 (s, 1H), 7.26 (s, 1H), 4.08 (s, 3H), 3.58 (s, 3H), 2.59 (s, 3H), 2.48 (s, 3H).

Example 9

4-(5-chloro-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



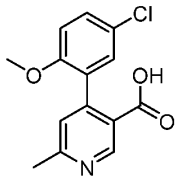
Step 1 4-(5-chloro-2-methoxyphenyl)-6-methylpyridine-3-carboxylate



To a stirred solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (600.0 mg, 3.23 mmol) and 5-chloro-2-methoxyphenylboronic acid (905.0 mg, 4.85 mmol) in dioxane (6 mL)

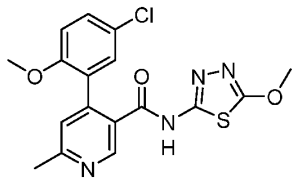
were added water (2 mL) and $Pd(PPh_3)_4$ (375.0 mg, 0.32 mmol) and K_2CO_3 (1.3 g, 9.72 mmol). The resulting mixture was stirred at 80 °C for 2 hr under nitrogen atmosphere before concentrated under vacuum. The crude residue was applied to a 40 g C18 column, purified by Combi Flash (Biotage Isolera Prime), and eluted with 5~50% acetonitrile in water within 45 min to afford methyl 4-(5-chloro-2-methoxyphenyl)-6-methylpyridine-3-carboxylate (730.0 mg, 76%) as a yellow oil. MS (ESI) calculated for ($C_{15}H_{14}ClNO_3$) $(M+1)^+$, 292.1; found, 292.0.

Step 2 4-(5-chloro-2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid



To a stirred solution of methyl 4-(5-chloro-2-methoxyphenyl)-6-methylpyridine-3-carboxylate (100.0 mg, 0.34 mmol) in tetrahydrofuran (1 mL) were added $LiOH.H_2O$ (58.0 mg, 1.38 mmol) and water (0.3 mL). The resulting mixture was stirred at 25 °C for 1 hr. The residue was acidified to pH 7 with citric acid. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 4-(5-chloro-2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (93.0 mg, crude) as a white solid. MS (ESI) calculated for ($C_{14}H_{12}ClNO_3$) $(M+1)^+$, 278.1; found, 278.1.

Step 3 4-(5-chloro-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

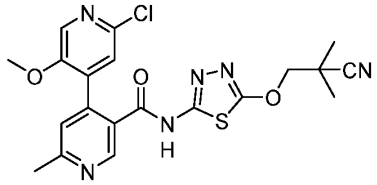


To a mixture of 5-methoxy-1,3,4-thiadiazol-2-amine (57.0 mg, 0.43 mmol) in acetonitrile (3 mL) were added 4-(5-chloro-2-methoxyphenyl)-6-methylnicotinic acid (93.0 mg, 0.36 mmol) and NMI (89.0 mg, 1.08 mmol). A solution of TCFH (111.0 mg, 0.39 mmol) in acetonitrile (1 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The reaction mixture was applied to a 40 g C18 column, purified by Combi Flash (Biotage Isolera Prime), and eluted with 5~40% acetonitrile in water within 45 min to

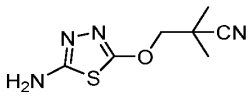
afford 4-(5-chloro-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (91.3 mg, 64%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{15}ClN_4O_3S$) $(M+1)^+$, 391.0, found 391.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.70 (s, 1H), 7.48 – 7.40 (m, 2H), 7.35 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.07 (s, 3H), 3.50 (s, 3H), 2.57 (s, 3H).

Example 10

2'-chloro-N-(5-(2-cyano-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

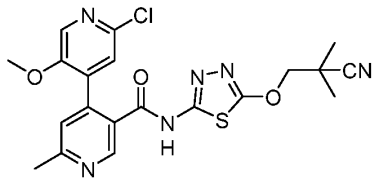


Step-1: 3-((5-amino-1,3,4-thiadiazol-2-yl)oxy)-2,2-dimethylpropanenitrile



To a solution of NaH (303.0 mg, 7.57 mmol, 60%) in Tetrahydrofuran (5 mL) was added a solution of 3-hydroxy-2,2-dimethylpropanenitrile (500.0 mg, 5.04 mmol) in Tetrahydrofuran (2 mL) dropwise at 0 °C and stirred at 0 °C for 30 min. To the above solution was added 5-bromo-1,3,4-thiadiazol-2-amine (908.0 mg, 5.04 mmol) at 0 °C under nitrogen. The resulting solution was then stirred at 0 °C for 1.5 hr. The reaction mixture was quenched by the addition of water. The resulting mixture was concentrated under vacuum. The residue was dissolved in DMF (5 mL) and purified by Combi Flash which applied to 80 g C18 column that was eluted with 5~70% acetonitrile in water within 30 min to afford 3-((5-amino-1,3,4-thiadiazol-2-yl)oxy)-2,2-dimethylpropanenitrile (50.0 mg, 5%) as a yellow solid.MS (ESI) calc'd for ($C_7H_{10}N_4OS$) (M+1)+, 199.1; found 199.2.

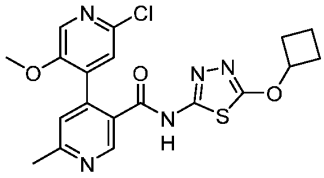
Step-2: 2'-chloro-N-(5-(2-cyano-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



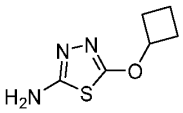
To a solution of Intermediate G (70.0 mg, 0.25 mmol) and 3-((5-amino-1,3,4-thiadiazol-2-yl)oxy)-2,2-dimethylpropanenitrile (50.0 mg, 0.25 mmol) in N,N-Dimethylformamide (2 mL) were added DIEA (98 mg, 0.76 mmol) and HATU (142.5 mg, 037 mmol) at 20 ºC .The resulting solution was stirred at 80 ºC under nitrogen for 2 hr. The resulting mixture was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 30 min.to afford 2'-chloro-N-(5-(2-cyano-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (51.6 mg, 43%) as a white solid. MS (ESI) calc'd for ($C_{20}H_{19}ClN_6O_3S$) $(M+1)^+$, 459.1; found, 459.0. 1H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 4.49 (s, 2H), 3.64 (s, 3H), 2.60 (s, 3H), 1.42 (s, 6H).

Example 11

2'-chloro-N-(5-cyclobutoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



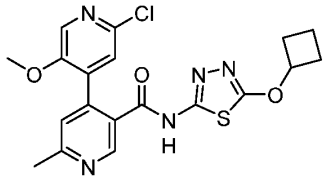
Step 1 5-cyclobutoxy-1,3,4-thiadiazol-2-amine



To a solution of NaH (416.0 mg, 10.40 mmol, 60%) in Tetrahydrofuran (THF) (5 mL) were added cyclobutanol (500.0 mg, 6.93 mmol) dropwise at 0 ºC. The resulting solution was then stirred at 0 ºC for 30 min under nitrogen. To the above solution was added 5-bromo-1,3,4-thiadiazol-2-amine (1.3 g, 6.93 mmol) at 0 ºC under nitrogen. The resulting solution was then stirred at 0 ºC for 1 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (1 mL) and was applied to a 20 g silica gel column that was purified by Combi Flash (Biotage Isolera Prime), eluted with 0~50% ethyl acetate in petroleum ether within 30 min to afford 5-cyclobutoxy-1,3,4-thiadiazol-2-amine (140.0 mg, 12%) as a yellow solid. MS (ESI) calc'd for ($C_6H_9N_3OS$) $(M+1)^+$,172.1, found 172.1.

Step 2 2'-chloro-N-(5-cyclobutoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-

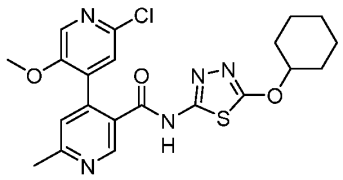
bipyridine)-3-carboxamide



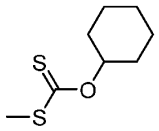
To a solution of Intermediate G (146.0 mg, 0.53 mmol) in Acetonitrile (1 mL) were added 5-cyclobutoxy-1,3,4-thiadiazol-2-amine (90.0 mg, 0.53 mmol) and NMI (216.0 mg, 2.63 mmol). To the above was added TCFH (162.0 mg, 0.58 mmol) at 23 °C. The resulting solution was stirred at 23°C for 1 hr. The mixture was dissolved in DMF (1 mL) and was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) that was eluted with 5~50% acetonitrile in water within 30 min to afford 2'-chloro-N-(5-cyclobutoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (24.7 mg, 11 %) as a white solid. MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$ 432.1; found 432.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.79 (s, 1H), 8.17 (s, 1H), 7.53 – 7.34 (m, 2H), 5.22 – 5.16 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.59 – 2.18 (m, 4H), 1.77 – 1.85 (m, 1H), 1.71 – 1.53 (m, 1H).

Example 12

2'-chloro-N-(5-(cyclohexyloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



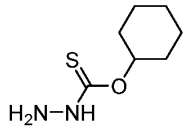
Step 1 O-cyclohexyl S-methyl carbonodithioate



To a degassed mixture of NaH (200.0 mg, 4.99 mmol, 60%) in Tetrahydrofuran (6 mL) was added cyclohexanol (500.0 mg, 4.99 mmol) dropwise at 0 °C and stirred at 0 °C for 30 min. To the above solution was added CS_2 (570.0 mg, 7.49 mmol)) dropwise at 0 °C and stirred at 0 °C for 20 min. To the above solution was added MeI (1.1 g, 7.49 mmol) dropwise at 0 °C and stirred at 0 °C for 30 min. The reaction mixture was quenched by the addition of water

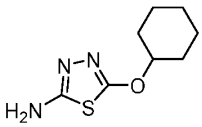
and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (3 mL) and was applied to a 20 g silica gel column, purified by Combi Flash (Biotage Isolera Prime), eluted with 0~10% ethyl acetate in petroleum ether within 20 min to afford O-cyclohexyl S-methyl carbonodithioate (400.0 mg, 42%) as a colorless oil. MS (ESI) calc'd for ($C_8H_{14}OS$) $(M+1)^+$, 191.0; found, 191.1.

Step 2 O-cyclohexyl hydrazinecarbothioate



To a degassed solution of O-cyclohexyl S-methyl carbonodithioate (400.0 mg, 2.10 mmol) in Methanol (4 mL) was added hydrazine (126.1 mg, 3.15 mmol) at 0 °C under nitrogen atmosphere. The resulting solution was then stirred at 23 °C for 1 hr. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-cyclohexyl hydrazinecarbothioate (320.1 mg, crude) as a white solid. MS (ESI) calc'd for ($C_7H_{14}N_2OS$) $(M+1)^+$, 175.1; found, 175.1.

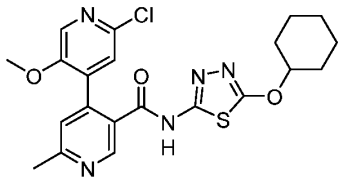
Step 3 5-(cyclohexyloxy)-1,3,4-thiadiazol-2-amine



To a degassed solution of O-cyclohexyl hydrazinecarbothioate (320.0 mg, 1.84 mmol) in Methanol (4 mL) was added TEA (372.0 mg, 3.67 mmol) and BrCN (270.0 mg, 2.57 mmol) at 23 °C under nitrogen atmosphere. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash which applied to 20 g silica gel column, purified by Combi Flash (Biotage Isolera Prime), eluted with 0~30% ethyl acetate in petroleum ether within 25 min to afford 5-(cyclohexyloxy)-1,3,4-thiadiazol-2-amine (220.0 mg, 57%) as a white solid. MS (ESI) calc'd for ($C_8H_{13}N_3OS$) $(M+1)^+$,200.1, found 200.1.

Step 4 2'-chloro-N-(5-(cyclohexyloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-

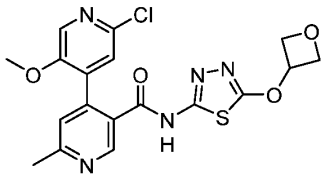
bipyridine)-3-carboxamide



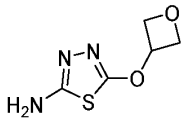
To a solution of Intermediate G (280.1 mg, 1.01 mmol) in N,N-Dimethylformamide (2 mL) were added 5-(cyclohexyloxy)-1,3,4-thiadiazol-2-amine (200.0 mg, 1.01 mmol) and 1-methylimidazole (247.2 mg, 3.01 mmol). To the above was added a solution of TCFH (310.0 mg, 1.10 mmol) in Acetonitrile (1 mL) at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The mixture was diluted with DMF (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 30 min to afford 2'-chloro-N-(5-(cyclohexyloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (240.1 mg, 52%) as a white solid. MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_3S$) $(M+1)^+$, 460.1, found 460.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.94 – 4.83 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.10 – 1.99 (m, 2H), 1.75 – 1.67 (m, 2H), 1.56 – 1.49 (m, 3H), 1.45 – 1.23 (m, 3H).

Example 13

2'-chloro-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



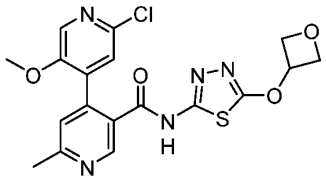
Step 1 5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-amine



To a degassed solution of NaH (405.2 mg, 10.12 mmol, 60%) in tetrahydrofuran (8 mL) was added oxetan-3-ol (500.1 mg, 6.75 mmol) at 0 °C and stirred at 0 °C for 30 min. To the above mixture was added 5-bromo-1,3,4-thiadiazol-2-amine (1.2 g, 6.75 mmol) under nitrogen. The resulting solution was then stirred at 0 °C for 1 hr. The reaction mixture was quenched by the

addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1.5 mL), applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~20% acetonitrile in water within 20 min to afford 5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-amine (112.2 mg, 9%) as a yellow solid. MS (ESI) calc'd for ($C_5H_7N_3O_2S$) $(M+1)^+$, 174.0; found 174.0.

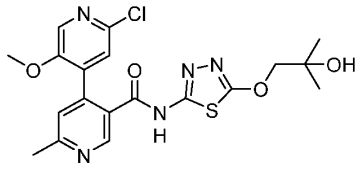
Step 2 2'-chloro-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



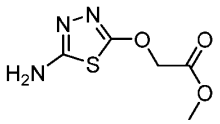
To a solution of 5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-amine (100.0 mg, 0.58 mmol) in N,N-dimethylformamide (1 mL) and acetonitrile (1 mL) were added Intermediate G (161.2 mg, 0.58 mmol) and 1-methylimidazole (142.2 mg, 1.73 mmol). To the above mixture was added a solution of TCFH (178.3 mg, 0.64 mmol) in Acetonitrile (1 mL) at 23 °C. The mixture was stirred at 23 °C for 2 hr under nitrogen. The resulting mixture was dissolved in DMF (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 30 min to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (65.3 mg, 25%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{16}ClN_5O_4S$) $(M+1)^+$, 434.1; found, 434.0. 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.72 – 5.62 (m, 1H), 4.94 – 4.86 (m, 2H), 4.69 – 4.61 (m, 2H), 3.63 (s, 3H), 2.59 (s, 3H).

Example 14

2'-chloro-N-(5-(2-hydroxy-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

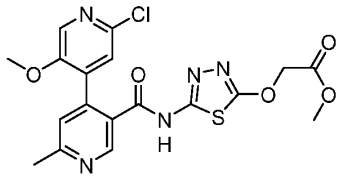


Step-1: methyl 2-((5-amino-1,3,4-thiadiazol-2-yl)oxy)acetate



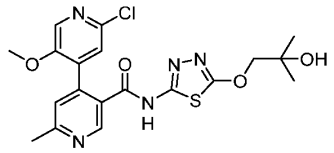
To a degassed solution of methyl 2-hydroxyacetate (3.0 g, 33.3 mmol) in Tetrahydrofuran (30 mL) was added NaH (2.0 g, 50.0 mmol, 60%) in portions at 0 °C. The resulting solution was stirred at 0 °C for 1 hr under nitrogen. To the above solution was added 5-bromo-1,3,4-thiadiazol-2-amine (6.0 g, 33.3 mmol) at 0 °C. The resulting solution was then stirred at 0 °C for 2 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by normal phase flash chromatography which applied to 40 g silica gel column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 0~66% ethyl acetate in petroleum ether within 30 min to afford methyl 2-((5-amino-1,3,4-thiadiazol-2-yl)oxy)acetate (418.0 mg, 6 %) as a white solid. MS (ESI) calculated for ($C_5H_7N_3O_3S$) $(M+1)^+$, 190.0; found, 190.0.

Step-2: methyl 2-((5-(2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamido)-1,3,4-thiadiazol-2-yl)oxy)acetate



To a stirred solution of methyl 2-((5-amino-1,3,4-thiadiazol-2-yl)oxy)acetate (200.0 mg, 1.06 mmol) in N,N-Dimethylformamide (2 mL) were sequentially added Intermediate G (295.0 mg, 1.06 mmol) and 1-methyl-1H-imidazole (347.0 mg, 4.23 mmol). A solution of TCFH (445.0 mg, 1.59 mmol) in acetonitrile (2 mL) was added thereto at 23 °C. The mixture was stirred at 23 °C for 1 h. The resulting mixture was diluted in DMF (2 mL) and was applied to a 40 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~34% acetonitrile in water within 30 min to afford methyl 2-((5-(2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamido)-1,3,4-thiadiazol-2-yl)oxy)acetate (350.0 mg, 72%) as a white solid. MS (ESI) calculated for ($C_{18}H_{16}ClN_5O_5S$) $(M+1)^+$, 450.1; found, 450.1.

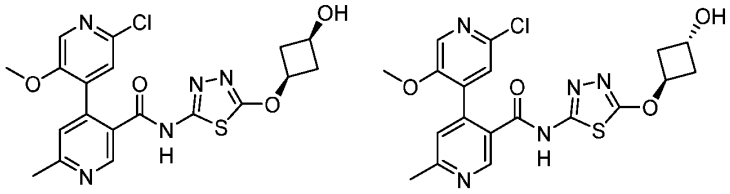
Step-3: 2'-chloro-N-(5-(2-hydroxy-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



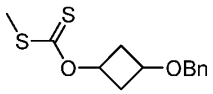
To a degassed solution of methyl methyl 2-((5-(2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamido)-1,3,4-thiadiazol-2-yl)oxy)acetate (100.0 mg, 0.22 mmol) in dry Tetrahydrofuran (1 mL) was added methylmagnesium bromide (0.3 mL, 0.90 mmol, 3 N in THF) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in Methanol (4 mL) and was purified by prep-HPLC with the following conditions: (Column: Xbridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH—HPLC; Flow rate: 60 mL/min; Gradient: 38% B to 55% B in 8 min, 55% B to 95% B in 8.2 min, 95% B to 95% B in 10 min, 95% B to 38% B in 11 min, 38% B; Wave Length: 254/220 nm; RT1 (min): 7; Injection Volume: 0.8 mL; Number Of Runs: 5) to afford 2'-chloro-N-(5-(2-hydroxy-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (41.7 mg, 41%) as a white solid. MS (ESI) calculated for ($C_{19}H_{20}ClN_5O_4S$) $(M+1)^+$, 450.1; found, 450.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.77 (s, 1H), 4.18 (s, 2H), 3.64 (s, 3H), 2.59 (s, 3H), 1.18 (s, 6H).

Example 15 and 16

2'-chloro-N-(5-((1s,3s)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and 2'-chloro-N-(5-((1r,3r)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

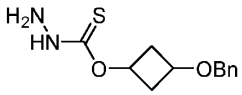


Step 1 O-(3-(benzyloxy)cyclobutyl) S-methyl carbonodithioate



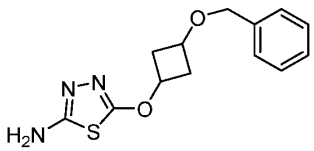
To a solution of NaH (242 mg, 6.06 mmol, 60%) in THF (5 mL) was added a solution of 3-(benzyloxy)cyclobutan-1-ol (900 mg, 5.06 mmol) in THF (5 mL) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. To the above mixture was added CS_2 (576 mg, 7.59 mmol) dropwise at 0 °C and stirred at 0 °C for 20 min. Then MeI (1.07 mg, 7.59 mmol) was added to the above mixture dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was quenched with water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The resulting residue was dissolved in acyl acetate (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~82% ethyl acetate in petroleum ether within 35 min to afford O-(3-(benzyloxy)cyclobutyl) S-methyl carbonodithioate (940 mg, 69%) as a yellow oil. MS (ESI) calculated for ($C_{13}H_{16}O_2S_2$) $(M+1)^+$, 269.06; found, 269.06.

Step 2 O-(3-(benzyloxy)cyclobutyl) hydrazinecarbothioate



To a mixture of S-methyl O-(3-(benzyloxy)cyclobutyl) S-methyl carbonodithioate (940 mg, 3.50 mmol) in MeOH (5 mL) was added Hydrazine (241 mg, 3.80 mmol 80%). The mixture was stirred at 0 °C for 1 hour. The resulting mixture was concentrated under vacuum and then diluted with water. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-(3-(benzyloxy)cyclobutyl) hydrazinecarbothioate (830 mg, crude) as a yellow oil. MS (ESI) calculated for ($C_{12}H_{16}N_2O_2S$) $(M+1)^+$, 253.09; found, 253.09.

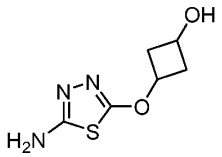
Step 3 5-(3-(benzyloxy)cyclobutoxy)-1,3,4-thiadiazol-2-amine



To a mixture of O-(3-(benzyloxy)cyclobutyl) hydrazinecarbothioate (860 mg, 3.40 mmol) and Et_3N (689 mg, 6.81 mmol) in MeOH (5 mL) was added BrCN (394 mg, 3.74 mmol). The mixture was stirred at 23 °C for 1 h. The resulting mixture was quenched with water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed

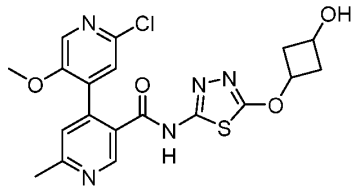
with brine, dried over anhydrous sodium sulfate and filtered. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 0~55% ethyl acetate in petroleum ether within 35 min to afford 5-(3-(benzyloxy)cyclobutoxy)-1,3,4-thiadiazol-2-amine (410 mg, 43%) as a white solid. MS (ESI) calculated for $(C_{13}H_{15}N_3O_2S)$ $(M+1)^+$, 278.09; found, 278.09.

Step 4 3-((5-amino-1,3,4-thiadiazol-2-yl)oxy)cyclobutan-1-ol



To a stirred solution of 5-(3-(benzyloxy)cyclobutoxy)-1,3,4-thiadiazol-2-amine (320 mg, 1.154 mmol) in Dichloromethane (5 mL) was added BBr_3 (0.545 mL, 5.77 mmol) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. The reaction mixture was quenched with the addition of water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was dissolved in DMF (3 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~35% acetonitrile in water within 25 min to afford 3-((5-amino-1,3,4-thiadiazol-2-yl)oxy)cyclobutan-1-ol (105 mg, 48%) as a white solid. MS (ESI) calculated for $(C_6H_9N_3O_2S)$ $(M+1)^+$, 188.04; found, 188.04.

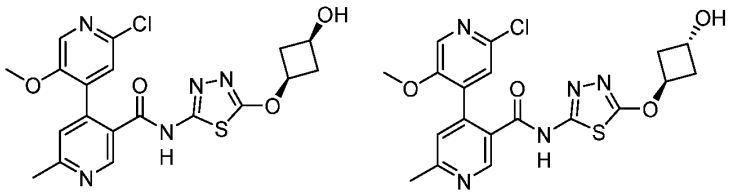
Step 5 2'-chloro-N-(5-(3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 3-((5-amino-1,3,4-thiadiazol-2-yl)oxy)cyclobutan-1-ol (100 mg, 0.534 mmol) in N,N-Dimethylformamide (0.5 mL) and Acetonitrile (0.5 mL) were added 1-methylimidazole (0.213 mL, 2.67 mmol), Intermediate G (149 mg, 0.534 mmol), and TCFH (165 mg, 0.588 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 1 h. The resulting residue was dissolved in DMF (0.5 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~42% acetonitrile in water within 25 min to afford 2'-chloro-N-(5-(3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-

methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (50 mg, 19%) as a yellow solid. MS (ESI) calculated for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.1; found, 448.1.

Step 6 2'-chloro-N-(5-((1s,3s)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and 2'-chloro-N-(5-((1r,3r)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



The mixture of compounds (50 mg) was dissolved in DMF (7 mL) which was purified by prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH----Preparative; Flow rate: 25 mL/min; Gradient: 40% B to 50% B in 12 min, 50% B to 95% B in 12.2 min, 95% B to 95% B in 14 min, 95% B to 5% B in 14.2 min, 5% B to 5% B in 16 min; Wave Length: 254 nm; Injection Volume: 0.6 mL; Number Of Runs: 11) to afford 2'-chloro-N-(5-((1r,3r)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (18.8 mg, 37.1 % yield) as a white solid and 2'-chloro-N-(5-((1s,3s)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (5.8 mg, 11.43 % yield) as a white solid.

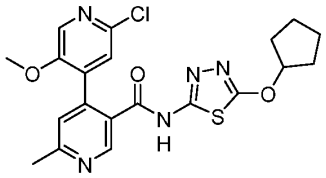
2'-chloro-N-(5-((1s,3s)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.1; found, 448.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.24 (d, J = 6.0 Hz, 1H), 4.72 (d, J = 6.0 Hz, 1H), 3.83 (d, J = 6.0 Hz, 1H), 3.63 (s, 3H), 2.82 – 2.76 (m, 2H), 2.59 (s, 3H), 2.10 – 1.96 (m, 2H).

2'-chloro-N-(5-((1r,3r)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.1; found, 448.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 5.29 – 5.25 (m, 2H), 4.39 (d, J = 6.0 Hz, 1H), 3.63 (s, 3H), 2.58 (s, 3H), 2.43 – 2.38 (m, 2H), 2.36 – 2.31 (m, 2H).

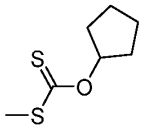
2'-chloro-N-(5-((1s,3s)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide was re-synthesized following the above procedure using (1s,3s)-3-(benzyloxy)cyclobutan-1-ol as starting material to confirm absoluye stereochemistry.

Example 17

2'-chloro-N-(5-(cyclopentyloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

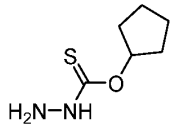


Step 1 O-cyclopentyl S-methyl carbonodithioate



To a degassed solution of cyclopentanol (500 mg, 5.80 mmol) in dry Tetrahydrofuran (THF) (2 mL) was added NaH (464 mg, 11.61 mmol) in potions at 0 °C and stirred at 25 °C for30 min. To the above solution were sequentially added CS_2 (0.525 mL, 8.71 mmol) and MeI (0.544 mL, 8.71 mmol) at 25 °C. The resulting mixture was then stirred at 25 °C for 30 min. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (3 mL) and was applied to a 20 g silica gel column that was eluted with 0~30% ethyl acetate in petroleum ether within 25 min to afford O-cyclopentyl S-methyl carbonodithioate (972 mg, 93% yield) as a colorless oil. MS (ESI) calc'd for $(C_7H_{12}OS_2)$ $(M+1)^+$,177.0, found 177.0.

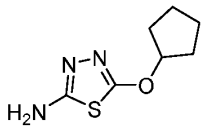
Step 2 O-cyclopentyl hydrazinecarbothioate



To a stirred solution of O-cyclopentyl S-methyl carbonodithioate (970 mg, 5.50 mmol) in Methanol (5 mL) was added N2H4·H2O (344 mg, 5.50 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The reaction mixture was quenched by the addition of

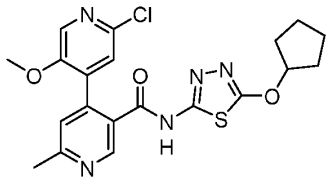
water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-cyclopentyl hydrazinecarbothioate (826 mg, crude) as a yellow oil. The crude procedure was used in the next step without further purification. MS (ESI) calc'd for ($C_6H_{12}N_2OS$) $(M+1)^+$,161.11, found 161.1.

Step 3 5-(cyclopentyloxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of O-cyclopentyl hydrazinecarbothioate (826 mg, 5.15 mmol) in Ethanol (5 mL) were added TEA (0.719 mL, 5.15 mmol) and BrCN (546 mg, 5.15 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (5 mL) and was applied to a 40 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 30 min to afford 5-(cyclopentyloxy)-1,3,4-thiadiazol-2-amine (627 mg, 44% yield) as a yellow solid. MS (ESI) calc'd for ($C_7H_{11}N_3OS$) $(M+1)^+$,185.1, found 185.1.

Step 4 2'-chloro-N-(5-(cyclopentyloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

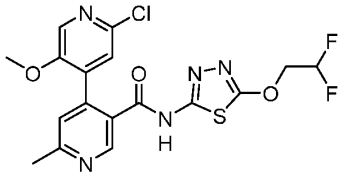


To a stirred solution of Intermediate G (301 mg, 1.080 mmol) and 5-(cyclopentyloxy)-1,3,4-thiadiazol-2-amine (200 mg, 1.080 mmol) in ACN (2 mL) and N,N-Dimethylformamide (1 mL) were added 1-methylimidazole (0.430 mL, 5.40 mmol) and TCFH (333 mg, 1.188 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. The reaction mixture (3 mL) was purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 50% B in 8 min, 50% B to 95% B in 8.2 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 11 min, 5% B; Wave

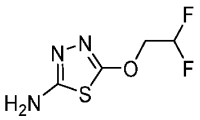
Length: 254 nm; RT1 (min): 6; Injection Volume: 0.5 mL; Number Of Runs: 5) to afford 2'-chloro-N-(5-(cyclopentyloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (51.7 mg, 10% yield) as a white solid MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_3S$) $(M+1)^+$ 446.1; found 446.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.82 (s, 1H), 8.16 (s, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 5.29 – 5.28 (m, 1H) , 3.63 (s, 3H), 2.58 – 2.51 (m, 3H), 1.99 – 1.91 (m, 2H), 1.85 – 1.82 (m, 2H), 1.72 – 1.59 (m, 4H).

Example 18

2'-chloro-N-(5-(2,2-difluoroethoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

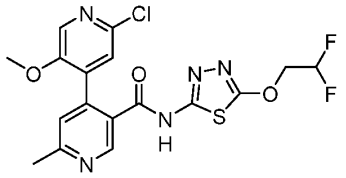


Step 1 5-(2,2-difluoroethoxy)-1,3,4-thiadiazol-2-amine



To a degassed solution of 2,2-difluoroethan-1-ol (1 g, 12.19 mmol) in dry Tetrahydrofuran (THF) (10 mL) was added sodium hydride (0.975 g, 24.38 mmol, 60%) in portions at 0 °C and stirred for 30 min under nitrogen. Then 5-bromo-1,3,4-thiadiazol-2-amine (2.63 g, 14.63 mmol) was added to the above mixture at 0 °C. The resulting solution was stirred at 0~5 °C for 30 min. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (4 mL) and was applied to a 80 g C18 column that was eluted with 5~36% acetonitrile in water within 20 min to afford5-(2,2-difluoroethoxy)-1,3,4-thiadiazol-2-amine (330 mg, 12% yield) as a white solid. MS (ESI) calculated for ($C_4H_5F_2N_3OS$) $(M+1)^+$, 182.0, found 182.1.

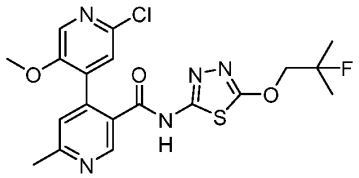
Step 2 2'-chloro-N-(5-(2,2-difluoroethoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



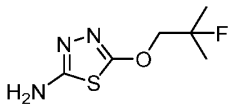
To a solution of Intermediate G (250 mg, 0.897 mmol) in Acetonitrile (3 mL) were sequentially added NMI (221 mg, 2.69 mmol), 5-(2,2-difluoroethoxy)-1,3,4-thiadiazol-2-amine (244 mg, 1.346 mmol) and TCFH (302 mg, 1.076 mmol) at 23 °C and stirred at 30 °C for 2 h. The organic solvent was removed under vacuum. The resulting residue was dissolved in DMF (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g C18 column that was eluted with 5~53% acetonitrile in water within 22 min to afford 2'-chloro-N-(5-(2,2-difluoroethoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (34.9 mg, 9% yield) as a white solid. MS (ESI) calculated for ($C_{17}H_{14}ClF_2N_5O_3S$) $(M+1)^+$, 442.0, found 442.0. ^1H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.43 (s, 1H), 6.65 – 6.25 (m, 1H), 4.85 – 4.62 (m, 2H), 3.63 (s, 3H), 2.59 (s, 3H).

Example 19

2'-chloro-N-(5-(2-fluoro-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



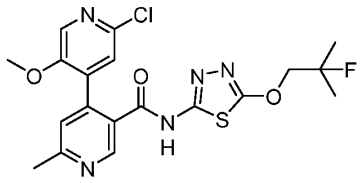
Step-1: 5-(2-fluoro-2-methylpropoxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of 2-fluoro-2-methylpropan-1-ol (600.0 mg, 6.52 mmol) in THF (10 mL) was added NaH (313.0 mg, 7.82 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 30 min under nitrogen atmosphere. Then 5-bromo-1,3,4-thiadiazol-2-amine (1.4 g, 7.82 mmol) was added to the above mixture at 0 °C. The resulting solution was stirred at 0 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL)

which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 20 min to afford 5-(2-fluoro-2-methylpropoxy)-1,3,4-thiadiazol-2-amine (150.0 mg, 25%) as a white solid. MS (ESI) calculated for ($C_6H_{10}FN_3OS$) $(M+1)^+$, 192.2; found, 192.1.

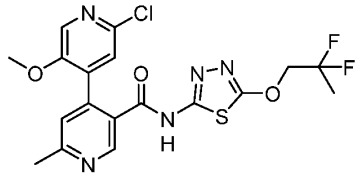
Step-2: 2'-chloro-N-(5-(2-fluoro-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



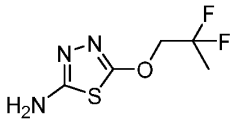
To a stirred solution of 5-(2-fluoro-2-methylpropoxy)-1,3,4-thiadiazol-2-amine (130.0 mg, 0.68 mmol) in acetonitrile (1 mL) were added Intermediate G (189.0 mg, 0.68 mmol) and 1-methylimidazole (278.8 mg, 3.40 mmol). To the above solution was added a solution of TCFH (191.0 mg, 0.68 mmol) in acetonitrile (1 mL) at 23 °C. The resulting solution was stirred at 23 °C for 1 hr. The reaction mixture (4 mL) was purified by prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH-----Preparative; Flow rate: 60 mL/min; Gradient: 50% B to 70% B in 8 min, 70% B; Wave Length: 254 nm; RT1 (min): 7.2) to afford 2'-chloro-N-(5-(2-fluoro-2-methylpropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (142.0 mg, 46%) as a white solid. MS (ESI) calculated for ($C_{19}H_{19}ClFN_5O_3S$) $(M+1)^+$, 452.1; found, 452.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 4.48 (d, J = 20.8 Hz, 2H), 3.63 (s, 3H), 2.67 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H).

Example 20

6'-chloro-N-(5-(2,2-difluoropropoxy)-1,3,4-thiadiazol-2-yl)-3'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide

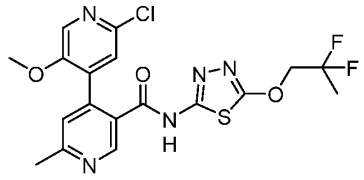


Step-1: 5-(2,2-difluoropropoxy)-1,3,4-thiadiazol-2-amine



To a degassed solution of 2,2-difluoropropan-1-ol (1.0 g, 10.41 mmol) in dry Tetrahydrofuran (10 mL) was added sodium hydride (0.8 g, 20.82 mmol) in portions at 0 °C and stirred for 30 min. Then 5-bromo-1,3,4-thiadiazol-2-amine (1.8 g, 10.41 mmol) was added to the above mixture at 0 °C. The resulting solution was stirred at 0 °C for 30 min. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (4 mL) and was applied to a 80 g C18 column, purified by Combi Flash (Biotage Isolera Prime) that was eluted with 5~36% acetonitrile in water within 20 min to afford 5-(2,2-difluoropropoxy)-1,3,4-thiadiazol-2-amine (300.0 mg, 9%) as a brown solid. MS (ESI) calc'd for ($C_5H_7F_2N_3OS$) $(M+1)^+$, 196.0, found 196.0.

Step-2: 6'-chloro-N-(5-(2,2-difluoropropoxy)-1,3,4-thiadiazol-2-yl)-3'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide

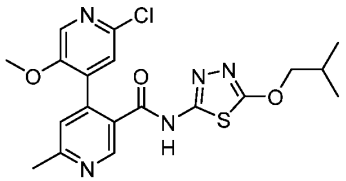


To a solution of Intermediate G (200.0 mg, 0.71 mmol) in Acetonitrile (4 mL) were sequentially added 1-methyl-1H-imidazole (206.0 mg, 2.51 mmol), 5-(2,2-difluoropropoxy)-1,3,4-thiadiazol-2-amine (140.0 mg, 0.71 mmol)) and TCFH (201.0 mg, 0.71 mmol) at 20 °C. The mixture was stirred at 30 °C for 16 h. The organic solvent was removed under vacuum. The residue was dissolved in DMF (2 mL) and purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 * 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH --HPLC; Flow rate: 60 mL/min; Gradient: 44 % B to 58 % B in 8 min, 58 % B to 95 % B in 8.2 min, 95 % B to 95 % B in 9.5 min, 95 % B to 2 % B in 11 min, 2 % B; Wave Length: 254 nm; RT1(min): 7; Injection Volume: 0.7 mL; Number Of Runs: 3) to afford 2'-chloro-N-(5-(2,2-difluoropropoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (24.7 mg, 7%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{16}ClF_2N_5O_3S$) $(M+1)^+$, 456.0, found 456.0. ^1H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.82 (s, 1H),

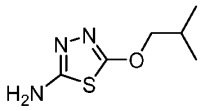
8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.74 (t, J = 12.8 Hz, 2H), 3.63 (s, 3H), 2.59 (s, 3H), 1.74 (t, J = 19.2 Hz, 3H).

Example 21

2'-chloro-N-(5-isobutoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

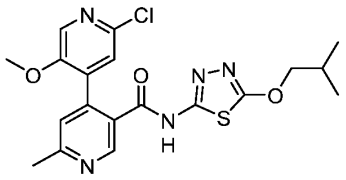


Step-1: 5-isobutoxy-1,3,4-thiadiazol-2-amine



To a degassed solution of 2-methylpropan-1-ol (1.0 g, 13.49 mmol) and in dry Tetrahydrofuran (10 mL) was added NaH (540.0 mg, 13.49 mmol, 60%) in potions at 0 °C. The resulting solution was stirred at 0 °C for 40 min. To the above solution was added 5-bromo-1,3,4-thiadiazol-2-amine (2.4 g, 13.49 mmol) at 0 °C. The resulting mixture was then stirred at 0 °C for 1 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which was applied to a 40 g silica gel column that was eluted with 0~40% ethyl acetate in petroleum ether within 30 min to afford 5-isobutoxy-1,3,4-thiadiazol-2-amine (25.0 mg, 1%) as a white solid. MS (ESI) calc'd for ($C_6H_{11}N_3OS$) $(M+1)^+$, 174.1; found, 174.0.

Step-2: 2'-chloro-N-(5-isobutoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

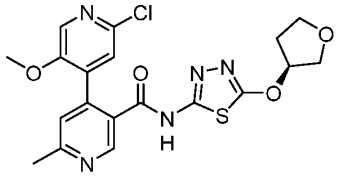
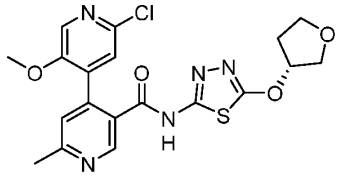


To a mixture of Intermediate G (40.0 mg, 0.14 mmol) in Acetonitrile (3 mL) were added 5-isobutoxy-1,3,4-thiadiazol-2-amine (24.0 mg, 0.14 mmol) and 1-methyl-1H-imidazole (58.0

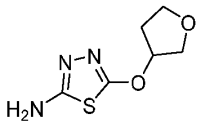
mg, 0.71 mmol). A solution of TCFH (60.0 mg, 0.21 mmol) in Acetonitrile (1 mL) was added thereto dropwise. The mixture was stirred at 30 °C for 16 hr. The solvents were removed under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 40 min to afford 2'-chloro-N-(5-isobutoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (21.1 mg, 45%) as a white solid. MS (ESI) calc'd for ($C_{19}H_{20}ClN_5O_3S$) $(M+1)^+$, 434.1, found 434.0. ^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.21 (d, J = 6.4 Hz, 2H), 3.64 (s, 3H), 2.59 (s, 3H), 2.15 – 2.03 (m, J = 6.8 Hz, 1H), 0.97 (d, J = 6.4 Hz, 6H).

Example 22 and 23

(S)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide and (R)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

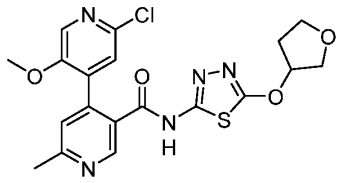
Step 1 5-((tetrahydrofuran-3-yl) oxy)-1,3,4-thiadiazol-2-amine



To a degassed solution of tetrahydrofuran-3-ol (1.0 g, 11.35 mmol) in dry Tetrahydrofuran (20 mL) in portions at 0 °C and stirred at 0 °C for 30 min. To the above mixture was added 5-bromo-1,3,4-thiadiazol-2-amine (2.0 g, 11.35 mmol) at 0 °C. The resulting solution was stirred at 23 °C for 1 h under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2.5 mL), applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~30% acetonitrile in water within 30 min to afford 5-((tetrahydrofuran-3-yl) oxy)-1,3,4-thiadiazol-2-amine (80.0 mg, 3%) as a yellow solid. MS (ESI) calc'd for ($C_6H_9N_3O_2S$) $(M+1)^+$, 188.1, found 188.2.

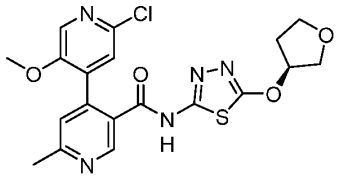
Step 2 2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-

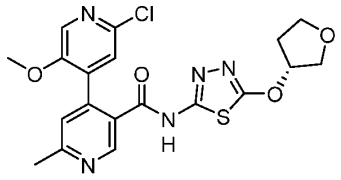
yl)-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 5-((tetrahydrofuran-3-yl) oxy)-1,3,4-thiadiazol-2-amine (80.0 mg, 0.43 mmol) in N,N-Dimethylformamide (1 mL) and acetonitrile (1 mL) were added Intermediate G (119.0 mg, 0.43 mmol) and 1-methylimidazole (175.0 mg, 2.13 mmol). To the above mixture was added a solution of TCFH (132.0 mg, 0.47 mmol) in acetonitrile (1 mL) at 23 °C. The resulting solution was stirred at 23 °C for 1 h. The resulting mixture was dissolved in DMF (3 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 * 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17 % B to 35 % B in 8 min, 35 % B to 95 % B in 8.2 min, 95 % B to 95 % B in 9.5 min, 95 % B to 5 % B in 11 min, 5 % B; Wave Length: 254 nm; RT1(min): 7.3; Injection Volume: 0.5 mL; Number Of Runs: 8) to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (100.0 mg, 49%) as a white solid. MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.0, found 448.0.

Step 3 (S)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide and (R)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide





The racemic compound (99.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRAL ART Cellulose-SC, 2 * 25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 50 % B to 50 % B in 15.5 min; Wave Length: 220/254 nm; RT1(min): 9.82; RT2(min): 13.73; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 1 mL; Number Of Runs: 8) to afford (S)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (24.3 mg, 24%) as a white solid with retention time at 9.82

minute and (R)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (20.9 mg, 21%) as a white solid with retention time at 13.73 minute.

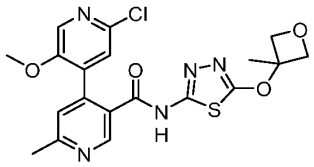
(S)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.0, found 448.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.89 (s, 1H), 8.14 (s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 5.44 (s, 1H), 3.91 – 3.81 (m, 3H), 3.81 – 3.70 (m, 1H), 3.63 (s, 3H), 2.56 (s, 3H), 2.28 – 2.20 (m, 1H), 2.13 – 2.05 (m, 1H).

(R)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.0, found 448.0. 1H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.83 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 5.49 (s, 1H), 3.91 – 3.81 (m, 3H), 3.81 – 3.72 (m, 1H), 3.64 (s, 3H), 2.58 (s, 3H), 2.34 – 2.20 (m, 1H), 2.20 – 2.11 (m, 1H).

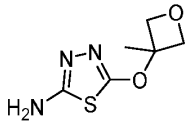
(R)-2'-chloro-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide was re-synthesized using the above procedure with (R)-tetrahydrofuran-3-ol as starting material to confirm absolute stereochemistry.

Example 24

2'-chloro-5'-methoxy-6-methyl-N-(5-((3-methyloxetan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



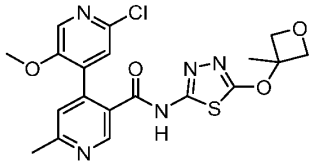
Step-1: 5-((3-methyloxetan-3-yl)oxy)-1,3,4-thiadiazol-2-amine



To a degassed solution of 3-methyloxetan-3-ol (500.0 mg, 5.67 mmol) in dry tetrahydrofuran (10 mL) was added sodium hydride (340.0 mg, 8.51 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 1 h under nitrogen atmosphere. Then 5-bromo-1,3,4-thiadiazol-2-amine (1.0 g, 5.67 mmol) was added to the above mixture at 0 °C. The mixture was stirred at room temperature for 2 h. The resulting mixture was quenched with water and extracted with ethyl

acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 0~90% ethyl acetate in petroleum ether within 40 min to afford 5-((3-methyloxetan-3-yl)oxy)-1,3,4-thiadiazol-2-amine (35.0 mg, 1 %) as a yellow oil. MS (ESI) calc'd for ($C_6H_9N_3O_2S$) $(M+1)^+$, 188.0; found 188.0.

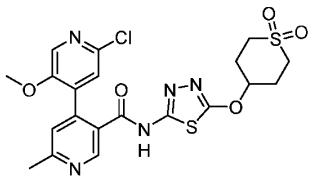
Step-2: 2'-chloro-5'-methoxy-6-methyl-N-(5-((3-methyloxetan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



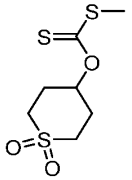
To a stirred solution of 5-((3-methyloxetan-3-yl)oxy)-1,3,4-thiadiazol-2-amine (60.0 mg, 0.32 mmol) and Intermediate G (93.0 mg, 0.35 mmol) in acetonitrile (1.5 mL) were sequentially added 1-methylimidazole (131.2 mg, 1.60 mmol) and TCFH (90.0 mg, 0.32 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 2 h under nitrogen. The resulting residue was dissolved in acetonitrile (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 544% acetonitrile in water within 25 min and further purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 30% B in 8 min, 30% B; Wave Length: 254 nm; RT1 (min): 7.85) to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-((3-methyloxetan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (30.0 mg, 20%) as a white solid. MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.1; found 448.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 4.80 (d, J = 7.2 Hz, 2H), 4.55 (d, J = 7.2 Hz, 2H), 3.64 (s, 3H), 2.59 (s, 3H), 1.80 (s, 3H).

Example 25

2'-chloro-N-(5-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

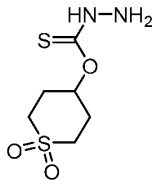


Step 1 O-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl) S-methyl carbonodithioate



To a degassed solution of 4-hydroxytetrahydro-2H-thiopyran 1,1-dioxide (300.0 mg, 2.00 mmol) in dry Tetrahydrofuran (THF) (6 mL) was added NaH (160.0 mg, 4.00 mmol, 60%) in portions at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 30 min. To the above solution was added CS_2 (228.0 mg, 3.0 mmol) at 0 °C under nitrogen. The resulting solution was then stirred at 0 °C for 20 min. To the above solution was added MeI (426.0 mg, 3.0 mmol) at 0 °C under nitrogen. The resulting mixture was then stirred at 23 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 20 g silica gel column that was eluted with 0~40% ethyl acetate in petroleum ether within 30 min to afford O-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl) S-methyl carbonodithioate (370.0 mg, 76%) as a white solid MS (ESI) calculated for ($C_7H_{12}O_3S_3$) $(M+1)^+$, 241.0; found, 241.0.

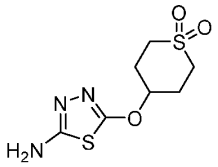
Step 2 O-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl) hydrazinecarbothioate



To a stirred solution of O-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl) S-methyl carbonodithioate (350.0 mg, 1.46 mmol) in Methanol (5 mL) was added Hydrazinium hydroxide solution (58.0 mg, 1.46 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 1 h. The resulting mixture was concentrated under vacuum to afford O-(1,1-

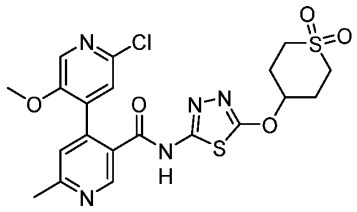
dioxidotetrahydro-2H-thiopyran-4-yl) hydrazinecarbothioate (322.0 mg, crude) as a yellow solid. MS (ESI) calculated for ($C_6H_{12}N_2O_3S_2$) $(M+1)^+$, 225.0; found, 225.0.

Step 3 4-((5-amino-1,3,4-thiadiazol-2-yl)oxy)tetrahydro-2H-thiopyran 1,1-dioxide



To a stirred solution of O-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl) hydrazinecarbothioate (322.0 mg, 1.44 mmol) in Methanol (3 mL) were sequentially added TEA (436.3 mg, 4.32 mmol) and cyanic bromide (167.0 mg, 1.58 mmol) at 0 °C. The resulting solution was stirred at 23 °C for 2 hours. The reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum afford 4-((5-amino-1,3,4-thiadiazol-2-yl)oxy)tetrahydro-2H-thiopyran 1,1-dioxide (230.0 mg, 46%) as an yellow solid MS (ESI) calculated for ($C_7H_{11}N_3O_3S_2$) $(M+1)^+$, 250.0; found, 250.0.

Step 4 2'-chloro-N-(5-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

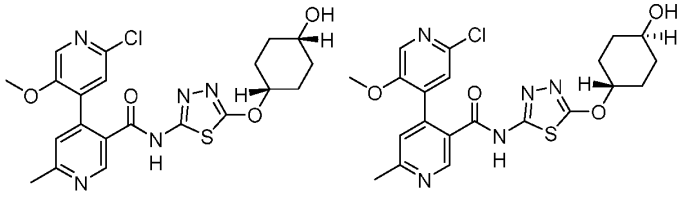


To a stirred solution of 4-((5-amino-1,3,4-thiadiazol-2-yl)oxy)tetrahydro-2H-thiopyran 1,1-dioxide (190.0 mg, 0.76 mmol) and Intermediate G (234.0 mg, 0.84 mmol) in acetonitrile (0.5 mL) were sequentially added 1-methylimidazole (0.3 mL) and TCFH (214.0 mg, 0.76 mmol) in acetonitrile (0.2 mL) at 23 °C under nitrogen. The resulting solution was stirred at 23 °C for 2 hours. The mixture was dissolved in acetonitrile (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 30 min to afford a off-white solid (88% purity). The product was dissolved in DMF (3 mL) and was further purified by prep-HPLC with the following conditions: (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water(0.05% TFA), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient:

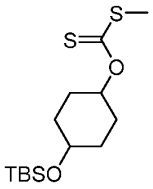
53% B to 68% B in 10 min, 68% B to 95% B in 10.2 min, 95% B to 95% B in 12 min, 95% B to 5% B in 12.2 min, 5% B to 5% B in 14 min; Wave Length: 254 nm; RT1(min): 8; Injection Volume: 0.7 mL; Number Of Runs: 4) to afford 2'-chloro-N-(5-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (100.0 mg, 25%) as a white solid. MS (ESI) calculated for ($C_{20}H_{20}ClN_5O_5S_2$) $(M+1)^+$, 510.1; found, 510.2. ^1H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.15 (s, 1H), 7.65 – 7.48(m, 2H), 5.25 – 5.15 (m, 1H), 3.62 (s, 3H), 3.29 – 3.10 (m, 4H), 2.63 (s, 3H), 2.44 – 2.26 (m, 4H).

Example 26 and 27

2'-chloro-N-(5-(((1s,4s)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide and 2'-chloro-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide



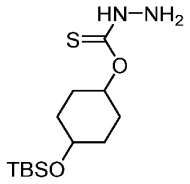
Step 1 O-(4-((tert-butyldimethylsilyl)oxy)cyclohexyl) S-methyl carbonodithioate



To a degassed solution of 4-((tert-butyldimethylsilyl)oxy)cyclohexan-1-ol (550.0 mg, 2.39 mmol) in dry tetrahydrofuran (4 mL) was added NaH (191.0 mg, 4.77 mmol, 60%) at 0 °C and stirred at 0 °C for 30 min under nitrogen atmosphere. Then CS_2 (0.2 mL, 3.58 mmol) was added to the above mixture at 0 °C and stirred at 0 °C for 20 min. To the above solution was added MeI (0.2 mL, 3.58 mmol) at 0 °C under nitrogen. The resulting mixture was then stirred at 0 °C for 1 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which

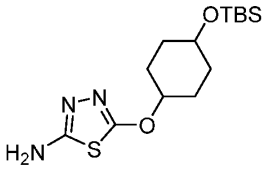
applied to a 40 g silica gel column that was eluted with 0~20% ethyl acetate in petroleum ether within 20 min to afford O-(4-((tert-butyldimethylsilyl)oxy)cyclohexyl) S-methyl carbonodithioate (711.0 mg, 74% yield) as a yellow oil.

Step 2 O-(4-((tert-butyldimethylsilyl)oxy)cyclohexyl) hydrazinecarbothioate



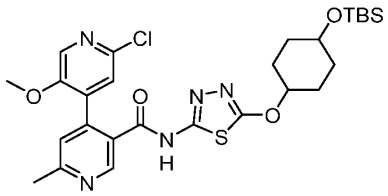
To a stirred solution of O-(4-((tert-butyldimethylsilyl)oxy)cyclohexyl) S-methyl carbonodithioate (710.0 mg, 2.22 mmol) in methanol (4 mL) was added hydrazine (0.1 mL, 2.22 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 30 min. The volatiles were removed under vacuum to afford O-(4-((tert-butyldimethylsilyl)oxy)cyclohexyl) hydrazinecarbothioate (670.0 mg, crude) as a light yellow oil. MS (ESI) calculated for ($C_{13}H_{28}N_2O_2SSi$) $(M+1)^+$, 305.0; found, 305.3.

Step 3 5-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)oxy)-1,3,4-thiadiazol-2-amine



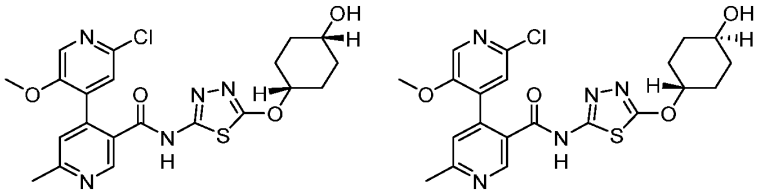
To a stirred solution of O-(4-((tert-butyldimethylsilyl)oxy)cyclohexyl) hydrazinecarbothioate (730.0 mg, 2.40 mmol) in methanol (3 mL) were sequentially added TEA (0.7 mL, 4.79 mmol) and BrCN (279.0 mg, 2.64 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 1 hr. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 40 min to afford 5-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)oxy)-1,3,4-thiadiazol-2-amine (290.0 mg, 33%) as a white solid. MS (ESI) calculated for ($C_{14}H_{27}N_3O_2SSi$) $(M+1)^+$, 330.0; found, 659.5.

Step 4 N-(5-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 5-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)oxy)-1,3,4-thiadiazol-2-amine (290.0 mg, 0.88 mmol) in acetonitrile (5 mL) were sequentially added Intermediate G (270.0 mg, 0.97 mmol), 1-Methylimidazole (361.0 mg, 4.40 mmol). Then a solution of TCFH (247.0 mg, 0.88 mmol) in acetonitrile (1 mL) was added to the above mixture at 20 °C. The resulting solution was stirred at 20 °C for 16 hr. The volatiles were removed under vacuum. The resulting residue was dissolved in DMF (4 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 40 min to afford N-(5-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (400.0 mg, 75 %) as a white solid. MS (ESI) calculated for ($C_{27}H_{36}ClN_5O_4SSi$) $(M+1)^+$, 590.0; found, 590.4.

Step 5 2'-chloro-N-(5-(((1s,4s)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide, and 2'-chloro-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide



To a mixture of N-(5-((4-((tert-butyldimethylsilyl)oxy)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (400.0 mg, 0.68 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.4 mL). The mixture was stirred at 20 °C for 30 min. The organic solvent was removed under vacuum. The residue was diluted with water. The aqueous layer was basified with $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 25~90% acetonitrile in water within 45 min to afford 2'-chloro-N-

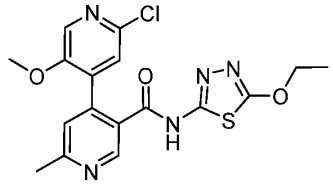
(5-((4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (204.0 mg, 63%) as a white solid. The mixture of compounds (204.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 14 mL/min; Gradient: 80% B to 80% B in 29 min; Wave Length: 220/254 nm; RT1(min): 16.46; RT2(min): 20.27; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.5 mL; Number Of Runs: 8) to afford 2'-chloro-N-(5-(((1s,4s)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide, (45.6 mg, 22%) as a white solid with the first peak on chiral HPLC and 2'-chloro-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (98.5 mg, 48%) as a white solid with the second peak on chiral HPLC. The absolute stereochemistry was not determined and was arbitrarily assigned.

2'-chloro-N-(5-(((1s,4s)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide: MS (ESI) calculated for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.0; found, 476.2, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.93 – 4.90 (m, 1H), 4.55 – 4.54 (m, 1H), 3.63 – 3.59 (m, 4H), 2.58 (s, 3H), 1.99 – 1.91 (m, 4H), 1.75 – 1.72 (m, 4H).

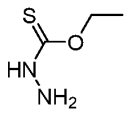
2'-chloro-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide: MS (ESI) calculated for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.0; found, 476.2, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.81 (s, 1H), 8.16 (s, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 4.89 – 4.82 (m, 1H), 4.61 – 4.60 (m, 1H), 3.63 (s, 3H), 3.62 – 3.45 (m, 1H), 2.59 (s, 3H), 2.14 – 2.08 (m, 2H), 1.86 – 1.82 (m, 2H), 1.60 – 1.50 (m, 2H), 1.38 – 1.24 (m, 2H).

Example 28

2'-chloro-N-(5-ethoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

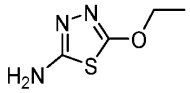


Step-1: O-ethyl hydrazinecarbothioate



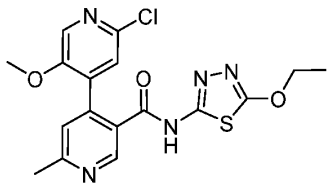
A mixture of potassium O-ethyl carbonodithioate (2.0 g, 12.48 mmol) and Hydrazine hydrate (0.8 g, 12.48 mmol) in Methanol (20 mL) were stirred at 20 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-ethyl hydrazinecarbothioate (1.4 g, crude) as a yellow oil. MS (ESI) calc'd for ($C_3H_8N_2OS$) $(M+1)^+$, 121.0, found 121.0.

Step-2: 5-ethoxy-1,3,4-thiadiazol-2-amine



To a mixture of O-ethyl hydrazinecarbothioate (1.4 g, 9.32 mmol) in Methanol (10 mL) were added NaOH (0.8 g, 18.64 mmol) and cyanic bromide (1.1 g, 10.25 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 30 min. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in DMF (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 column, eluted with 5~40% acetonitrile in water within 45 min to afford 5-ethoxy-1,3,4-thiadiazol-2-amine (280 mg, 10 %) as a red solid. MS (ESI) calc'd for ($C_4H_7N_3OS$) $(M+1)^+$, 146.0, found 146.0.

Step-3: 2'-chloro-N-(5-ethoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

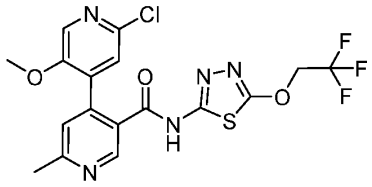


To a mixture of 5-ethoxy-1,3,4-thiadiazol-2-amine (268.0 mg, 0.92 mmol) in acetonitrile (2 mL) were added Intermediate G (260.0 mg, 0.84 mmol), and NMI (344.0 mg, 4.20 mmol). A solution of TCFH (259.0 mg, 0.92 mmol) in acetonitrile (1 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The resulting mixture was dissolved in DMF (6 mL) and was purified by Prep-HPLC with the following

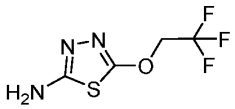
conditions: (Column: XBridge Shield RP18 OBD Column, 30 * 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25 % B to 40 % B in 8 min, 40% B to 95 % B in 8.2 min, 95 % B to 95 % B in 9.5 min, 95 % B to 5 % B in 11 min, 5% B; Wave Length: 254 nm; RT1 (min): 7.5; Injection Volume: 1 mL; Number Of Runs: 6) to afford 2'-chloro-N-(5-ethoxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (144.3 mg, 42%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{16}ClN_5O_3S$) $(M+1)^+$, 406.0, found 406.0. ^1H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 8.83 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 4.48 – 4.42 (m, 2H), 3.63 (s, 3H), 2.58 (s, 3H), 1.37 (t, J = 8.0 Hz, 3H).

Example 29

2'-chloro-5'-methoxy-6-methyl-N-(5-(2,2,2-trifluoroethoxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

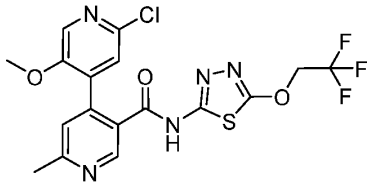


Step-1: 5-(2,2,2-trifluoroethoxy)-1,3,4-thiadiazol-2-amine



To a solution of 2,2,2-trifluoroethan-1-ol (1.0 g, 10.00 mmol) in Tetrahydrofuran (30 mL) was added NaH (0.80 g, 19.99 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 1 hr. To the above solution was added 5-bromo-1,3,4-thiadiazol-2-amine (1.8 g, 10.00 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the crude (1.3 g, crude) as a grey solid. The resulting residue was dissolved in DMF (8 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5 ~ 23% acetonitrile in water within 39 min to afford 5-(2,2,2-trifluoroethoxy)-1,3,4-thiadiazol-2-amine (583.0 mg, 25%) as a grey solid. MS (ESI) calc'd for ($C_4H_4F_3N_3OS$) $(M+1)^+$, 200.0, found 200.0.

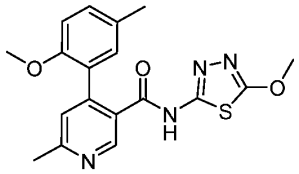
Step-2: 2'-chloro-5'-methoxy-6-methyl-N-(5-(2,2,2-trifluoroethoxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



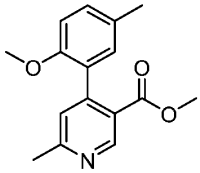
To a mixture of Intermediate G (100.0 mg, 0.35 mmol) in Acetonitrile (2 mL) were added 5-(2,2,2-trifluoroethoxy)-1,3,4-thiadiazol-2-amine (100.0 mg, 0.423 mmol) and 1-methyl-1H-imidazole (87.0 mg, 1.05 mmol). A solution of TCFH (148.0 mg, 0.52 mmol) in Acetonitrile (1 mL) was added thereto dropwise under nitrogen. The resulting solution was stirred at 20 °C for 2 hr under nitrogen. The resulting mixture was purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g C18 columm that was eluted with 5~54 % acetonitrile in water within 45 min to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-(2,2,2-trifluoroethoxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (60.7 mg, 36%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{13}ClF_3N_5O_3S$) $(M+1)^+$, 460.0, found 460.0. ^1H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.16 – 5.22 (m, 2H), 3.63 (s, 3H), 2.60 (s, 3H).

Example 30

N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxy-5-methylphenyl)-6-methylnicotinamide



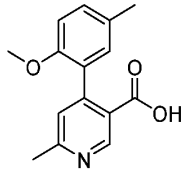
Step-1: methyl 4-(2-methoxy-5-methylphenyl)-6-methylpyridine-3-carboxylate



A degassed mixture of methyl 4-chloro-6-methylpyridine-3-carboxylate (500.0 mg, 2.69 mmol), 2-methoxy-5-methylphenylboronic acid (894.2 mg, 5.388 mmol), $Pd(dppf)Cl_2$ (394.21 mg, 0.53 mmol), Potassium carbonate (744.6 mg, 5.38 mmol) in dioxane (10.0 mL) and Water (1.0 mL) was stirred at 110 °C for 2 h under nitrogen. The solvent was removed under vacuum. The residue was purified by flash column chromatography with 0~44% ethyl acetate in petroleum ether to afford methyl 4-(2-methoxy-5-methylphenyl)-6-methylpyridine-

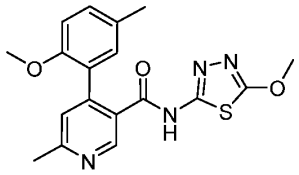
3-carboxylate (800.0 mg, 57%) as a yellow oil. MS (ESI) calc'd for (C16H17NO3) (M+1)+, 272.1, found 272.1.

Step-2: 4-(2-methoxy-5-methylphenyl)-6-methylpyridine-3-carboxylic acid



A mixture of methyl 4-(2-methoxy-5-methylphenyl)-6-methylpyridine-3-carboxylate (700.0 mg, 2.58 mmol), NaOH (309.5 mg, 7.74 mmol) in THF (10.0 mL) and Water (3.0 mL) was stirred at room temperature for 16 h. The reaction mixture was acidified with HCl (1 N) to pH ~ 4. The aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford 4-(2-methoxy-5-methylphenyl)-6-methylpyridine-3-carboxylic acid (550.0 mg, crude) as a yellow oil. MS (ESI) calc'd for (C15H15NO3) (M+1)+, 258.1, found 258.4.

Step-3: N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxy-5-methylphenyl)-6-methylnicotinamide

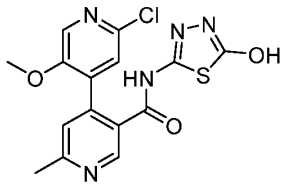


To a stirred solution of 4-(2-methoxy-5-methylphenyl)-6-methylnicotinic acid (100.0 mg, 0.39 mmol) in Acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (51.1 mg, 0.39 mmol) and 1-methylimidazole (160.0 mg, 1.94 mmol) at 23 oC. To the above solution was added a solution of TCFH (109.6 mg, 0.39 mmol) in Acetonitrile (1 mL) at 23 oC under nitrogen. The resulting mixture was then stirred at 23 oC for 2 hr under nitrogen. The mixture was diluted with DMF (2 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 43% B in 8 min, 43% B to 95% B in 8.2 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 254 nm; RT1(min): 7.4; Injection Volume: 0.5 mL; Number Of Runs: 5) to afford N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxy-5-methylphenyl)-6-methylnicotinamide (72.6 mg, 50%) as a white solid. MS (ESI) calc'd for (C18H18N4O3S)

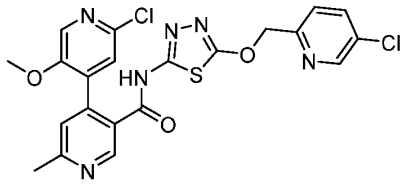
(M+1)+, 371.1; found, 371.1. 1H NMR (400 MHz, DMSO-d6) δ 12.69 (s, 1H), 8.65 (s, 1H), 7.29 (s, 1H), 7.26 – 7.15 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 4.06 (s, 3H), 3.46 (s, 3H), 2.56 (s, 3H), 2.31 (s, 3H).

Example 31

2'-chloro-N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

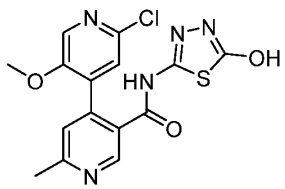


Step-1: 2'-chloro-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a solution of Intermediate G (300.0 mg, 1.08 mmol) in Acetonitrile (2 mL) were added Intermediate B (261.1 mg, 1.08 mmol) and 1-methylimidazole (441.2 mg, 5.38 mmol) at 20 °C under nitrogen. To the above solution was added a solution of TCFH (301.5 mg, 1.08 mmol) in Acetonitrile (2 mL) at 20 °C under nitrogen. The resulting mixture was then stirred at 20 °C for 1 hr. The mixture was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~55% acetonitrile in water within 30 min to afford 2'-chloro-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (372.0 mg, 63%) as a white solid. MS (ESI) calc'd for ($C_{21}H_{16}Cl_2N_6O_3S$) $(M+1)^+$, 503.1; found, 503.1.

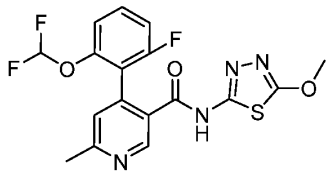
Step-2: 2'-chloro-N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



A solution of 2'-chloro-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (320.0 mg, 0.64 mmol) in concentrated hydrochloric acid (1 mL) was stirred at 20 °C for 1 hr. The mixture was diluted with water. The aqueous layer was neutralized with $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 25 min to afford 2'-chloro-N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (61.4 mg, 25% yield) as a white solid. MS (ESI) calc'd for $(C_{15}H_{12}ClN_5O_3S)$ $(M+1)^+$, 378.1 found 378.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.35 – 12.30 (m, 2H), 8.75 (s, 1H), 8.20 (s, 1H), 7.52 (s, 1H), 7.47 (s, 1H), 3.72 (s, 3H), 2.58 (s, 3H).

Example 32

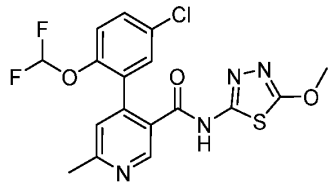
4-(2-(difluoromethoxy)-6-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



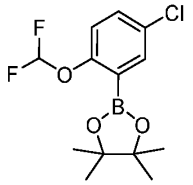
A mixture of Intermediate D (65.0 mg, 0.19 mmol) in Acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (28.4 mg, 0.21 mmol) and NMI (81.0 mg, 0.98 mmol). A solution of TCFH (60.6 mg, 0.21 mmol) in Acetonitrile (0.5 mL) was added thereto dropwise under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The resulting mixture was dissolved in DMF (2 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 * 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25 % B to 38 % B in 8 min, 38 % B to 95 % B in 8.2 min, 95 % B to 95 % B in 9.5 min, 95 % B to 5% B in 11 min, 5 % B; Wave Length: 254 nm; RT1(min): 7.67; Injection Volume: 0.7 mL; Number Of Runs: 3) to afford 4-(2-(difluoromethoxy)-6-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (54.4 mg, 67%) as a white solid, MS (ESI) calc'd for $(C_{17}H_{13}F_3N_4O_3S)$ $(M+1)^+$, 411.0, found 411.1. ^1H NMR (400 MHz, Methanol-d_4) δ 8.98 (s, 1H), 7.49 – 7.43 (m, 1H), 7.32 (s, 1H), 7.14 – 7.05 (m, 2H), 6.92 – 6.55 (m, 1H), 4.08 (s, 3H), 2.65 (s, 3H).

Example 33

4-(5-chloro-2-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

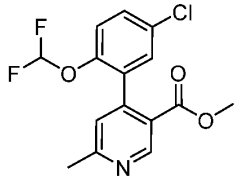


Step-1: 2-(5-chloro-2-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a stirred solution of 2-bromo-4-chloro-1-(difluoromethoxy)benzene (1.0 g, 3.88 mmol) in 1,4-Dioxane (10 mL) were sequentially added potassium acetate (1.1 g, 11.65 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.2 g, 4.66 mmol) and PdCl2(dppf) (280.0 mg, 0.39 mmol) at 25 oC. The resulting solution was stirred at 80 oC for 16 hr under nitrogen. The solvents were removed under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 0~25% ethyl acetate in petroleum ether within 30 min to afford 2-(5-chloro-2-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (800.0 mg, 67%) as a brown solid. MS (ESI) calc'd for (C13H16BClF2O3) (M+1)+, 305.0, found 305.1.

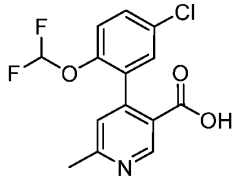
Step-2: methyl 4-(5-chloro-2-(difluoromethoxy)phenyl)-6-methylnicotinate



To a stirred solution of 2-(5-chloro-2-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (800.0 mg, 2.63 mmol) in 1,4-Dioxane (10 mL) and Water (0.5 mL) were sequentially added K2CO3 (1.1 g, 7.88 mmol), PdCl2(dppf) (192.0 mg, 0.26 mmol) and methyl 4-chloro-6-methylnicotinate (683.0 mg, 3.68 mmol) at 25 oC. The resulting solution was stirred at 80 oC for 2 hr under nitrogen. The mixture was diluted with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed

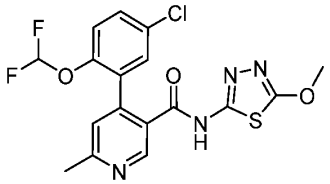
with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 0~80% ethyl acetate in petroleum ether within 30 min to afford methyl 4-(5-chloro-2-(difluoromethoxy)phenyl)-6-methylnicotinate (1.2 g, 98%) as white solid. MS (ESI) calc'd for (C15H12ClF2NO3) (M+1)+, 328.0, found 328.1.

Step-3: 4-(5-chloro-2-(difluoromethoxy)phenyl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(5-chloro-2-(difluoromethoxy)phenyl)-6-methylnicotinate (1.2 g, 3.66 mmol) in Tetrahydrofuran (10 mL) and Water (5 mL) was added lithium hydroxide (87.8 mg, 3.66 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with 2 N HCl to pH ~4 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(5-chloro-2-(difluoromethoxy)phenyl)-6-methylnicotinic acid (900 mg, crude) as a light-yellow oil. MS (ESI) calc'd for (C14H10ClF2NO3) (M+1)+, 314.0, found 314.0.

Step-4: 4-(5-chloro-2-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

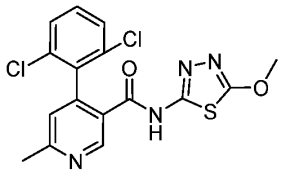


To a stirred solution of 4-(5-chloro-2-(difluoromethoxy)phenyl)-6-methylnicotinic acid (200.0 mg, 0.57 mmol) in Acetonitrile (2 mL) were sequentially added 1-methyl-1H-imidazole (236 mg, 2.87 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (77.1 mg, 0.57 mmol) at 25 °C. To the above solution was added a solution of TCFH (161.0 mg, 0.57 mmol) at 25 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 2 hr. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~100% acetonitrile in water within 40 min to afford 4-(5-chloro-2-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-

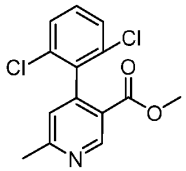
6-methylnicotinamide (52.0 mg, 21%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{13}ClF_2N_4O_3S$) $(M+1)^+$, 427.0, found 427.0. ^1H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.85 (s, 1H), 7.60 – 7.51 (m, 2H), 7.38 (s, 1H), 7.31 – 7.21 (m, 1H), 7.04 – 6.82 (m, 1H), 4.07 (s, 3H), 2.59 (s, 3H).

Example 34

4-(2,6-dichlorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

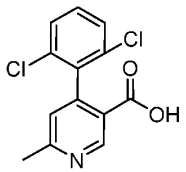


Step-1: methyl 4-(2,6-dichlorophenyl)-6-methylnicotinate



To a stirred solution of methyl 4-chloro-6-methylnicotinate (500.0 mg, 2.69 mmol) and (2,6-dichlorophenyl)boronic acid (1.0 g, 5.39 mmol) in Toluene (5 mL) were sequentially added tris(dibenzylideneacetone)dipalladium(0) (247.0 mg, 0.27 mmol) and K_2CO_3 (1.1 g, 8.08 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 16 hr under nitrogen atmosphere. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~20% ethyl acetate in petroleum ether within 30 min to afford methyl 4-(2,6-dichlorophenyl)-6-methylnicotinate (498.0 mg, 61%) as a yellow solid. MS (ESI) calculated for ($C_{14}H_{11}Cl_2NO_2$) $(M+1)^+$, 296.0; found, 296.0.

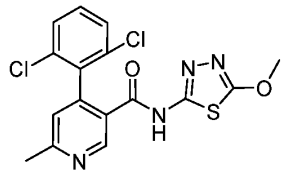
Step-2: 4-(2,6-dichlorophenyl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(2,6-dichlorophenyl)-6-methylnicotinate (490.0 mg, 1.66 mmol) in Methanol (3 mL) was added sodium hydroxide (265.0 mg, 6.62 mmol) in water (3 mL) at 20 °C. The resulting solution was stirred at 80 °C for 30 min. The organic solvent was

removed under vacuum. The aqueous layer was acidified with citric acid to pH 5~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(2,6-dichlorophenyl)-6-methylnicotinic acid (430.0 mg, crude) as a yellow solid. MS (ESI) calculated for ($C_{13}H_9Cl_2NO_2$) $(M+1)^+$, 282.0; found, 282.0.

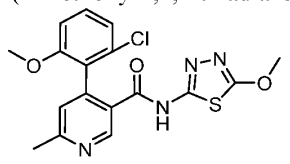
Step-3: 4-(2,6-dichlorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



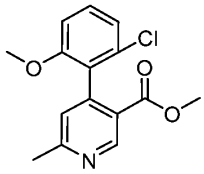
To a stirred solution of 4-(2,6-dichlorophenyl)-6-methylnicotinic acid (300.0 mg, 1.06 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (139.0 mg, 1.06 mmol) in acetonitrile (3 mL) was added 1-methylimidazole (437.0 mg, 5.32 mmol). To the above solution was added a solution of TCFH (298.0 mg, 1.06 mmol) in acetonitrile at 20 °C under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The resulting mixture was dissolved in DMF (3 mL) and was purified by prep-HPLC with the following conditions: (Column: Atlantis HILIC OBD Column, 19*150 mm*5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 48% B in 8 min, 48% B; Wave Length: 254 nm; RT1 (min): 7.8) to afford 4-(2,6-dichlorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (29.1 mg, 7% yield) as a white solid. MS (ESI) calculated for ($C_{16}H_{12}Cl_2N_4O_2S$) $(M+1)^+$, 395.0; found, 395.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 9.04 (s, 1H), 7.65 – 7.55 (m, 2H), 7.48 – 7.40 (m, 1H), 7.33 – 7.20 (m, 1H), 4.06 (s, 3H), 2.61 (s, 3H).

Example 35

4-(2-chloro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

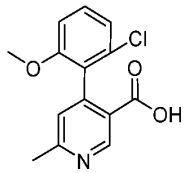


Step-1: methyl 4-(2-chloro-6-methoxyphenyl)-6-methylnicotinate



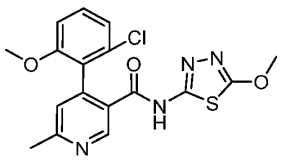
To a stirred solution of methyl 4-chloro-6-methylnicotinate (500.0 mg, 2.69 mmol) in 1,4-Dioxane (5 mL) were sequentially added water (1.0 mL), K_2CO_3 (1.1 g, 8.08 mmol) and $Pd(dppf)Cl_2$ (220.0 mg, 0.27 mmol) at 17 °C. The resulting solution was stirred at 80 °C for 1 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 35 min to afford methyl 4-(2-chloro-6-methoxyphenyl)-6-methylnicotinate (635.0 mg, 80%) as a yellow oil. MS (ESI) calculated for ($C_{15}H_{14}ClNO_3$) $(M+1)^+$, 292.0; found, 292.2.

Step-2: 4-(2-chloro-6-methoxyphenyl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(2-chloro-6-methoxyphenyl)-6-methylnicotinate (635.0 mg, 2.18 mmol) in methanol (4 mL) were sequentially added water (4 mL) and NaOH (348.0 mg, 8.71 mmol) at 17 °C. The resulting solution was stirred at 80 °C for 30 min before diluted with water. The aqueous layer was acidified with citric acid to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(2-chloro-6-methoxyphenyl)-6-methylnicotinic acid (600.0 mg, crude) as a brown solid. MS (ESI) calculated for ($C_{14}H_{12}ClNO_3$) $(M+1)^+$, 278.0; found, 278.0.

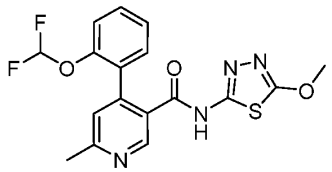
Step-3: 4-(2-chloro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



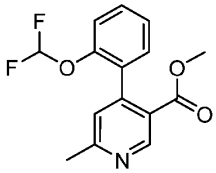
To a stirred solution of 4-(2-chloro-6-methoxyphenyl)-6-methylnicotinic acid (300.0 mg, 1.08 mmol) in acetonitrile (2 mL) were sequentially added 5-methoxy-1,3,4-thiadiazol-2-amine (156.0 mg, 1.19 mmol) and 1-Methylimidazole (443.0 mg, 5.40 mmol) at 17 °C. To the above solution was added a solution of TCFH (303.0 mg, 1.08 mmol) in acetonitrile (1 mL) at 17 °C under nitrogen. The resulting mixture was then stirred at 17 °C for 1 hr. The solvents were removed under vacuum. The resulting residue was dissolved in DCM (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~10% methanol in dichloromethane within 20 min to afford 4-(2-chloro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (86.1 mg, 20%) as a white solid. MS (ESI) calculated for ($C_{17}H_{15}ClN_4O_3S$) $(M+1)^+$, 391.0; found, 391.15. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.86 (s, 1H), 7.39 – 7.35 (m, 1H), 7.25 (s, 1H), 7.14 – 7.11 (m, 1H), 7.04 – 7.02 (m, 1H), 4.06 (s, 3H), 3.60 (s, 3H), 2.57 (s, 3H).

Example 36

4-(2-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



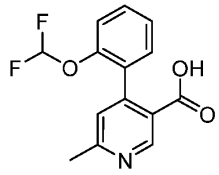
Step-1: methyl 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinate



To a stirred solution of methyl 4-chloro-6-methylnicotinate (1.0 g, 5.39 mmol) in 1,4-dioxane (5 mL) were sequentially added Bis (pinacolato) diboron (2.7 g, 10.78 mmol), potassium acetate (1.6 g, 16.16 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (1.2 g, 1.62 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 4 hr under nitrogen. To the above mixture were added a mixture of 1-bromo-2-(difluoromethoxy)benzene (1.0 g, 4.50 mmol), water (2 mL), potassium carbonate (1.9 g, 13.50 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (800.0 mg, 1.09 mmol) in dioxane (10 mL) at 23 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated

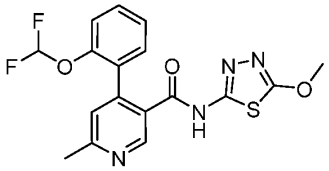
under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 80.0 g silica gel column and eluted with 0~14% methanol in dichloromethane within 40 min to afford methyl 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinate (1.1 g, 97% yield) as a brown oil. MS (ESI) calc'd for ($C_{15}H_{13}F_2NO_3$) $(M+1)^+$, 294.1; found, 294.1.

Step-2: 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinate (1.0 g, 3.41 mmol) in methanol (4 mL) were added water (4 mL) and sodium hydroxide (546.0 mg, 13.64 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 2 hr under nitrogen. The organic solvent was removed under vacuum. The aqueous layer was acidified with sat. citric acid solution to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinic acid (823.0 mg, 70% yield) as a brown solid. MS (ESI) calc'd for ($C_{14}H_{11}F_2NO_3$) $(M+1)^+$, 280.1, found 280.1.

Step-3: 4-(2-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

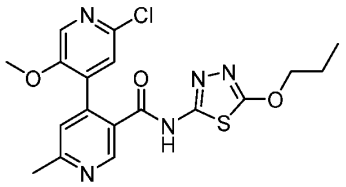


To a stirred solution of 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinic acid (200.0 mg, 0.72 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (103.0 mg, 0.79 mmol) in acetonitrile (2 mL) was added 1-methylimidazole (293.5 mg, 3.58 mmol). Then TCFH (201.0 mg, 0.72 mmol) in acetonitrile (1 mL) was added to the above mixture at 20 °C. The resulting solution was stirred at 20 °C for 2 hr under nitrogen. The resulting residue was dissolved in acetonitrile (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 30 min to afford 4-(2-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (143.0

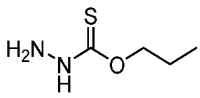
mg, 50% yield) as a white solid. MS (ESI) calc'd for ($C_{17}H_{14}F_2N_4O_3S$) $(M+1)^+$, 393.1; found 393.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 7.53 – 7.39 (m, 2H), 7.37 – 7.30 (m, 2H), 7.23 – 6.84 (m, 2H), 4.06 (s, 3H), 2.59 (s, 3H).

Example 37

2'-chloro-5'-methoxy-6-methyl-N-(5-propoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

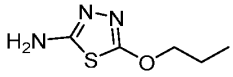


Step-1: O-propyl hydrazinecarbothioate



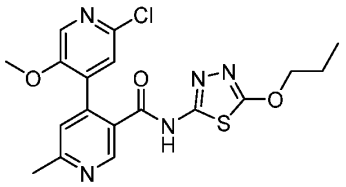
To a solution of potassium O-propyl carbonodithioate (2.0 g, 11.47 mmol) in Methanol (15 mL) was added hydrazine (0.5 mL, 13.77 mmol) at 16 °C. The resulting solution was stirred at 16 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-propyl hydrazinecarbothioate (2.3 g, crude) as a yellow oil.

Step-2: 5-propoxy-1,3,4-thiadiazol-2-amine



To a solution of O-propyl hydrazinecarbothioate (2.0 g, 8.94 mmol) in Methanol (10 mL) was added TEA (1.2 mL, 8.94 mmol) and cyanic bromide (1.0 g, 9.84 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 30 min. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in DMF (4 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~24 % acetonitrile in water within 43 min to afford 5-propoxy-1,3,4-thiadiazol-2-amine (97.0 mg, 6%) as a yellow solid. MS (ESI) calc'd for ($C_5H_9N_3OS$) $(M+1)^+$, 160.0; found 160.0.

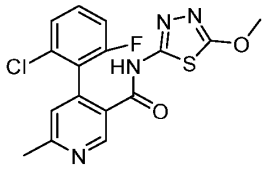
Step-3: 2'-chloro-5'-methoxy-6-methyl-N-(5-propoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



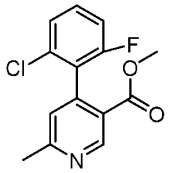
To a mixture of 5-propoxy-1,3,4-thiadiazol-2-amine (89.0 mg, 0.49 mmol) in Acetonitrile (4 mL) were added Intermediate G (120.0 mg, 0.40 mmol), and 1-methyl-1H-imidazole (101.0 mg, 1.22 mmol). A solution of TCFH (172.0 mg, 0.61 mmol) in Acetonitrile (1 mL) was added thereto dropwise under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The organic solvent was removed under vacuum. The residue was dissolved in DMF (5 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C_{18} Column, 30 * 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 40% B in 8 min, 40% B; Wave Length: 254 nm; RT1 (min): 7.82) to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-propoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (102.9 mg, 59%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{18}ClN_5O_3S$) $(M+1)^+$, 420.0; found 420.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.83 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 4.33 – 4.37 (t, J = 6.4 Hz, 2H), 3.63 (s, 3H), 2.58 (s, 3H), 1.73 – 1.81 (m, 2H), 0.94 – 0.98 (t, J = 7.6 Hz, 3H).

Example 38

4-(2-chloro-6-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



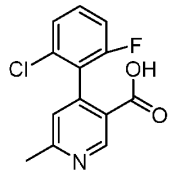
Step 1 methyl 4-(2-chloro-6-fluorophenyl)-6-methylnicotinate



To a stirred solution of (2-chloro-6-fluorophenyl)boronic acid (2.0 g, 11.47 mmol) in 1,4-Dioxane (10 mL) were added methyl 4-chloro-6-methylnicotinate (532.2 mg, 2.87 mmol),

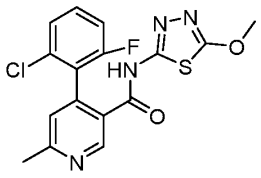
potassium carbonate (1.1g, 8.60 mmol) and Water (2 mL) at 23 °C. To the above solution was added Pd(dtbpf)Cl_2 (187.2 mg, 0.28 mmol) at 23 °C under nitrogen. The resulting mixture was then stirred at 80 °C under nitrogen for 2 hr. The reaction mixture was dilution by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 80 g silica gel column that was eluted with 0~60% ethyl acetate in petroleum ether within 30 min to afford methyl 4-(2-chloro-6-fluorophenyl)-6-methylnicotinate (200.0 mg 24%) as a yellow oil. MS (ESI) calc'd for ($C_{14}H_{11}ClFNO_2$) $(M+1)^+$, 280.0; found, 280.0.

Step 2 4-(2-chloro-6-fluorophenyl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(2-chloro-6-fluorophenyl)-6-methylnicotinate (200.0 mg, 0.72 mmol) in Tetrahydrofuran (1mL) and Water (1 mL) was added LiOH (34.2 mg, 1.44 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 1 hr before diluted with water. The aqueous layer was acidified with citric acid to pH ~3 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 25 min to afford 4-(2-chloro-6-fluorophenyl)-6-methylnicotinic acid (100.0 mg, 50%) as a white solid. MS (ESI) calc'd for ($C_{13}H_9ClFNO_2$) $(M+1)^+$, 266.0; found, 266.1.

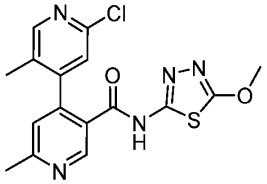
Step 3 4-(2-chloro-6-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



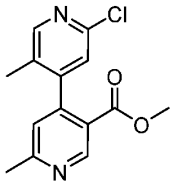
To a stirred solution of 4-(2-chloro-6-fluorophenyl)-6-methylnicotinic acid (80.0 mg, 0.30 mmol) in Acetonitrile (2 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (39.5 mg, 0.30 mmol) and 1-methylimidazole (124.2 mg, 1.50 mmol) at 23 °C. To the above solution was added a solution of TCFH (85.0 mg, 0.30 mmol) in Acetonitrile (0.5 mL) at 23 °C under nitrogen. The resulting mixture was then stirred at 23 °C for 2 hr under nitrogen. The mixture was dissolved in DMF (4 mL) and purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 8 min, 45% B to 95% B in 8.2 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 254 nm; RT1(min): 7; Injection Volume: 1.5 mL; Number Of Runs: 4) to afford 4-(2-chloro-6-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (51.3 mg, 45%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{12}ClFN_4O_2S$) $(M+1)^+$, 379.0; found, 379.0. ^1H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 9.01 (s, 1H), 7.53 – 7.28 (m, 4H), 4.05 (s, 3H), 2.60 (s, 3H).

Example 39

2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-5',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



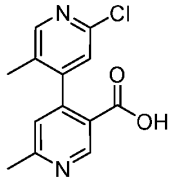
Step-1: methyl 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylate



To a solution of methyl 4-chloro-6-methylnicotinate (1.5 g, 7.89 mmol) in 1,4-Dioxane (5 mL) and Water (1 mL) were added methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (4.4 g, 15.88 mmol), K_2CO_3 (1.6 g, 11.8 mmol) and $PdCl_2$(dppf) (0.8 g, 1.19 mmol) at 20 °C under nitrogen. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 0~50% ethyl acetate in petroleum

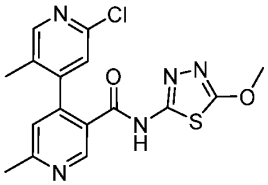
ether within 35 min to afford methyl 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (1.1 g, 96%) as a yellow solid. MS (ESI) calc'd for ($C_{14}H_{13}ClN_2O_2$) $(M+1)^+$, 277.1; found, 277.1.

Step-2: 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (500.0 mg, 1.81 mmol) in Tetrahydrofuran (2 mL) was added a solution of lithium hydroxide (43.3 mg, 1.81 mmol) in Water (2 mL) at 20 °C. The resulting solution was stirred at 20 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (384.0 mg, crude) as a yellow solid.MS (ESI) calc'd for ($C_{13}H_{11}ClN_2O_2$) $(M+1)^+$, 263.1; found, 263.1.

Step-3: 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-5',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

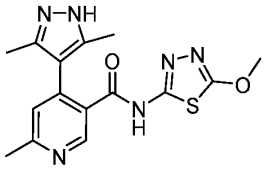


To a solution of 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (150.0 mg, 0.57 mmol) in Acetonitrile (2 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (74.9 mg, 0.57 mmol) and 1-methylimidazole (234.5 mg, 2.86 mmol) at 20 °C under nitrogen. To the above solution was added a solution of TCFH (160.0 mg, 0.57 mmol) in Acetonitrile (2 mL) at 20 °C under nitrogen. The mixture was then stirred at 20 °C for 1 hr. The resulting mixture was dissolved with DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~55% acetonitrile in water within 30 min to afford 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-5',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (48.5 mg, 22%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{14}ClN_5O_2S$) $(M+1)^+$,

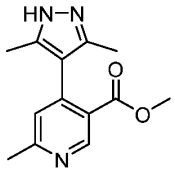
376.1; found 376.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.98 (s, 1H), 8.30 (s, 1H), 7.29 – 7.36 (m, 2H), 4.04 (s, 3H), 2.58 (s, 3H), 1.98 (s, 3H).

Example 40

4-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

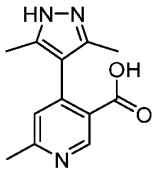


Step-1: methyl 4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-methylnicotinate



To a stirred solution of methyl 4-chloronicotinate (500.0 mg, 2.91 mmol) in 1,4-Dioxane (5 mL) were sequentially added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (971.0 mg, 4.37 mmol), water (1.0 mL), K_2CO_3 (1.2 g, 8.74 mmol) and $Pd(dppf)Cl_2$ (238.0 mg, 0.29 mmol) at 17 °C. The resulting solution was stirred at 80 °C for 16 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 80.0 g silica gel column and eluted with 0~10% methanol in dichloromethane within 25 min to afford methyl 4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-methylnicotinate (202.0 mg, 26%) as a red solid. MS (ESI) calculated for ($C_{13}H_{15}N_3O_2$) $(M+1)^+$, 246.0; found, 246.2.

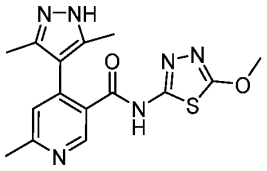
Step-2: 4-(3,5-dimethyl-4H-pyrazol-4-yl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(3,5-dimethyl-4H-pyrazol-4-yl)-6-methylnicotinate (160.0 mg, 0.65 mmol) in methanol (2 mL) was added a solution of NaOH (104.0 mg, 2.61 mmol) in water (2 mL) at 17 °C. The resulting solution was stirred at 17 °C for 30 min before diluted with water. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~6 and extracted with ethyl acetate. The combined organic layers were

washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~7% acetonitrile in water within 20 min to afford 4-(3,5-dimethyl-4H-pyrazol-4-yl)-6-methylnicotinic acid (42.0 mg, 27%) as a white solid. MS (ESI) calculated for ($C_{12}H_{13}N_3O_2$) $(M+1)^+$, 231.0; found, 231.

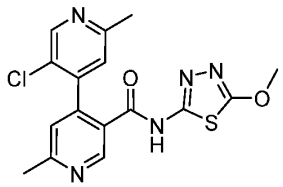
Step-3: 4-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



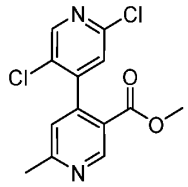
To a stirred solution of 4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-methylnicotinic acid (140.0 mg, 0.61 mmol) in acetonitrile (2 mL) were sequentially added 5-methoxy-1,3,4-thiadiazol-2-amine (87.0 mg, 0.67 mmol) and 1-Methylimidazole (249.0 mg, 3.03 mmol) at 17 °C. To the above solution was added a solution of TCFH (170.0 mg, 0.61 mmol) in acetonitrile (1 mL) at 17 °C under nitrogen. The resulting mixture was then stirred at 17 °C for 1 hr. The organic solvent was removed under vacuum. The residue was dissolved in DMF (3 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 7% B to 27% B in 8 min, 27% B; Wave Length: 254 nm; RT1(min): 7) to afford 4-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (60.4 mg, 29%) as a white solid. MS (ESI) calculated for ($C_{15}H_{16}N_6O_2S$) $(M+1)^+$, 345.0; found, 345.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.68 (s, 1H), 7.18 (s, 1H), 4.06 (s, 3H), 2.59 (s, 3H), 2.08 – 1.87 (m, 6H).

Example 41

5'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

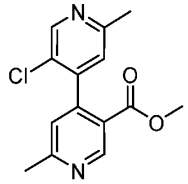


Step-1: methyl 2',5'-dichloro-6-methyl-(4,4'-bipyridine)-3-carboxylate



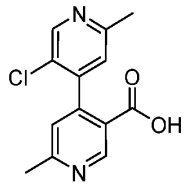
To a stirred solution of (2,5-dichloropyridin-4-yl)boronic acid (0.5 g, 2.69 mmol) in 1,4-Dioxane (10 mL) were sequentially added methyl 4-chloro-6-methylnicotinate (1.0 g, 5.39 mmol), $PdCl_2$(DTBPF) (0.3 g, 0.53 mmol) and K_2CO_3 (2.2 g, 16.16 mmol) at 25 °C. The resulting solution was stirred at 80 °C for 2h under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 50~80% ethyl acetate in petroleum ether within 30 min to afford methyl 2',5'-dichloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (400.0 mg, 20%) as a light-yellow solid. MS (ESI) calc'd for ($C_{13}H_{10}Cl_2N_2O_2$) $(M+1)^+$, 297.0, found 297.0.

Step-2: 5'-chloro-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate



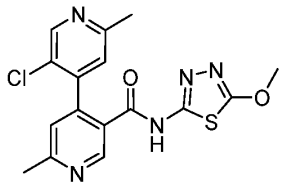
To a stirred solution of methyl 2',5'-dichloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (400.0 mg, 1.34 mmol) in Tetrahydrofuran (3 mL) was added trimethylaluminum (4 mL, 4.04 mmol) at 25 °C. The resulting solution was stirred at 85 °C for 16 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford crude product as a yellow oil. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 20 g silica gel column and eluted with 30-60% ethyl acetate in petroleum ether within 30 min to afford methyl 5'-chloro-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (270.0 mg, 58%) as a colorless oil. MS (ESI) calc'd for ($C_{14}H_{13}ClN_2O_2$) $(M+1)^+$, 277.0, found 277.1.

Step-3: 5'-chloro-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 5'-chloro-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (270.0 mg, 0.78 mmol) in Tetrahydrofuran (3 mL) and Water (1 mL) was added lithium hydroxide (18.6 mg, 0.78 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 h before diluted with water. The organic solvent was removed under vacuum. The aqueous layer was acidified with 2 *N* HCl to pH ~4 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 5'-chloro-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (150.0 mg, crude) as a white solid. MS (ESI) calc'd for ($C_{13}H_{11}ClN_2O_2$) (M+1), 263.0, found 263.0.

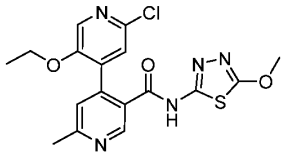
Step-4: 5'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



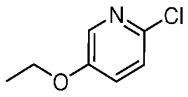
To a stirred solution of 5'-chloro-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (150.0 mg, 0.51 mmol) in Acetonitrile (2 mL) were sequentially added 1-methyl-1H-imidazole (211.0 mg, 2.57 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (81.0 mg, 0.61 mmol) at 25 °C. To the above solution was added TCFH (159.0 mg, 0.56 mmol) at 25 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 2 hr. The suspension was filtered. The filter cake was washed by water (20 mL x 3) and tert-Butyl methyl ether (20 mL). The solid was collected and dried under vacuum to afford 5'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (79.0 mg, 40%) as a light-yellow solid. MS (ESI) calc'd for ($C_{16}H_{14}ClN_5O_2S$) $(M+1)^+$, 376.0, found 376.1. ^{1}H NMR (400 MHz, Methanol-d_4) δ 13.10 (s, 1H), δ 8.97 (s, 1H), 8.51 (s, 1H), 7.36 – 7.30 (m, 2H), 4.06 (s, 3H), 2.69 (s, 3H), 2.59 (s, 3H).

Example 42

2'-chloro-5'-ethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

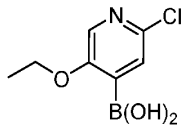


Step 1 2-chloro-5-ethoxypyridine



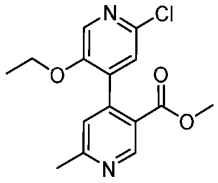
To a stirred solution of 6-chloropyridin-3-ol (1.0 g, 7.72 mmol) in N, N-Dimethylformamide (15 mL) were sequentially added K_2CO_3 (2.1 g, 15.44 mmol) and iodoethane (1.4 g, 8.97 mmol) at 20 °C. The resulting solution was stirred at 40 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (4 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~20% ethyl acetate in petroleum ether within 30 min to afford 2-chloro-5-ethoxypyridine (827.0 mg, 67%) as a white solid. MS (ESI) calculated for (C_7H_8ClNO) $(M+1)^+$, 158.0; found, 158.0.

Step 2 (2-chloro-5-ethoxypyridin-4-yl)boronic acid



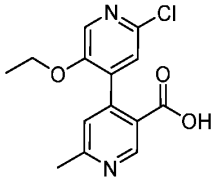
To a stirred solution of 2-chloro-5-ethoxypyridine (800.0 mg, 5.08 mmol) in Tetrahydrofuran (30 mL) was added lithium diisopropylamide (5 ml, 10.00 mmol, 2 N in THF) dropwise at -78 °C. The resulting solution was stirred at -78 °C for 3 hr under nitrogen. To the above solution was added triisopropyl borate (1.9 g, 10.15 mmol) dropwise at -78 °C under nitrogen. The mixture was then stirred at -78 °C for 2 hr before acidified with HCl (2 N) to pH 4~5 at 0 °C. The resulting mixture was stirred at 0 °C to room temperature for 30 min, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford (2-chloro-5-ethoxypyridin-4-yl)boronic acid (650.0 mg, crude) as a yellow solid. MS (ESI) calculated for ($C_7H_9BClNO_3$) $(M+1)^+$, 202.0; found, 202.0.

Step 3 methyl 2'-chloro-5'-ethoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



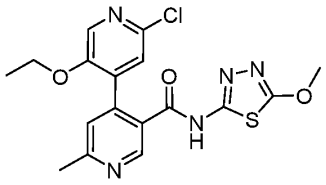
To a stirred solution of methyl 4-chloro-6-methylnicotinate (500.0 mg, 2.69 mmol) in 1,4-Dioxane (7 mL) were sequentially added water (1.5 mL), (2-chloro-5-ethoxypyridin-4-yl)boronic acid (543.0 mg, 2.69 mmol), Dichloro(1,1'-bis(di-t-butylphosphino)ferrocene)palladium(II) (176.0 mg, 0.27 mmol) and K_2CO_3 (1.1 g, 8.08 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 3 h under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column, eluted with 0~3% methanol in dichloromethane within 20 min to afford methyl 2'-chloro-5'-ethoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (360.0 mg, 43%) as a colorless oil. MS (ESI) calculated for ($C_{15}H_{15}ClN_2O_3$) $(M+1)^+$, 307.1; found, 307.1.

Step 4 2'-chloro-5'-ethoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-5'-ethoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (350.0 mg, 1.14 mmol) in Methanol (3 mL) was added a solution of sodium hydroxide (183.0 mg, 4.56 mmol) in water (3 mL) at 20 °C. The resulting solution was stirred at 80 °C for 1 hr. The mixture was diluted with water. The volatiles were removed under vacuum. The aqueous layer was acidified with citric acid to pH 5~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-5'-ethoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (330.0 mg, crude) as a pink solid. MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_3$) $(M+1)^+$, 293.1; found, 293.1.

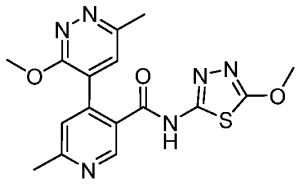
Step 5 2'-chloro-5'-ethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



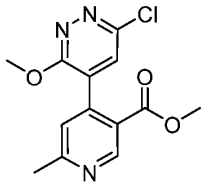
To a stirred solution of 2'-chloro-5'-ethoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (310.0 mg, 1.06 mmol) in acetonitrile (4 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (153.0 mg, 1.17 mmol) and 1-methylimidazole (435.0 mg, 5.30 mmol). To the above solution was added a solution of TCFH (297.0 mg, 1.06 mmol) in acetonitrile (1 mL) at 20 °C under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The resulting mixture was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~70% acetonitrile in water within 30 min to afford a yellow solid (88% purity). The product was dissolved in DMF (3 mL) and further purified by prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 55% B to 65% B in 8 min, 65% B to 95% B in 8.2 min, 95% B to 95% B in 10 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 220\254 nm; RT1(min): 8; Injection Volume: 500 mL; Number Of Runs: 5) to afford 2'-chloro-5'-ethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (70.5 mg, 16 %) as a white solid. MS (ESI) calculated for ($C_{17}H_{16}ClN_5O_3S$) $(M+1)^+$, 406.1; found, 406.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.83 (s, 1H), 8.13 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.08 (s, 3H), 3.97 – 3.87 (m, 2H), 2.59 (s, 3H), 1.12 – 1.04 (m, 3H).

Example 43

N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinamide

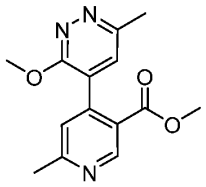


Step 1; methyl 4-(6-chloro-3-methoxypyridazin-4-yl)-6-methylnicotinate



To a stirred solution of methyl 4-chloro-6-methylnicotinate (1.0 g, 5.39 mmol) in 1,4-dioxane (5 mL) were sequentially added Bis (pinacolato) diboron (2.7 g, 10.78 mmol), potassium acetate (1.6 g, 16.16 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (1.2 g, 1.62 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 4 hr under nitrogen. To the above mixture were added water (0.4 mL), potassium carbonate (299.0 mg, 2.17 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (158.0 mg, 0.22 mmol) in 1,4-dioxane (2 mL) at 23 °C. The resulting solution was stirred at 80 °C for 16 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in acetonitrile (2 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~38% acetonitrile in water within 30 min to afford methyl 4-(6-chloro-3-methoxypyridazin-4-yl)-6-methylnicotinate (114.0 mg, 50%) as a yellow oil. MS (ESI) calc'd for ($C_{13}H_{12}ClN_3O_3$) $(M+1)^+$, 294.1; found, 294.1.

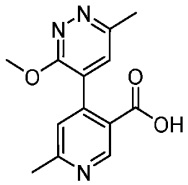
Step-2: methyl 4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinate



To a stirred solution of methyl 4-(6-chloro-3-methoxypyridazin-4-yl)-6-methylnicotinate (100.0 mg, 0.34 mmol) in 1,4-dioxane (1 mL) were sequentially added trimethylboroxine (51.0 mg, 0.41 mmol), cesium carbonate (333.0 mg, 1.02 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (25.0 mg, 0.03 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 16 hr under nitrogen. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in acetonitrile (2 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~28% acetonitrile in water within 30 min to afford methyl 4-(3-methoxy-6-methylpyridazin-4-yl)-6-

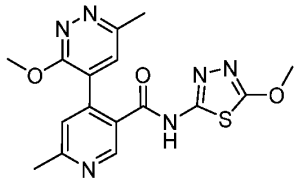
methylnicotinate (75.0 mg, 79%) as a yellow oil. MS (ESI) calc'd for ($C_{14}H_{15}N_3O_3$) $(M+1)^+$, 274.1, found 274.1.

Step-3: 4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinate (55.0 mg, 0.20 mmol) in methanol (0.9 mL) were added water (0.3 mL) and lithium hydroxide (19.0 mg, 0.81 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 0.5 hr under nitrogen. The resulting residue was acidified by citric acid which was applied to a 20.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~28% acetonitrile in water within 30 min to afford 4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinic acid (47.0 mg, 89%) as a yellow solid. MS (ESI) calc'd for ($C_{13}H_{13}N_3O_3$) $(M+1)^+$, 260.1, found 260.1.

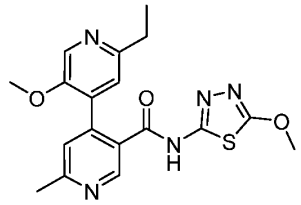
Step-4: N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinamide



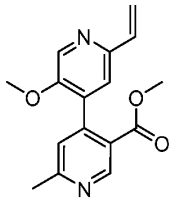
To a stirred solution of 4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinic acid (47.0 mg, 0.18 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (26.0 mg, 0.20 mmol) in acetonitrile (1 mL) was added 1-methylimidazole (74.6 mg, 0.91 mmol). Then TCFH (51.0 mg, 0.18 mmol) in acetonitrile (1 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The resulting residue was dissolved in acetonitrile (1 mL) which was applied to a 20.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~34% acetonitrile in water within 30 min to afford N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(3-methoxy-6-methylpyridazin-4-yl)-6-methylnicotinamide (31.0 mg, 45%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{16}N_6O_3S$) $(M+1)^+$, 373.1; found 373.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.86 (s, 1H), 7.62 (s, 1H), 7.46 (s, 1H), 4.08 (s, 3H), 3.74 (s, 3H), 2.60 (s, 6H).

Example 44

2'-ethyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

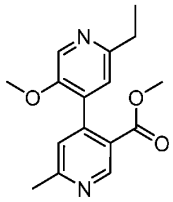


Step-1: methyl 5'-methoxy-6-methyl-2'-vinyl-(4,4'-bipyridine)-3-carboxylate



To a solution of methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (400.0 mg, 1.33 mmol) in 1,4-Dioxane (8 mL) were added Pd(dppf)Cl_2 (87.0 mg, 0.13 mmol), K_2CO_3 (370.0 mg, 2.68 mmol) and trifluoro(vinyl)-l4-borane potassium salt (179.0 mg, 1.33 mmol), water (2 mL) at 20 °C. The resulting solution was stirred at 80 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in DCM (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~26 % ethyl acetate in petroleum ether within 35 min to afford methyl 5'-methoxy-6-methyl-2'-vinyl-(4,4'-bipyridine)-3-carboxylate (350.0 mg, 65%) as a red oil. MS (ESI) calc'd for ($C_{16}H_{16}N_2O_3$) $(M+1)^+$, 285.1, found 285.1.

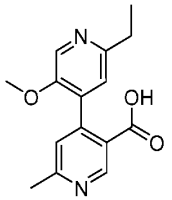
Step-2: methyl 2'-ethyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



A mixture of methyl 5'-methoxy-6-methyl-2'-vinyl-(4,4'-bipyridine)-3-carboxylate (342.0 mg, 0.85 mmol) in Methanol (2 mL) was added Pd/C (dry, 50.0 mg) under hydrogen atmosphere. The resulting solution was stirred at 20 °C for 2 hr under hydrogen atmosphere. The

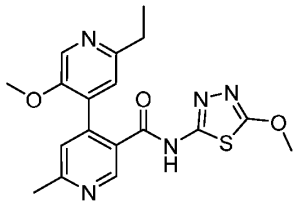
suspension was filtered. The filtrate was collected and concentrated under vacuum. The residue was dissolved in DCM (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~7 % methanol in dichloromethane within 35 min to afford methyl 2'-ethyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (300.0 mg, 96%) as a yellow oil. MS (ESI) calc'd for ($C_{16}H_{18}N_2O_3$) $(M+1)^+$, 287.1, found 287.1.

Step-3: 2'-ethyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a solution of methyl 2'-ethyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (300.0 mg, 0.81 mmol) in Tetrahydrofuran (THF) (3 mL) were added LiOH (78.0 mg, 3.27 mmol) and Water (1.0 mL) at 17 °C. The resulting solution was stirred at 50 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-ethyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (246.0 mg, 88%) as a red oil. MS (ESI) calc'd for ($C_{15}H_{16}N_2O_3$) $(M+1)^+$, 273.1, found 273.1.

Step-4: 2'-ethyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

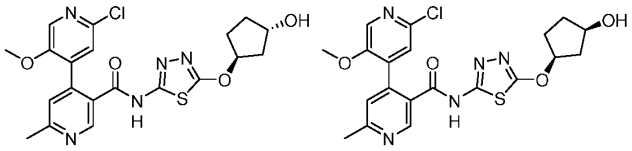


To a mixture of 5-methoxy-1,3,4-thiadiazol-2-amine (69.4 mg, 0.52 mmol) in Acetonitrile (2 mL) were added 2'-ethyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (150.0 mg, 0.44 mmol) and 1-methyl-1H-imidazole (109.0 mg, 1.32 mmol). A solution of TCFH (185.0 mg, 0.66 mmol) in Acetonitrile (1 mL) was added thereto dropwise under nitrogen. The organic solvent was removed under vacuum. The resulting residue was dissolved in DMF (5 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera

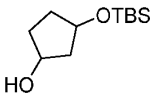
Prime), eluted with 5~23% acetonitrile in water within 34 min to afford a white solid (70%). The product (70%) was dissolved in DMF (5 mL) and further purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 * 150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 40% B in 8 min, 40% B to 95% B in 8.2 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 254 nm; RT1(min): 5.6; Injection Volume: 1.5 mL; Number Of Runs: 3) to afford 2'-ethyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (51.1 mg, 29%) as a white solid. MS (ESI) calc'd for $(C_{18}H_{19}N_5O_3S)$ $(M+1)^+$, 386.1, found 386.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.76 (s, 1H), 8.22 (s, 1H), 7.36 (s, 1H), 7.24 (s, 1H), 4.06 (s, 3H), 3.60 (s, 3H), 2.74 – 2.76 (m, 2H), 2.58 (s, 3H), 1.24 (t, J = 7.6 Hz, 3H).

Example 45 and 46

2'-chloro-N-(5-(((1s,3s)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide, and 2'-chloro-N-(5-(((1s,3r)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide,

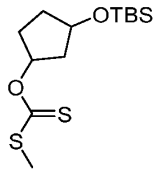


Step 1 3-((tert-butyldimethylsilyl)oxy)cyclopentan-1-ol



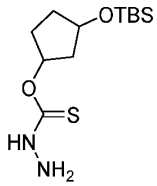
To a stirred solution of cyclopentane-1,3-diol (1.0 g, 9.79 mmol) in dichloromethane (5 mL) were sequentially added TBS-Cl (1.5 g, 9.79 mmol) and imidazole (0.7 g, 9.79 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2 hr. The organic solvent was removed under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~10% methanol in dichloromethane within 30 min to afford 3-((tert-butyldimethylsilyl)oxy)cyclopentan-1-ol (620.0 mg, 25%) as a colorless oil.

Step 2 O-(3-((tert-butyldimethylsilyl)oxy)cyclopentyl) S-methyl carbonodithioate



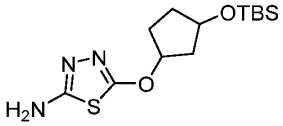
To a degassed solution of 3-((tert-butyldimethylsilyl)oxy)cyclopentan-1-ol (600.0 mg, 2.77 mmol) in dry tetrahydrofuran (4 mL) was added NaH (222.0 mg, 5.55 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 30 min under nitrogen atmosphere. Then CS_2 (0.3 mL, 4.16 mmol) was added to the above mixture at 0 °C and stirred at 0 °C for 20 min. To the above solution was added MeI (0.3 mL, 4.16 mmol) at 0 °C under nitrogen. The resulting mixture was then stirred at 0 °C for 1 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~30% ethyl acetate in petroleum ether within 20 min to afford O-(3-((tert-butyldimethylsilyl)oxy)cyclopentyl) S-methyl carbonodithioate (744.0 mg, 74%) as a yellow oil.

Step 3 O-(3-((tert-butyldimethylsilyl)oxy)cyclopentyl) hydrazinecarbothioate



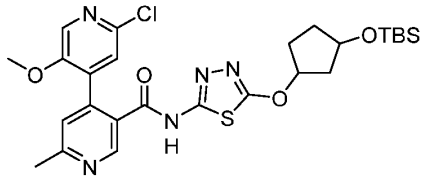
To a stirred solution of O-(3-((tert-butyldimethylsilyl)oxy)cyclopentyl) S-methyl carbonodithioate (710.0 mg, 2.32 mmol) in methanol (5 mL) was added hydrazine (0.1 mL, 2.32 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 1 hr. The solvents were removed under vacuum to afford O-(3-((tert-butyldimethylsilyl)oxy)cyclopentyl) hydrazinecarbothioate (673.0 mg, crude) as a colorless oil. MS (ESI) calculated for ($C_{12}H_{26}N_2O_2SSi$) $(M+1)^+$, 291.0; found, 291.3.

Step 4 5-((3-((tert-butyldimethylsilyl)oxy)cyclopentyl)oxy)-1,3,4-thiadiazol-2-amine



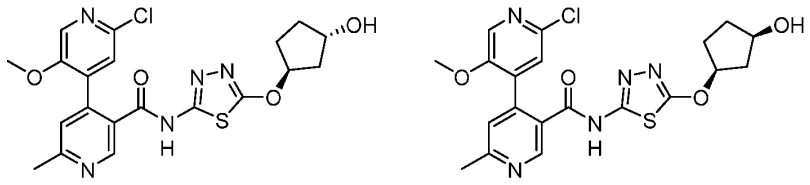
To a stirred solution of O-(3-((tert-butyldimethylsilyl)oxy)cyclopentyl) hydrazinecarbothioate (670.0 mg, 2.31 mmol) in methanol (4 mL) were sequentially added TEA (0.7 mL, 4.61 mmol) and BrCN (366.0 mg, 3.46 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (4 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 15~80% acetonitrile in water within 30 min to afford 5-((3-((tert-butyldimethylsilyl)oxy)cyclopentyl)oxy)-1,3,4-thiadiazol-2-amine (301.0 mg, 34%) as a yellow solid. MS (ESI) calculated for ($C_{13}H_{25}N_3O_2SSi$) $(M+1)^+$, 316.0; found, 316.3.

Step 5 2-(5-((3-((tert-butyldimethylsilyl)oxy)cyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridin)-3-yl)ethan-1-one



To a stirred solution of 5-((3-((tert-butyldimethylsilyl)oxy)cyclopentyl)oxy)-1,3,4-thiadiazol-2-amine (300.0 mg, 0.95 mmol) in acetonitrile (3 mL) were added Intermediate G (240.6 mg, 0.86 mmol) and 1-Methylimidazole (354.0 mg, 4.32 mmol) at 23 °C. To the above solution was added a solution of TCFH (242.0 mg, 0.86 mmol) in acetonitrile (1 mL) at 23 °C under nitrogen. The resulting mixture was then stirred at 23 °C for 1 hr. The solvents were removed under vacuum. The resulting residue was dissolved in DMF (4 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~70% acetonitrile in water within 35 min to afford 2-(5-((3-((tert-butyldimethylsilyl)oxy)cyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridin)-3-yl)ethan-1-one (330.0 mg, 66%) as a white solid. MS (ESI) calculated for ($C_{26}H_{34}ClN_5O_4SSi$) $(M+1)^+$, 576.0; found, 576.4.

Step 6 2'-chloro-N-(5-(((1s,3s)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and 2'-chloro-N-(5-(((1s,3r)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of N-(5-((3-((tert-butyldimethylsilyl)oxy)cyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (330.0 mg, 0.57 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (0.8 mL) at 0 °C. The resulting solution was stirred at 23 °C for 2 hr. The organic solvent was removed under vacuum. The mixture was diluted with water. The aqueous layer was basified with $NaHCO_3$ to pH 7~8 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (6 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~80% acetonitrile in water within 30 min to afford a mixture of 2'-chloro-N-(5-((3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (160.0 mg, 59 %) as a white solid. The mixture of compounds (160.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 40% B in 8 min, 40% B; Wave Length: 254 nm; RT1(min): 6.25) to afford 2'-chloro-N-(5-(((1s,3s)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide, (9.0 mg, 6% yield) as a white solid with the first peak on chiral HPLC and 2'-chloro-N-(5-(((1s,3r)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide, (70.2 mg, 43% yield) as a white solid with the second peak on chiral HPLC. The absolute stereochemistry was not determined and was arbitrarily assigned.

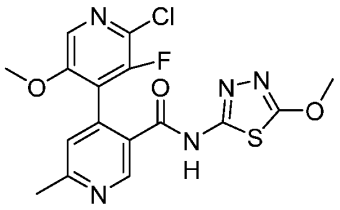
2'-chloro-N-(5-(((1s,3s)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for $(C_{20}H_{20}ClN_5O_4S)$ $(M+1)^+$, 462.0; found, 462.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.83 (s, 1H), 8.15 (s, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 5.25 – 5.11 (m, 1H), 4.68 – 4.53 (m, 1H), 4.27 – 4.09 (m, 1H), 3.63 (s, 3H), 2.67 (s, 3H), 2.35 – 2.28 (m, 1H), 2.02 – 1.76 (m, 2H), 1.74 – 1.73 (m, 3H).

2'-chloro-N-(5-(((1s,3r)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for $(C_{20}H_{20}ClN_5O_4S)$ $(M+1)^+$,

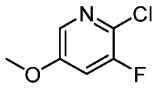
462.0; found, 462.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 5.39 – 5.26 (m, 1H), 4.64 – 4.50 (m, 1H), 4.27 – 4.13 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.20 – 2.18 (m, 1H), 2.00 – 1.70 (m, 2H), 1.74 – 1.73 (m, 2H), 1.54 – 1.50 (m, 1H).

Example 47

2'-chloro-3'-fluoro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

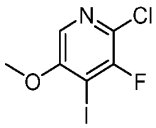


Step-1: 2-chloro-3-fluoro-5-methoxypyridine



To a solution of 6-chloro-5-fluoropyridin-3-ol (20.0 g, 135.60 mmol) in Acetone (150 mL) were added MeI (17 mL, 271.00 mmol) and K_2CO_3 (37.5 g, 271.00 mmol) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 25 °C for 16 h under nitrogen before concentrated under vacuum. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 330 g silica gel column and eluted with 0~22% ethyl acetate in petroleum ether within 45 min to afford 2-chloro-3-fluoro-5-methoxypyridine (16.0 g, 80%) as a colorless oil. MS (ESI) calc'd for (C_6H_5ClFNO) $(M+1)^+$, 162.0; found 162.0.

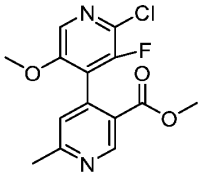
Step-2: 2-chloro-3-fluoro-4-iodo-5-methoxypyridine



To a degassed solution of 2-chloro-3-fluoro-5-methoxypyridine (16.0 g, 99.00 mmol) in dry Tetrahydrofuran (160 mL) was added n-butyllithium (44 mL, 110.00 mmol, 2.5 N in hexane) dropwise at -60 °C and stirred at -60 °C for 1 hr under nitrogen atmosphere. Then iodine

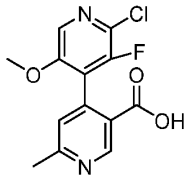
(27.6 g, 109.00 mmol) was added to the above mixture at -60 °C. The resulting solution was stirred at -60 ~ 20 °C for 2 hr. The reaction mixture was quenched by the addition of saturated sodium thiosulfate aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 330 g silica gel column and eluted with 0~50% ethyl acetate in petroleum ether within 40 min to afford 2-chloro-3-fluoro-4-iodo-5-methoxypyridine (22.0 g, 73%) as a white solid MS (ESI) calc'd for ($C_6H_4ClFINO$) (M+1)+, 287.9; found, 287.9.

Step-3: methyl 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a degassed solution of methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (7.2 g, 26.10 mmol) and 2-chloro-3-fluoro-4-iodo-5-methoxypyridine (5.0 g, 17.39 mmol) in dry 1,4-Dioxane (50 mL) were added Water (10 mL), (1,1′-Bis(diphenylphosphino)ferrocene)dichloropalladium(II),complex with dichloromethane (4.2 g , 5.15 mmol) and K_2CO_3 (7.2 g, 52.20 mmol) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 25 °C for 2 h under nitrogen atmosphere. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 120 g silica gel column and eluted with 0~46% ethyl acetate in petroleum ether within 45 min to afford methyl 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (2.8 g, 53%) as a white solid. MS (ESI) calc'd for ($C_{14}H_{12}ClFN_2O_3$) $(M+1)^+$, 311.1; found, 311.1.

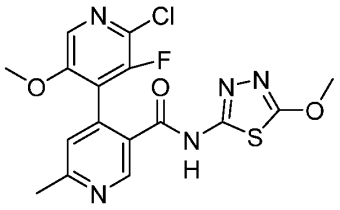
Step-4: 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (2.8 g, 9.17 mmol) in Methanol (10 mL) were added NaOH (1.4 g, 36.70 mmol) and Water (10 mL) at 25 °C. The resulting solution was stirred at 25 °C for 2 h before diluted

with water. The organic solvent was removed under vacuum. The aqueous layer was acidified with Citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (1.3 g, crude) as a yellow oil.MS (ESI) calc'd for ($C_{13}H_{10}ClFN_2O_3$) $(M+1)^+$, 297.0, found 297.0.

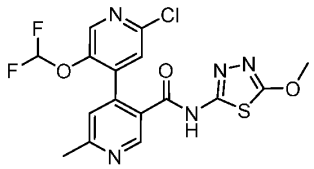
Step-5: 2'-chloro-3'-fluoro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



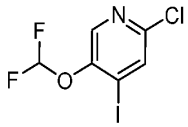
To a solution of 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (130.0 mg, 0.43 mmol) in dry acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (57.0 mg, 0.43 mmol) and 1-methyl-1H-imidazole (180.0 mg, 2.15 mmol) at 25 °C. Then a solution of TCFH (123 mg, 0.44 mmol) in acetonitrile was added to the above mixture at 25 °C. The resulting solution was stirred at 25 °C for 2 hr. The mixture was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 40 min to afford 2'-chloro-3'-fluoro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (21.4 mg, 11%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{13}ClF_2N_2O_3S$) $(M+1)^+$, 410.0, found 410.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 4.07 (s, 3H), 3.74 (s, 3H), 2.60 (s, 3H).

Example 48

2'-chloro-5'-(difluoromethoxy)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

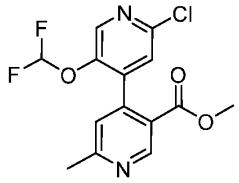


Step-1: 2-chloro-5-(difluoromethoxy)-4-iodopyridine



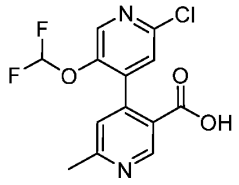
To a stirred solution of 6-chloro-4-iodopyridin-3-ol (10.0 g, 39.14 mmol) in N,N-Dimethylformamide (DMF) (50 mL) were added sodium 2-chloro-2,2-difluoroacetate (11.9 g, 78.20 mmol) and Cs_2CO_3 (16.6 g, 50.80 mmol) at 25 °C. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to a 330 g silica gel column that was eluted with 0~25% ethyl acetate in petroleum ether within 40 min to afford 2-chloro-5-(difluoromethoxy)-4-iodopyridine (10.5 g, 79%) as a white solid. MS (ESI) calc'd for $(C_6H_3ClF_2INO)$ $(M+1)^+$, 305.4; found 305.4.

Step-2: methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate



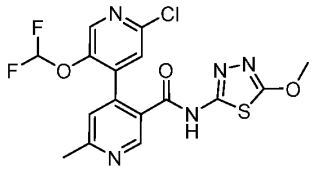
To a degassed solution of methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (5.0 g, 18.04 mmol) in 1,4-Dioxane (40 mL) were added 2-chloro-5-(difluoromethoxy)-4-iodopyridine (5.5 g, 18.04 mmol), Water (8 mL), K_2CO_3 (7.5 g, 54.1 mmol) and (1,1′-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) complex with dichloromethane (4.4 g , 5.41 mmol) at 23 °C under nitrogen atmosphere. The resulting solution was stirred at 80 °C for 2 h under nitrogen atmosphere. The suspension was filtered. The filtrate was concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 120 g silica gel column and eluted with 0~56% ethyl acetate in petroleum ether within 40 min to afford methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate (5.7 g, 63%) as a white solid. MS (ESI) calc'd for $(C_{14}H_{11}ClF_2N_2O_3)$ $(M+1)^+$, 329.0; found, 329.0.

Step-3: 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate (3.0 g, 9.13 mmol) in Methanol (20 mL) were added NaOH (1.4 g, 36.50 mmol) and Water (20 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h before diluted with water. The organic solvent was removed under vacuum. The aqueous layer was acidified with Citric acid to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (2.5 g, crude) as a yellow oil. MS (ESI) calc'd for ($C_{13}H_9ClF_2N_2O_3$) $(M+1)^+$, 315.0, found 315.0.

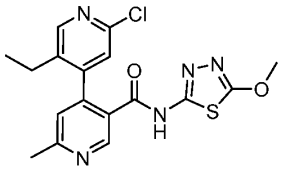
Step-4: 2'-chloro-5'-(difluoromethoxy)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



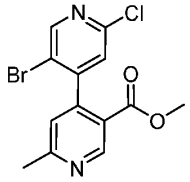
To a stirred solution of 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (50.0 mg, 0.15 mmol) in Acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (22.0 mg, 0.17 mmol) and 1-methyl-1H-imidazole (65.0 mg, 0.79 mmol) at 25 °C. Then a solution of TCFH (44.0 mg, 0.15 mmol) in acetonitrile (0.5 mL) was added to the above mixture at 25 °C. The resulting solution was stirred at 25 °C for 1 hr. The resulting mixture was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 40 min to afford 2'-chloro-5'-(difluoromethoxy)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (27.5 mg, 38% yield) as a white solid. MS (ESI) calc'd for ($C_{16}H_{12}ClF_2N_5O_3S$) $(M+1)^+$,428.0, found 428.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.97 (s, 1H), 8.33 (s, 1H), 7.72 (s, 1H), 7.45 (s, 1H), 7.31 – 6.80 (m, 1H), 4.07 (s, 3H), 2.61 (s, 3H).

Example 49

2'-chloro-5'-ethyl-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

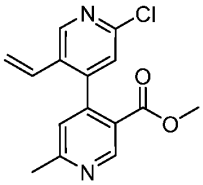


Step-1: methyl 5'-bromo-2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate



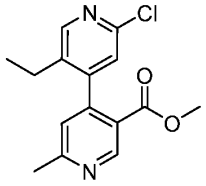
To a degassed solution of methyl 4-chloro-6-methylnicotinate (1.0 g, 5.39 mmol) in 1,4-Dioxane (10 mL) were sequentially added Bis(pinacolato)diboron (2.7 g, 10.78 mmol), potassium acetate (1.6 g, 16.16 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (1.2 g, 1.62 mmol) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at °C for 3 hours under nitrogen. To the above mixture were added a solution of 5-bromo-2-chloro-4-iodopyridine (1.0 g, 3.61 mmol), water (2 mL), potassium carbonate (1.5 g, 10.83 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (0792.0 mg, 1.08 mmol) in 1,4-Dioxane (10 mL) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 80 g silica gel column and eluted with 0~10% methanol in dichloromethane within 40 min to afford methyl 5'-bromo-2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (2.1 g, 99%) as a brown oil. MS (ESI) calculated for ($C_{13}H_{10}BrClN_2O_2$) $(M+1)^+$, 341.0; found, 341.0.

Step-2: methyl 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylate



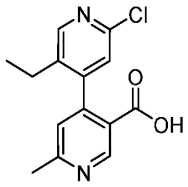
To a stirred solution of methyl 5'-bromo-2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (400.0 mg, 1.17 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (180.0 mg, 1.17 mmol) in Toluene (2 mL) was added 1,1'-Bis (di-t-butylphosphino)ferrocene palladium dichloride (76.0 mg, 0.12 mmol) at 20 °C under nitrogen atmosphere. To the above solution was added potassium phosphate (994.0 mg, 4.68 mmol) in water (0.2 mL) at 50 °C. The resulting solution was stirred at 100 °C for 16 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (4 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~40% ethyl acetate in petroleum ether within 30 min to afford methyl 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylate (260.0 mg, 67%) as a brown oil. MS (ESI) calculated for ($C_{15}H_{13}ClN_2O_2$) $(M+1)^+$, 289.1; found, 289.1.

Step-3: methyl 2'-chloro-5'-ethyl-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of methyl 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylate (250.0 mg, 0.87 mmol) in Ethyl acetate (10 mL) was added platinum(IV) oxide (25.0 mg, 0.11 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 1 hour under hydrogen atmosphere. The suspension was filtered. The filtrate was collected and concentrated under vacuum to afford methyl 2'-chloro-5'-ethyl-6-methyl-(4,4'-bipyridine)-3-carboxylate (240.0 mg, crude) as a brown oil. MS (ESI) calculated for ($C_{15}H_{15}ClN_2O_2$) $(M+1)^+$, 291.1; found, 291.1.

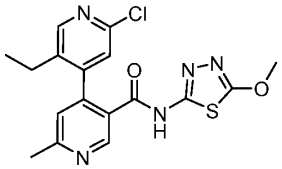
Step-4: 2'-chloro-5'-ethyl-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-5'-ethyl-6-methyl-(4,4'-bipyridine)-3-carboxylate (240.0 mg, 0.83 mmol) in Methanol (3 mL) was added a solution of sodium hydroxide (132.0

mg, 3.30 mmol) in water (3 mL) at 20 °C. The resulting solution was stirred at 80 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH 5~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-5'-ethyl-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (190.0 mg, crude) as a white solid. MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_2$) $(M+1)^+$, 277.1; found, 277.1.

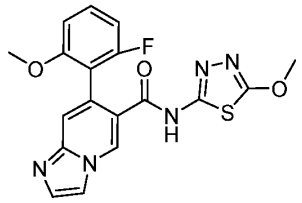
Step-5: 2'-chloro-5'-ethyl-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



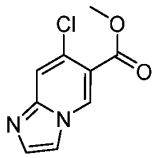
To a stirred solution of 2'-chloro-5'-ethyl-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (210.0 mg, 0.76 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (100.0 mg, 0.76 mmol) in acetonitrile (1 mL) was added 1-methyl-1H-imidazole (312.0 mg, 3.79 mmol). To the above solution was added a solution of TCFH (213.0 mg, 0.76 mmol) in acetonitrile (1 mL) at 20 °C under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 30 min to afford a yellow solid (90% purity). The yellow solid (90% purity) was dissolved in DMF (2 mL) and purified by prep-HPLC with the following conditions: (Column: Atlantis HILIC OBD Column, 19*150mm*5um; Mobile Phase A: Water(0.1%FA), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 65% B to 65% B in 8 min, 65% B to 95% B in 8.2 min, 95% B to 95% B in 10 min, 95% B to 65% B in 11 min, 65% B; Wave Length: 220\254 nm; RT1(min): 7; Injection Volume: 0.4 mL; Number Of Runs: 5) to afford 2'-chloro-5'-ethyl-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (64.5 mg, 21%) as a white solid. MS (ESI) calculated for ($C_{17}H_{16}ClN_5O_2S$) $(M+1)^+$, 390.1; found, 390.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.97 (s, 1H), 8.36 (s, 1H), 7.33 (s, 1H), 7.29 (s, 1H), 4.06 (s, 3H), 2.60 (s, 3H), 2.41 – 2.29 (m, 2H), 1.00 – 0.92 (m, 3H).

Example 50

7-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)imidazo(1,2-a)pyridine-6-carboxamide

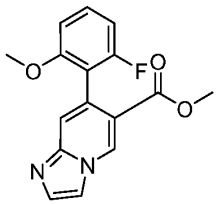


Step-1: methyl 7-chloroimidazo(1,2-a)pyridine-6-carboxylate



To a solution of methyl 6-amino-4-chloronicotinate (900.0 mg, 4.82 mmol) in Ethanol (6 mL) were added Sodium bicarbonate (689.0 mg, 8.20 mmol), 2-chloroacetaldehyde (4.3 g, 40% in water, 21.70 mmol) at 20 °C. The resulting solution was stirred at 80 °C under nitrogen for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting mixture was dissolved in DCM (6 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to an 80 g silica gel column that was eluted with 0~10 % methanol in dichloromethane within 35 min to afford methyl 7-chloroimidazo(1,2-a)pyridine-6-carboxylate (900.0 mg, 70%). MS (ESI) calc'd for ($C_9H_7ClN_2O_2$) $(M+1)^+$, 211.0, found 211.0.

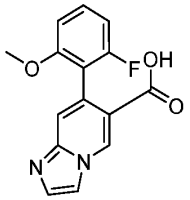
Step-2: methyl 7-(2-fluoro-6-methoxyphenyl)imidazo(1,2-a)pyridine-6-carboxylate



A mixture of methyl 7-chloroimidazo(1,2-a)pyridine-6-carboxylate (600.0 mg, 2.56 mmol), (2-fluoro-6-methoxyphenyl)boronic acid (654.0 mg, 3.85 mmol), XPhos (146.0 mg, 0.31 mmol) and XPhos Pd G3 (217.0 mg, 0.26 mmol) in 1,4-Dioxane (1 mL) and Water (0.3 mL) was stirred at 80 °C for 2 hr under nitrogen. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting mixture was dissolved in DMF (5 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~35 % acetonitrile in water within 40 min

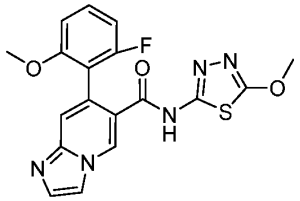
to afford methyl 7-(2-fluoro-6-methoxyphenyl)imidazo(1,2-a)pyridine-6-carboxylate (200.0 mg, 23%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{13}FN_2O_3$) $(M+1)^+$, 301.0, found 301.0.

Step-3: 7-(2-fluoro-6-methoxyphenyl)imidazo(1,2-a)pyridine-6-carboxylic acid



A mixture of methyl 7-(2-fluoro-6-methoxyphenyl)imidazo(1,2-a)pyridine-6-carboxylate (120.0 mg, 0.36 mmol) and LiOH (34.5 mg, 1.43 mmol) in Tetrahydrofuran (3 mL) and Water (1 mL) was stirred at 50 °C for 12 hr. The volatiles were removed under vacuum. The aqueous layer was acidified with citric acid to pH ~ 5. The solvents were removed under vacuum to afford 7-(2-fluoro-6-methoxyphenyl)imidazo(1,2-a)pyridine-6-carboxylic acid (950.0 mg, crude) as a yellow solid, which was used directly without further purification. MS (ESI) calc'd for ($C_{15}H_{11}FN_2O_3$) $(M+1)^+$, 287.0, found 286.9.

Step-4: 7-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)imidazo(1,2-a)pyridine-6-carboxamide

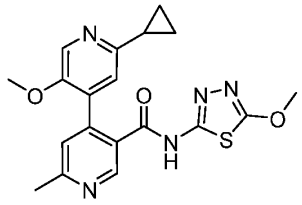


To a mixture of 7-(2-fluoro-6-methoxyphenyl)imidazo(1,2-a)pyridine-6-carboxylic acid (700.0 mg, 0.24 mmol) in Acetonitrile (3 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (38.5 mg, 0.29 mmol), and NMI (120.0 mg, 1.46 mmol). To the above solution was added a solution of TCFH (103.0 mg, 0.36 mmol) in Acetonitrile (1 mL) at 20 °C under nitrogen. The mixture was stirred at 20 °C for 2 hr under nitrogen. The volatiles were removed under vacuum. The residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~30% acetonitrile in water within 40 min to afford 7-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)imidazo(1,2-a)pyridine-6-carboxamide (30.9 mg, 30%) as a yellow solid. MS (ESI) calc'd for ($C_{18}H_{14}FN_5O_3S$) $(M+1)^+$, 400.0, found 400.0. ^{1}H NMR (400 MHz,

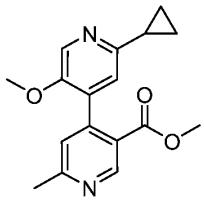
DMSO-d_6) δ 12.82 (s, 1H), 9.13 (s, 1H), 8.12 (d, J = 1.2 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.54 (s, 1H), 7.45 – 7.32 (m, 1H), 6.97 – 6.75 (m, 2H), 4.07 (s, 3H), 3.59 (s, 3H).

Example 51

2'-cyclopropyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

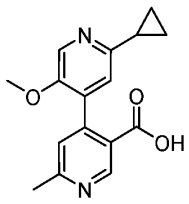


Step-1: methyl 2'-cyclopropyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



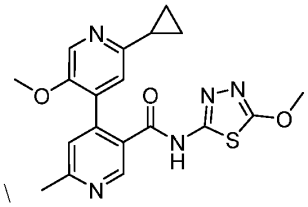
To a stirred solution of methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (800.0 mg, 2.73 mmol) in 1,4-Dioxane (10 mL) were added cyclopropylboronic acid (235.0 mg, 2.73 mmol) and K_3PO_4 (1.2 g, 5.47 mmol) at 20 °C. To the above solution was added PdAMphos (230.1 mg, 0.27 mmol) at 20 °C under nitrogen. The resulting mixture was then stirred at 80 °C for 2 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~70% ethyl acetate in petroleum ether within 25 min to afford methyl 2'-cyclopropyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (300.0 mg, 33%) as a yellow oil. MS (ESI) calc'd for ($C_{17}H_{18}N_2O_3$) $(M+1)^+$, 299.2; found, 299.2.

Step-2: 2'-cyclopropyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-cyclopropyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (300.0 mg, 1.01 mmol) in Tetrahydrofuran (2 mL) was added a solution of lithium hydroxide (24.1 mg, 1.01 mmol) in Water (2 mL) at 20 °C. The resulting solution was stirred at 20 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-cyclopropyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (111.0 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{16}H_{16}N_2O_3$) (M+1)+, 245.1; found, 245.1

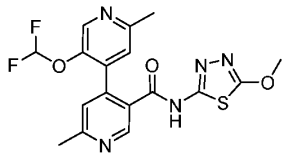
Step-3: 2'-cyclopropyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



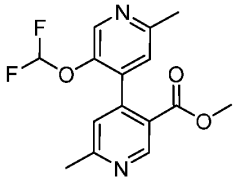
To a solution of 2'-cyclopropyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (100 mg, 0.35 mmol) in Acetonitrile (2 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (46.1 mg, 0.35 mmol) and 1-methylimidazole (144.3 mg, 1.76 mmol) at 20 °C under nitrogen. To the above solution was added a solution of TCFH (98.3 mg, 0.35 mmol) in Acetonitrile (2 mL) at 20 °C under nitrogen. The resulting mixture was then stirred at 20 °C for 1 hr. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~55% acetonitrile in water within 30 min to afford 2'-cyclopropyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (82.4 mg, 58%) as a white solid. MS (ESI) calc'd for ($C_{19}H_{19}N_5O_3S$) (M+1)+, 398.1; found 398.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.75 (s, 1H), 8.15 (s, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 4.07 (s, 3H), 3.56 (s, 3H), 2.59 (s, 3H), 2.13 – 2.16 (m, 1H), 0.98 – 0.85 (m, 4H).

Example 52

5'-(difluoromethoxy)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

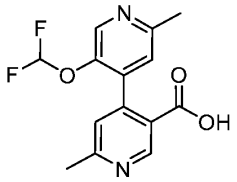


Step 1 methyl 5'-(difluoromethoxy)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate



To a degassed solution of methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate (150.0 mg, 0.45 mmol) in 1,2-Dimethoxyethane (2 mL) were added (1,1′-Bis(diphenylphosphino)ferrocene)dichloropalladium(II), K_2CO_3 (186.3 mg, 1.35 mmol) at 25 °C under nitrogen atmosphere. Then 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (63 mg, 0.50 mmol) was added to the above mixture at 120 °C. The resulting mixture was stirred at 120 °C for 3 hr. The suspension was filtered. The filtrate was concentrated under vacuum. The resulting residue was dissolved in acetonitrile (4 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~55% acetonitrile in water within 40 min to afford methyl 5'-(difluoromethoxy)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (70 mg, 42%) as a yellow oil MS (ESI) calc'd for ($C_{15}H_{14}F_2N_2O_3$) $(M+1)^+$, 309.1; found 309.1.

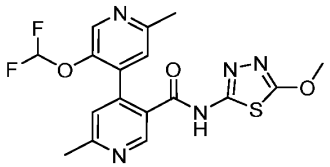
Step 2 5'-(difluoromethoxy)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 5'-(difluoromethoxy)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (70.0 mg, 0.227 mmol) in Methanol (1 mL) were added NaOH (36.0 mg, 0.91 mmol) and Water (1 mL) at 25 °C. The resulting solution was stirred at 25 °C for 2 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with Citric acid to pH ~7 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in acetonitrile (2 mL) which was applied to a 20 g C18

column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~30% acetonitrile in water within 30 min to afford 5'-(difluoromethoxy)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (60.0 mg, 89%) as a yellow oil. MS (ESI) calc'd for ($C_{14}H_{12}F_2N_2O_3$) $(M+1)^+$, 295.1; found, 295.1.

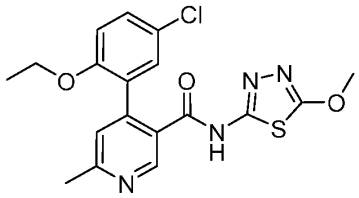
Step 3 5'-(difluoromethoxy)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



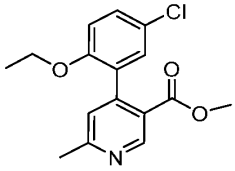
To a stirred solution of 5'-(difluoromethoxy)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (60.0 mg, 0.20 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (26.0 mg, 0.20 mmol) in Acetonitrile (1 mL) was added 1-methyl-1H-imidazole (84.0 mg, 1.02 mmol) at 25 °C. Then a solution of TCFH (56.0 mg, 0.20 mmol) in acetonitrile (0.5 mL) was added to the above mixture at 25 °C. The mixture was stirred at 25 °C for 1 hr. The resulting mixture was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~38% acetonitrile in water within 30 min to afford 5'-(difluoromethoxy)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (25.0 mg, 29%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{15}F_2N_5O_3S$) $(M+1)^+$,408.1, found 408.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.91 (s, 1H), 8.32 (s, 1H), 7.42 – 7.32 (m, 2H), 7.22 – 6.85 (m, 1H), 4.07 (s, 3H), 2.60 (s, 3H), 2.53 (s, 3H).

Example 53

4-(5-chloro-2-ethoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

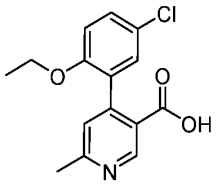


Step 1 methyl 4-(5-chloro-2-ethoxyphenyl)-6-methylnicotinate



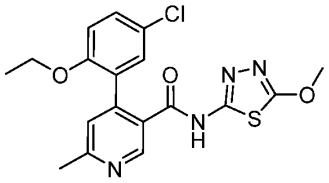
To a solution of methyl 4-chloro-6-methylnicotinate (500.0 mg, 2.56 mmol) in 1,4-Dioxane (8 mL) were added (5-chloro-2-ethoxyphenyl) boronic acid (513.0 mg, 2.56 mmol), $Pd(dppf)Cl_2$ (209.0 mg, 0.25 mmol), K_2CO_3 (707.0 mg, 5.12 mmol) and Water (2 mL) at 18 °C. The resulting solution was stirred at 80 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in DCM (6 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 80 g silica gel column that was eluted with 0~45% ethyl acetate in petroleum ether within 40 min to afford methyl 4-(5-chloro-2-ethoxyphenyl)-6-methylnicotinate (680.0 mg, 70%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{16}ClNO_3$) $(M+1)^+$, 306.0; found 306.0.

Step 2 4-(5-chloro-2-ethoxyphenyl)-6-methylnicotinic acid



To a solution of methyl 4-(5-chloro-2-ethoxyphenyl)-6-methylnicotinate (200.0 mg, 0.52 mmol) in Tetrahydrofuran (1.5 mL) were added LiOH (37.6 mg, 1.57 mmol) and Water (0.5 mL) at 20 °C. The resulting solution was stirred at 50 °C for 16 hr. The reaction mixture was diluted with water. The aqueous layer was acidified with citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(5-chloro-2-ethoxyphenyl)-6-methylnicotinic acid (160.0 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{15}H_{14}ClNO_3$) $(M+1)^+$, 292.0; found 292.0.

Step 3 4-(5-chloro-2-ethoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

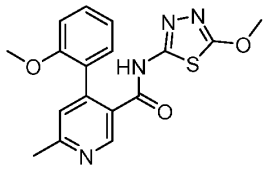


To a mixture of 4-(5-chloro-2-ethoxyphenyl)-6-methylnicotinic acid (160.0 mg, 0.43 mmol) in Acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (69.1 mg, 0.52 mmol)

and 1-methyl-1H-imidazole (108.0 mg, 1.31 mmol). A solution of TCFH (184.0 mg, 0.65 mmol) in Acetonitrile (1 mL) was added thereto dropwise under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The organic solvent was removed under vacuum. The residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~46% acetonitrile in water within 40 min to afford 4-(5-chloro-2-ethoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (42.0 mg, 23 %) as a white solid. MS (ESI) calc'd for ($C_{18}H_{17}ClN_4O_3S$) $(M+1)^+$, 405.0; found 405.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 8.73 (s, 1H), 7.40 – 7.33 (m, 3H), 6.97 – 6.99 (d, J = 8.8 Hz, 1H), 4.07 (s, 3H), 3.78 (d, J = 6.8 Hz, 2H), 2.58 (s, 3H), 1.06 – 1.09 (t, J = 6.8 Hz, 3H).

Example 54

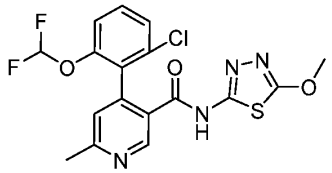
N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



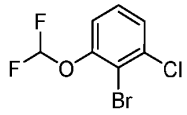
To a stirred solution of Intermediate C (310.0 mg, 1.27 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (167.0 mg, 1.27 mmol) in acetonitrile (2 mL) was added 1-methylimidazole (522.3 mg, 6.37 mmol). Then TCFH (358.0 mg, 1.27 mmol) in acetonitrile (1 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The resulting residue was dissolved in acetonitrile (2 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~38% acetonitrile in water within 30 min to afford N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide (219.0 mg, 47% yield) as a white solid. MS (ESI) calc'd for ($C_{17}H_{16}N_4O_3S$) $(M+1)^+$, 357.1; found 357.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 8.67 (s, 1H), 7.45 – 7.23 (m, 3H), 7.12 – 7.02 (m, 1H), 7.02 – 6.95 (m, 1H), 4.07 (s, 3H), 3.64 (s, 3H), 2.57 (s, 3H).

Example 55

4-(2-chloro-6-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

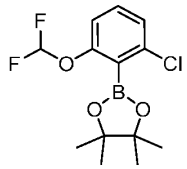


Step-1: 2-Bromo-1-chloro-3-(difluoromethoxy)benzene



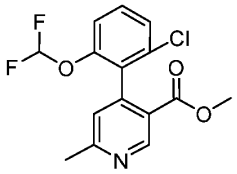
To a stirred solution of 2-bromo-3-chlorophenol (5.0 g, 24.10 mmol) in N,N-Dimethylformamide (30 mL) were added K_2CO_3 (10.0 g, 72.30 mmol) in Water (3 mL) at 23 °C. To the above solution was added Sodium chlorodifluoroacetate (7.4 g, 48.20 mmol) at 23 °C under nitrogen. The resulting solution was stirred at 100 °C for 16 hr. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (4 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~20% ethyl acetate in petroleum ether within 25 min to afford 2-bromo-1-chloro-3-(difluoromethoxy)benzene (4.9 g, 75%) as a colorless oil. MS (ESI) calc'd for ($C_7H_4BrClF_2O$) $(M+1)^+$, 256.9; found, 257.0.

Step-2: 2-(2-chloro-6-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



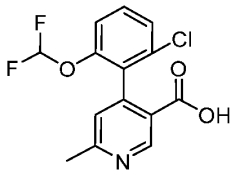
To a stirred solution of 2-bromo-1-chloro-3-(difluoromethoxy) benzene (4.9 g, 19.03 mmol) in 1,4-Dioxane (20 mL) were added Bis(pinacolato)diboron (9.7 g, 38.10 mmol), AcOK (3.7 g, 38.10 mmol) and $Pd(dppf)Cl_2$ (1.6 g, 1.90 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 3 hr under nitrogen. The organic solvent was removed under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 120 g silica gel column and eluted with 0~10% ethyl acetate in petroleum ether within 20 min to afford 2-(2-chloro-6-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 g, 22%) as a colorless oil. MS (ESI) calc'd for ($C_{13}H_{16}BClF_2O_3$) $(M+1)^+$, 305.1; found, 305.0.

Step-3: methyl 4-(2-chloro-6-(difluoromethoxy)phenyl)-6-methylnicotinate



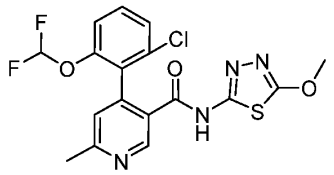
To a stirred solution of 2-(2-chloro-6-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 g, 5.25 mmol) in 1,4-Dioxane (6 mL) were added methyl 4-iodo-6-methylnicotinate (728.1 mg, 2.63 mmol, K_2CO_3 (1.4 g, 10.51 mmol) and Water (1.2 mL). To the above solution was added $Pd(dppf)Cl_2$ (429.0 mg, 0.53 mmol) at 23 °C under nitrogen. The resulting solution was stirred at 100 °C for 16 hr under nitrogen. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 30 min to afford methyl 4-(2-chloro-6-(difluoromethoxy)phenyl)-6-methylnicotinate (140.0 mg, 8%) as a white solid. MS (ESI) calc'd for ($C_{15}H_{12}ClF_2NO_3$) $(M+1)^+$, 328.0, found 328.2.

Step-4: 4-(2-chloro-6-(difluoromethoxy)phenyl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(2-chloro-6-(difluoromethoxy)phenyl)-6-methylnicotinate (140.0 mg, 0.43 mmol) in Tetrahydrofuran (1 mL) and Water (1 mL) was added LiOH (20.0 mg, 0.85 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 3 hr. The mixture was diluted with water. The aqueous layer was acidified with Citric acid to pH ~3 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 25 min to afford 4-(2-chloro-6-(difluoromethoxy)phenyl)-6-methylnicotinic acid (60.0 mg, 44%) as a white solid. MS (ESI) calc'd for ($C_{14}H_{10}ClF_2NO_3$) $(M+1)^+$, 314.0, found, 314.0.

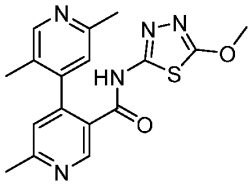
Step-5: 4-(2-chloro-6-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



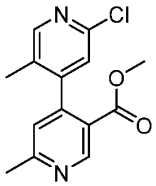
To a stirred solution of 4-(2-chloro-6-(difluoromethoxy)phenyl)-6-methylnicotinic acid (50.0 mg, 0.159 mmol) in Acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (21.0 mg, 0.16 mmol) and 1-methylimidazole (65.0 mg, 0.79 mmol). To the above solution was added a solution of TCFH (45.0 mg, 0.16 mmol) in Acetonitrile (0.5 mL). The mixture was then stirred at 23 °C for 2 hr. The resulting mixture was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 30 min to afford 4-(2-chloro-6-(difluoromethoxy)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (40.6 mg, 59%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{13}ClF_2N_4O_3S$) $(M+1)^+$, 427.0, found, 427.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.99 (s, 1H), 7.57 – 7.41 (m, 2H), 7.30 – 7.22 (m, 2H), 7.22 – 6.93 (m, 1H), 4.06 (s, 3H), 2.60 (s, 3H).

Example 56

N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxamide



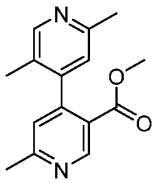
Step 1 methyl 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of 4-bromo-2-chloro-5-methylpyridine (1.0 g, 4.84 mmol) in 1,4-Dioxane (8 mL) were sequentially added methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (1.3 g, 4.84 mmol), water (1.6 mL) and K_2CO_3 (2.0 g, 14.53 mmol) at 23 °C. To the above solution was added $PdCl_2$(dppf) (354.0 mg, 0.48 mmol) at

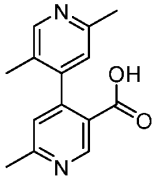
23 °C. The resulting solution was stirred at 80 °C for 2 hr. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 30 min to afford methyl 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (588.0 mg, 37%) as a brown oil. MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_2$) $(M+1)^+$, 277.1; found, 277.1.

Step 2 methyl 2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of methyl 2'-chloro-5',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (150.0 mg, 0.54 mmol) in 1,4-Dioxane (1 mL) were sequentially added Trimethylboroxine (136.0 mg, 1.08 mmol), K_2CO_3 (225.0 mg, 1.63 mmol) and water (0.2 mL) at 23 °C. To the above solution was added $PdCl_2$(dppf) (39.7 mg, 0.05 mmol) at 25 °C under nitrogen. The resulting mixture was then stirred at 120 °C for 1 hr under nitrogen. The volatiles were removed under vacuum and purified directly. The resulting residue was dissolved in DMF (3 mL) which was applied to an 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 30 min to afford methyl 2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxylate (60.0 mg, 41%) as a brown oil. MS (ESI) calculated for ($C_{15}H_{16}N_2O_2$) $(M+1)^+$, 257.1; found, 257.1.

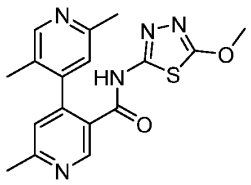
Step 3 2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxylate (160.0 mg, 0.63 mmol) in Methanol (2 mL) was added sodium hydroxide (50.4 mg, 1.26 mmol) in water (1 mL) at 20 °C. The resulting solution was stirred at room temperature for 4 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH 5~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting

residue was dissolved in DMF (2 mL) which was applied to an 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~30% acetonitrile in water within 30 min to afford 2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxylic acid (36.0 mg, 24%) as a yellow solid. MS (ESI) calculated for ($C_{14}H_{14}N_2O_2$) $(M+1)^+$, 243.1; found, 243.1.

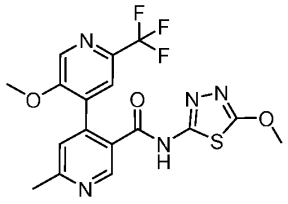
Step 4 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxamide



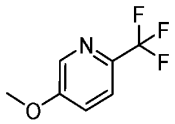
To a stirred solution of 2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxylic acid (36.0 mg, 0.15 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (19.5 mg, 0.15 mmol) in acetonitrile (1 mL) was added 1-methyl-1H-imidazole (61.0 mg, 0.74 mmol) at 25 °C. To the above solution was added a solution of TCFH (41.7 mg, 0.15 mmol) in acetonitrile (0.5 mL) at 25 °C. The resulting solution was stirred at 25 °C for 2 hr under nitrogen. The mixture was dissolved in DMF (3 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 30% B in 8 min, 30% B to 95% B in 8.2 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 254 nm; RT1(min): 7; Injection Volume: 1 mL; Number Of Runs: 4) to afford N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',5',6-trimethyl-(4,4'-bipyridine)-3-carboxamide (26.1 mg, 49%) as a white solid. MS (ESI) calculated for ($C_{17}H_{17}N_5O_2S$) $(M+1)^+$, 356.1; found, 356.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (br, 1H), 8.90 (s, 1H), 8.31 (s, 1H), 7.23 (s, 1H), 6.99 (s, 1H), 4.04 (s, 3H), 2.58 (s, 3H), 2.42 (s, 3H), 1.97 (s, 3H).

Example 57

5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxamide

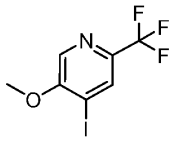


Step-1: 5-methoxy-2-(trifluoromethyl)pyridine



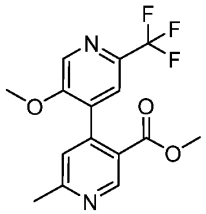
To a stirred solution of 6-(trifluoromethyl)pyridin-3-ol (4.0 g, 24.52 mmol) in N,N-Dimethylformamide (DMF) (40 mL) were added K_2CO_3 (10.2 g, 73.6 mmol) and MeI (1.8 mL, 29.4 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~10% ethyl acetate in petroleum ether within 20 min to afford 5-methoxy-2-(trifluoromethyl)pyridine (3.5 g, 80 %) as a colorless oil. MS (ESI) calculated for $(C_7H_6F_3NO)$ $(M+1)^+$, 178.0; found, 178.1.

Step-2: 4-iodo-5-methoxy-2-(trifluoromethyl)pyridine



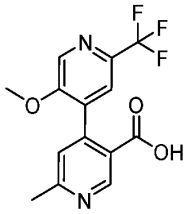
To a degassed solution of 5-methoxy-2-(trifluoromethyl)pyridine (1.0 g, 5.65 mmol) in dry tetrahydrofuran (THF) (5 mL) was added n-butyllithium (4.5 mL, 11.29 mmol, 2.5 M in hexane) dropwise at -60 °C and stirred at -60 °C for 1 hr under nitrogen atmosphere. Then a solution of I_2 (2.8 g, 11.29 mmol) in THF was added to the above mixture at -60 °C. The resulting solution was stirred from -60 °C to 23 °C for 2 hr. The reaction mixture was quenched by the addition of water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (8 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~90% acetonitrile in water within 35 min to afford 4-iodo-5-methoxy-2-(trifluoromethyl)pyridine (135.0 mg, 8% yield) as a yellow solid. MS (ESI) calculated for $(C_7H_5F_3INO)$ $(M+1)^+$, 304; found, 353.1.

Step-3: methyl 5'-methoxy-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxylate



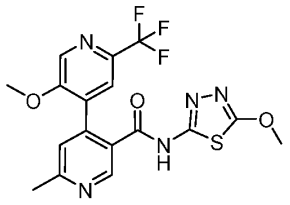
To a stirred solution of 4-iodo-5-methoxy-2-(trifluoromethyl)pyridine (300.0 mg, 0.99 mmol) in 1,4-Dioxane (1.5 mL) were sequentially added methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (412.0 mg, 1.49 mmol), water (0.3 mL) and K_2CO_3 (410.0 mg, 2.97 mmol) at 23 °C. To the above solution was added $PdCl_2(dppf)$ (72.4 mg, 0.10 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The resulting mixture was dissolved in DMF (4 mL) and was filtered. The filtrate was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~70% acetonitrile in water within 30 min to afford methyl 5'-methoxy-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxylate (140.0 mg, 43% yield) as a yellow oil. MS (ESI) calculated for ($C_{15}H_{13}F_3N_2O_3$) $(M+1)^+$, 327.0; found, 327.1.

Step-4: 5'-methoxy-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 5'-methoxy-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxylate (140.0 mg, 0.43 mmol) in methanol (1 mL) were added NaOH (68.6 mg, 1.72 mmol) and water (1.0 mL) at 23 °C. The resulting solution was stirred at 50 °C for 1 hr before diluted with water. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 25 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 30 min to afford 5'-methoxy-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxylic acid (80.0 mg, 59%) as a white solid. MS (ESI) calculated for ($C_{14}H_{11}F_3N_2O_3$) $(M+1)^+$, 313.0; found, 313.1.

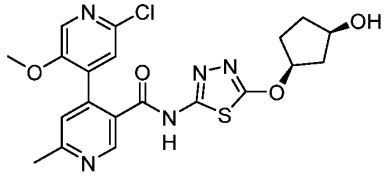
Step-5: 5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxamide

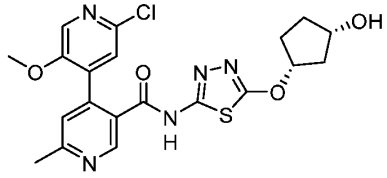


To a stirred solution of 5'-methoxy-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxylic acid (47.0 mg, 0.15 mmol) in acetonitrile (1 mL) under argon atmosphere were added 5-methoxy-1,3,4-thiadiazol-2-amine (21.7 mg, 0.17 mmol) and 1-Methylimidazole (61.5 mg, 0.75 mmol) at 23 °C. To the above solution was added a solution of TCFH (0.15 mmol) in acetonitrile (0.5 mL) at 23 °C under nitrogen. The resulting mixture was then stirred at 23 °C for 1 hr. The solvents were removed under vacuum. The residue was dissolved in DMF (2 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min, 35% B to 40% B in 15 min, 40% B; Wave Length: 254 nm; RT1(min): 7.7) to afford 5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-2'-(trifluoromethyl)-(4,4'-bipyridine)-3-carboxamide (14.3 mg, 22%) as a white solid. MS (ESI) calculated for ($C_{17}H_{14}F_3N_5O_3S$) $(M+1)^+$, 426; found, 426.10. ^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.86 (s, 1H), 8.54 (s, 1H), 7.88 (s, 1H), 7.43 (s, 1H), 4.05 (s, 3H), 3.74 (s, 3H), 2.59 (s, 3H).

Example 58 and 59

2'-chloro-N-(5-(((1S,3R)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and 2'-chloro-N-(5-(((1R,3S)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide





The mixture of compounds 2'-chloro-N-(5-(((1s,3r)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (42.6 mg) was

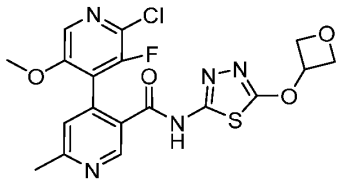
separated by prep-chiral HPLC with the following conditions: (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.1% FA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 15 mL/min; Gradient: 50% B to 50% B in 34 min; Wave Length: 220/254 nm; RT1(min): 18.26; RT2(min): 26.54; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 1.5 mL; Number Of Runs: 2) to afford 2'-chloro-N-(5-(((1S,3R)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (16.2 mg, 38% yield) as a white solid with the first peak on chiral HPLC and 2'-chloro-N-(5-(((1R,3S)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (16.6 mg, 39% yield) as a white solid with the second peak on chiral HPLC. The absolute stereochemistry was not determined and was arbitrarily assigned.

2'-chloro-N-(5-(((1S,3R)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.82 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.14 (s, 1H), 5.39 – 5.26 (m, 1H), 4.64 – 4.50 (m, 1H), 4.27 – 4.13 (m, 1H), 3.63 (s, 3H), 2.58 (s, 3H), 2.22 – 2.15 (m, 1H), 2.01 – 1.99 (m, 2H), 1.93 – 1.91 (m, 1H), 1.89 – 1.88 (m, 1H).

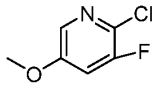
2'-chloro-N-(5-(((1R,3S)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.82 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 7.14 (s, 1H), 5.39 – 5.26 (m, 1H), 4.64 – 4.50 (m, 1H), 4.27 – 4.13 (m, 1H), 3.63 (s, 3H), 2.58 (s, 3H), 2.22 – 2.15 (m, 1H), 2.01 – 1.99 (m, 2H), 1.93 – 1.91 (m,1H), 1.89 – 1.88 (m, 1H).

Example 60

2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

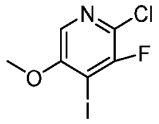


Step 1 2-chloro-3-fluoro-5-methoxypyridine



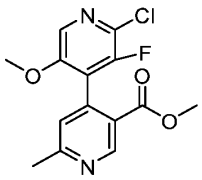
To a solution of 6-chloro-5-fluoropyridin-3-ol (3.0 g, 20.33 mmol) in acetone (15 mL) was added MeI (2.5 mL, 40.7 mmol) and K_2CO_3 (5.6 g, 40.7 mmol) at 20 °C under nitrogen atmosphere. The resulting solution was stirred at 20 °C for 18 hr under nitrogen. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120.0 g silica gel column that was eluted with 0~30% ethyl acetate in petroleum ether within 25 min to afford 2-chloro-3-fluoro-5-methoxypyridine (2.1 g, 63% yield) as a colorless oil. MS (ESI) calc'd for (C_6H_5ClFNO) $(M+1)^+$, 162.0; found 162.0.

Step 2 2-chloro-3-fluoro-4-iodo-5-methoxypyridine



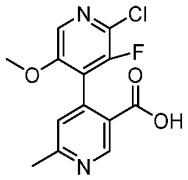
To a degassed solution of 2-chloro-3-fluoro-5-methoxypyridine (2.1 g, 13.00 mmol) in dry Tetrahydrofuran (5 mL) was added n-butyllithium (5.8 mL, 14.30 mmol, 2.5 M in hexane) dropwise at -60 °C and stirred at -60 °C for 1 hr under nitrogen atmosphere. Then iodine (3.6 g, 14.30 mmol) was added to the above mixture at -60 °C. The resulting solution was stirred at 20 °C for 2 hr under nitrogen. The reaction mixture was quenched by the addition of saturated sodium thiosulfate aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~15% ethyl acetate in petroleum ether within 30 min to afford 2-chloro-3-fluoro-4-iodo-5-methoxypyridine (3.5 g, 89% yield) as a white solid. MS (ESI) calc'd for ($C_6H_4ClFINO$) $(M+1)^+$, 287.9; found, 288.0.

Step 3 methyl 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



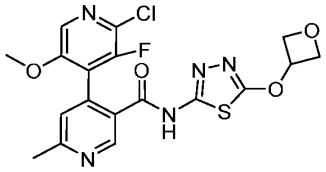
To a degassed solution of methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (3.0 g, 10.83 mmol) and 2-chloro-3-fluoro-4-iodo-5-methoxypyridine (2.1 g, 7.31 mmol) in 1,4-dioxane (20 mL) were sequentially added water (4 mL), potassium carbonate (3.0 g, 21.71 mmol) and (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (1.6 g, 2.19 mmol) at 25 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (10 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 30 min to afford methyl 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinate (2.2 g, 87% yield) as a white solid. MS (ESI) calc'd for ($C_{14}H_{12}ClFN_2O_3$) $(M+1)^+$, 311.1, found 311.1.

Step 4 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (800.0 mg, 2.57 mmol) in methanol (5 mL) were added water (5 mL) and sodium hydroxide (412.0 mg, 10.30 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with sat. citric acid solution to pH ~6. The resulting mixture was dissolved in acetonitrile (3 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 0~10% acetonitrile in water within 30 min to afford 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (260.0 mg, 32% yield) as a yellow oil. MS (ESI) calc'd for ($C_{13}H_{10}ClFN_2O_3$) $(M+1)^+$, 297.0, found 297.0.

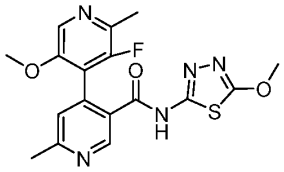
Step 5 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



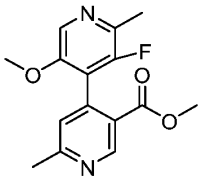
To a stirred solution of 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (100 mg, 0.34 mmol) and 5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-amine (58.4 mg, 0.34mmol, Example 13, Step 1) in acetonitrile (1 mL) was added 1-methylimidazole (110.7 mg, 1.35 mmol). Then TCFH (95.0 mg, 0.34 mmol) in acetonitrile (0.5 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The mixture was dissolved in acetonitrile (2 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 30% B in 8 min, 30% B; Wave Length: 254 nm; RT1(min): 7.5) to afford 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (56.0 mg, 36% yield) as a white solid. MS (ESI) calc'd for $(C_{18}H_{15}ClFN_5O_4S)$ $(M+1)^+$, 452.1; found 452.1. ^1H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.46 (s, 1H), 5.75 – 5.62 (m, 1H), 4.92 – 4.78 (m, 2H), 4.68 – 4.52 (m, 2H), 3.74 (s, 3H), 2.59 (s, 3H).

Example 61

3'-fluoro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



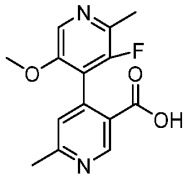
Step 1 methyl 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of methyl 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (800.0 mg, 2.57 mmol) in 1,4-dioxane (8 mL) were sequentially added

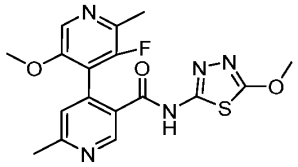
Trimethylboroxine (388.0 mg, 3.09 mmol), (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) (188.0 mg, 0.26 mmol) and potassium carbonate (1.0 g, 7.72 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 2 hr under nitrogen. The reaction solution was diluted with ethyl acetate, and the suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (3 mL) which was applied to a 80.0 C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 30 min to afford methyl 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (268.0 mg, 32% yield) as a brown oil. MS (ESI) calc'd for ($C_{15}H_{15}FN_2O_3$) $(M+1)^+$, 291.1; found 291.1.

Step 2 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylate (260.0 mg, 0.90 mmol) in methanol (1.5 mL) were added water (1.5 mL) and Sodium hydroxide (143.0 mg, 3.58 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 1 hr under nitrogen. The organic solvent was removed under vacuum. The aqueous layer was acidified with sat. citric acid solution to pH ~6. The resulting mixture was dissolved in acetonitrile (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 0~10% acetonitrile in water within 30 min to afford 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (168.0 mg, 64% yield) as a white solid. MS (ESI) calc'd for ($C_{14}H_{13}FN_2O_3$) $(M+1)^+$, 277.1; found, 277.1.

Step 3 3'-fluoro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

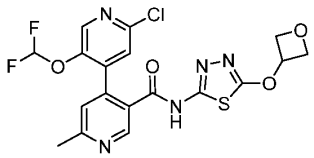


To a stirred solution of 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (140.0 mg, 0.51 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (67.0 mg, 0.51 mmol) in

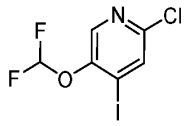
acetonitrile (1 mL) was added 1-methylimidazole (166.5 mg, 2.03 mmol). Then TCFH (142.0 mg, 0.51 mmol) in acetonitrile (1 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The resulting residue was dissolved in acetonitrile (5 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~43% acetonitrile in water within 30 min to afford 3'-fluoro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (85.0 mg, 43% yield) as a white solid. MS (ESI) calc'd for ($C_{17}H_{16}FN_5O_3S$) $(M+1)^+$, 390.1; found 390.2. ^1H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.91 (s, 1H), 8.17 (s, 1H), 7.39 (s, 1H), 4.07 (s, 3H), 3.68 (s, 3H), 2.59 (s, 3H), 2.43 (s, 3H).

Example 62

2'-chloro-5'-(difluoromethoxy)-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

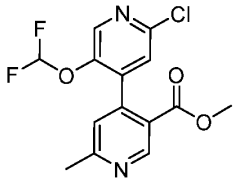


Step 1 2-chloro-5-(difluoromethoxy)-4-iodopyridine



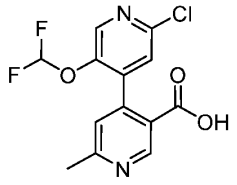
To a stirred solution of 6-chloro-4-iodopyridin-3-ol (2.0 g, 7.83 mmol) in N,N-Dimethylformamide (20 mL) were added sodium 2-chloro-2,2-difluoroacetate (2.4 g, 15.68 mmol) and Cs_2CO_3 (3.3 g, 10.18 mmol) at 25 °C. The resulting solution was stirred at 80 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (4 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to 80 g silica gel column that was eluted with 0~21% ethyl acetate in petroleum ether within 30 min to afford 2-chloro-5-(difluoromethoxy)-4-iodopyridine (1.9 g, 76%) as a white solid. MS (ESI) calculated for ($C_6H_3ClF_2INO$) $(M+1)^+$, 305.0; found, 305.7.

Step 2 methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate



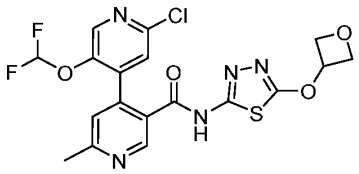
To a degassed solution of methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (2.3 g, 8.44 mmol) and 2-chloro-5-(difluoromethoxy)-4-iodopyridine (1.9 g, 6.22 mmol) in 1,4-Dioxane (9 mL) and water (1.8 mL) were added K_2CO_3 (2.3 g, 16.93 mmol) and (1,1′-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) complex with dichloromethane (1.4 g, 1.69 mmol) at 23 °C under nitrogen atmosphere. The resulting solution was stirred at 80 °C for 2 hr under nitrogen atmosphere. The suspension was filtered. The filtrate was concentrated under vacuum. The resulting residue was dissolved in DCM (10 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~45% ethyl acetate in petroleum ether within 30 min to afford methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate (1.7 g, 82%) as a yellow oil. MS (ESI) calculated for ($C_{14}H_{11}ClF_2N_2O_3$) $(M+1)^+$, 329.0; found, 329.10.

Step 3 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylate (1.7 g, 5.17 mmol) in methanol (5mL) was added a solution of NaOH (0.83 g, 20.69 mmol) in H_2O (1 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~6. The resulting mixture was diluted with DMF (2 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 35 min to afford 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (120.0 mg, 6%) as a white solid. MS (ESI) calculated for ($C_{13}H_9ClF_2N_2O_3$) $(M+1)^+$, 315.0; found, 315.10.

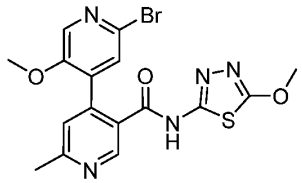
Step 4 2'-chloro-5'-(difluoromethoxy)-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



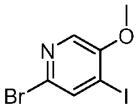
To a stirred solution of 2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (347.0 mg, 1.10 mmol) in acetonitrile (4 mL) were added 5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-amine (191.0 mg, 1.10 mmol, Example 13, Step 1) and 1-Methylimidazole (452.0 mg, 5.51 mmol) at 23 °C. To the above solution was added a solution of TCFH (309.0 mg, 1.10 mmol) in acetonitrile (2 mL) at 23 °C under nitrogen. The resulting mixture was then stirred at 23 °C for 1 hr. The reaction mixture (2 mL) was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 31% B in 8 min, 31% B to 95% B in 8.2 min, 95% B to 95% B in 9.5 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 254 nm; RT1(min): 7; Injection Volume: 0.5 mL; Number Of Runs: 3) to afford 2'-chloro-5'-(difluoromethoxy)-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (52.9 mg, 10%) as a white solid. MS (ESI) calculated for ($C_{18}H_{14}ClF_2N_5O_4S$) $(M+1)^+$, 470; found, 470.15. ^1H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 8.96 (s, 1H), 8.34 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H),7.32 – 6.82 (m, 1H), 5.70 – 5.64 (m, 1H),4.92 – 4.88(m, 2H), 4.66 – 4.62 (m, 2H), 2.68 (s, 3H).

Example 63

2'-bromo-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



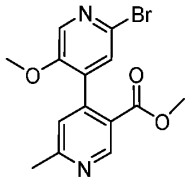
Step 1 2-bromo-4-iodo-5-methoxypyridine



To a stirred solution of methanol (380.0 mg, 11.84 mmol) in N,N-Dimethylformamide (15 mL) was added NaH (230.0 mg, 5.68 mmol) at 0 °C. The reaction mixture was stirred at 0 °C

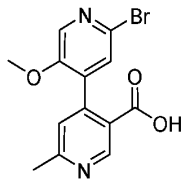
for 0.5 h. Then 2-bromo-5-fluoro-4-iodopyridine (1.4 g, 4.74 mmol) was added to the above mixture at 0 °C. The resulting solution was then stirred at 25 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 80.0 g silica gel column that was eluted with 0~20% ethyl acetate in petroleum ether within 25 min to afford 2-bromo-4-iodo-5-methoxypyridine (1.2 g, 54% yield) as a white solid. MS (ESI) calc'd for (C_6H_5BrINO) $(M+1)^+$, 313.9; found 313.9.

Step 2 methyl 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of 2-bromo-4-iodo-5-methoxypyridine (200.0 mg, 0.64 mmol) and methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (265.0 mg, 0.96 mmol) in 1,4-dioxane (2 mL) were sequentially added water (0.4 mL), potassium carbonate (264.0 mg, 1.91 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (52.0 mg, 0.06 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in acetonitrile (3 mL) which was applied to a 40.0 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 30 min to afford methyl 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (80.0 mg, 36% yield) as a colorless oil. MS (ESI) calc'd for ($C_{14}H_{13}BrN_2O_3$) $(M+1)^+$, 337.0, found 337.0.

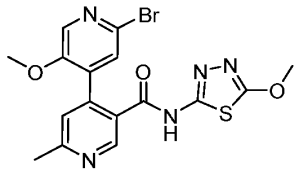
Step 3 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (175.0 mg, 0.52 mmol) in methanol (0.3 mL) were added water (0.3 mL) and sodium

hydroxide (83.0 mg, 2.08 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 hr under nitrogen. The organic solvent was removed under vacuum. The aqueous layer was acidified with sat. citric acid solution to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (100.0 mg, 58% yield) as a yellow solid. MS (ESI) calc'd for ($C_{13}H_{11}BrN_2O_3$) $(M+1)^+$, 323.0, found 323.1.

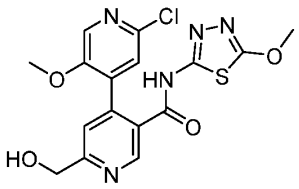
Step 4 2'-bromo-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



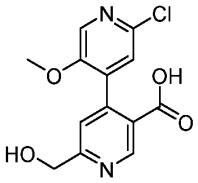
To a stirred solution of 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (100.0 mg, 0.31 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (40.0 mg, 0.31 mmol) in acetonitrile (1 mL) was added 1-methylimidazole (0.1 mL, 1.24 mmol). Then TCFH (87.0 mg, 0.31 mmol) in acetonitrile (1 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The reaction mixture was diluted with DMF (2 mL) and was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 50% B to 55% B in 10 min, 55% B to 95% B in 10.2 min, 95% B to 95% B in 12 min, 95% B to 5% B in 12.2 min, 5% B to 5% B in 14 min; Wave Length: 254 nm; RT1(min): 9; Injection Volume: 0.6 mL; Number Of Runs: 4) to afford 2'-bromo-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (45.0 mg, 33% yield) as a white solid. MS (ESI) calc'd for ($C_{16}H_{14}BrN_5O_3S$) $(M+1)^+$, 436.0; found 436.2. ^1H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.62 (s, 1H), 7.41 (s, 1H), 4.07 (s, 3H), 3.62 (s, 3H), 2.59 (s, 3H).

Example 64

2'-chloro-6-(hydroxymethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

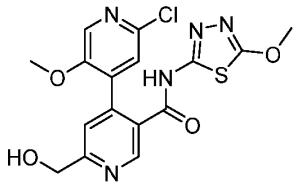


Step 1 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid



To a solution of ethyl 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (300.0 mg, 0.93 mmol) in Tetrahydrofuran (1.5 mL) were added LiOH (66.8 mg, 2.79 mmol) and Water (0.5 mL) at 18 °C. The resulting solution was stirred at 50 °C for 16 hr. The reaction mixture was diluted with water, acidified with citric acid to pH 4~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (120.0 mg, 39%) as a brown soild. MS (ESI) calc'd for ($C_{13}H_{11}ClN_2O_4$) $(M+1)^+$, 295.0; found 295.0.

Step 2 2'-chloro-6-(hydroxymethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

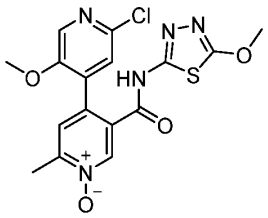


To a mixture of 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (250.0 mg, 0.76 mmol) in Acetonitrile (3 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (120.0 mg, 0.91 mmol) and 1-methyl-1H-imidazole (188.0 mg, 2.21 mmol). A solution of TCFH (321.0 mg, 1.14 mmol) in Acetonitrile (1 mL) was added thereto dropwise under nitrogen. The resulting solution was stirred at 18 °C for 2 hr. The solvent was removed under vacumm. The residue was dissolved in DMF (3 mL) and was purified by prep-HPLC with the following conditions: (Column: Xselect CSH C_{18} OBD Column 30*150 mm 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 30% B in 8 min, 30% B to 95% B in 8.2 min, 95% B to 95% B in 9.7 min, 95% B to 5% B

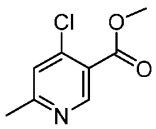
in 11 min, 5% B; Wave Length: 220 nm; RT1(min): 6.68; Injection Volume: 0.8 mL; Number Of Runs: 3) to afford 2'-chloro-6-(hydroxymethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (75.2 mg, 24%) as a white solid MS (ESI) calc'd for ($C_{16}H_{14}ClN_5O_4S$) $(M+1)^+$, 408.0; found 408.0. ^1H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.87 (s, 1H), 8.19 (s, 1H), 7.51 (s, 2H), 5.59 (t, J = 5.6 Hz, 1H), 4.67 (d, J = 5.6 Hz, 2H), 4.08 (s, 3H), 3.64 (s, 3H).

Example 65

2'-chloro-5'-methoxy-5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methyl-(4,4'-bipyridine) 1-oxide

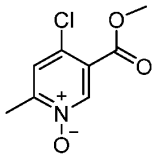


Step 1 methyl 4-chloro-6-methylnicotinate



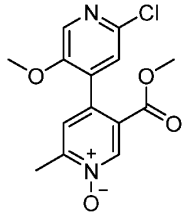
To a stirred solution of 4-chloro-6-methylnicotinic acid (10.0 g, 58.30 mmol) and potassium carbonate (24.1 g, 175.00 mmol) in N,N-Dimethylformamide (DMF) (150 mL) was added iodomethane (5.47 mL, 87.00 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 16 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~60% ethyl acetate in petroleum ether within 30 min to afford methyl 4-chloro-6-methylnicotinate (8.5 g, 78%) as a yellow oil. MS (ESI) calc'd for ($C_8H_8ClNO_2$) $(M+1)^+$, 186.0, found 186.0.

Step 2 4-chloro-5-(methoxycarbonyl)-2-methylpyridine 1-oxide



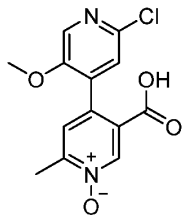
To a stirred solution of methyl 4-chloro-6-methylnicotinate (1.0 g, 5.39 mmol) in Dichloromethane (15 mL) was added mCPBA (1.3 g, 6.47 mmol). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was quenched by the addition of water and extracted with dichloromethane. The combined organic layers were washed with saturated sodium thiosulfate solution, saturated sodium carbonate solution and brine. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in ACN (6 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~18% acetonitrile in water within 22 min to afford 4-chloro-5-(methoxycarbonyl)-2-methylpyridine 1-oxide (870.0 mg, 78%) as a white solid. MS (ESI) calc'd for ($C_8H_8ClNO_3$) $(M+1)^+$, 202.0, found 202.0.

Step 3 2'-chloro-5'-methoxy-5-(methoxycarbonyl)-2-methyl-(4,4'-bipyridine) 1-oxide



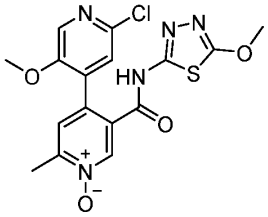
To a stirred solution of 4-chloro-5-(methoxycarbonyl)-2-methylpyridine 1-oxide (600.0 mg, 2.98 mmol) in 1,4-Dioxane (5 mL) and Water (1.7 mL) under nitrogen atmosphere were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (837.0 mg, 4.46 mmol), K_2CO_3 (1234.0 mg, 8.93 mmol) and (1,1'-Bis(di-tert-butylphosphino)ferrocene)dichlor (194.0 mg, 0.29 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 2 hr under nitrogen atmosphere before filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in DMF (5 mL) was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~28% acetonitrile in water within 30 min to afford 2'-chloro-5'-methoxy-5-(methoxycarbonyl)-2-methyl-(4,4'-bipyridine) 1-oxide (500.0 mg, 53%) as a yellow solid. MS (ESI) calc'd for ($C_{14}H_{13}ClN_2O_4$) $(M+1)^+$, 309.0, found 309.0.

Step 4 5-carboxy-2'-chloro-5'-methoxy-2-methyl-(4,4'-bipyridine) 1-oxide



To a stirred solution of 2'-chloro-5'-methoxy-5-(methoxycarbonyl)-2-methyl-(4,4'-bipyridine) 1-oxide (250.0 mg, 0.81 mmol) in Methanol (1.5 mL) and Water (1.5 mL) was added NaOH (130.0 mg, 3.24 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 hr. The mixture was acidified with citric acid to pH ~6, applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~34% acetonitrile in water within 20 min to afford 5-carboxy-2'-chloro-5'-methoxy-2-methyl-(4,4'-bipyridine) 1-oxide (220.0 mg, 90%) as a white solid. MS (ESI) calc'd for ($C_{13}H_{11}ClN_2O_4$) $(M+1)^+$, 295.0, found 295.0.

Step 5 2'-chloro-5'-methoxy-5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methyl-(4,4'-bipyridine) 1-oxide

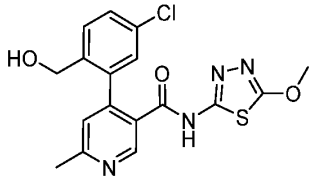


To a stirred solution of 5-carboxy-2'-chloro-5'-methoxy-2-methyl-(4,4'-bipyridine) 1-oxide (180.0 mg, 0.61 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (80.0 mg, 0.61 mmol) in Acetonitrile (3 mL) were added 1-methyl-1H-imidazole (251.0 mg, 3.05 mmol). A solution of TCFH (172.0 mg, 0.61 mmol) in Acetonitrile (1mL) was added thereto at 25 °C. The mixture was stirred at 25 °C for 3 hr. The resulting mixture (5 mL) was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~51% acetonitrile in water within 30 min to afford an off-white solid (85%), which was further purified by prep-HPLC with the following conditions: (Column: Xselect CSH F-Phenyl OBD column, 19 * 250 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 20 % B to 50 % B in 10 min, 50 % B; Wave Length: 254 nm; RT1 (min): 10) to afford 2'-chloro-5'-methoxy-5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methyl-(4,4'-bipyridine) 1-oxide (80.0 mg, 32%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{14}ClN_5O_4S$) $(M+1)^+$, 408.0, found 408.1. ^1H NMR (400 MHz, DMSO-d_6) δ

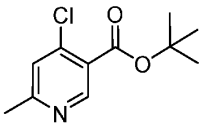
13.03 (s, 1H), 8.63 (s, 1H), 8.15 (s, 1H), 7.69 (s, 1H), 7.54 (s, 1H), 4.07 (s, 3H), 3.62 (s, 3H), 2.44 (s, 3H).

Example 66

4-(5-chloro-2-(hydroxymethyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

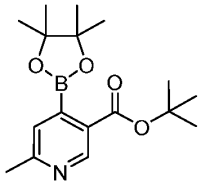


Step 1 tert-butyl 4-chloro-6-methylnicotinate



To a stirred solution of 4-chloro-6-methylnicotinic acid (5.0 g, 29.10 mmol) in Dichloromethane (50 mL) were added di-tert-butyl dicarbonate (9.5 g, 43.70 mmol) and DMAP (356.1 mg, 2.91 mmol) at 0 °C. The resulting solution was stirred at 23 °C for 16 h. The organic solvent was removed under vacuum. The resulting residue was dissolved in DCM (10 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~30% ethyl acetate in petroleum ether within 35 min to afford tert-butyl 4-chloro-6-methylnicotinate (3.0 g, 45%) as a colorless oil. MS (ESI) calc'd for ($C_{11}H_{14}ClNO_2$) $(M+1)^+$, 228.0; found 228.1.

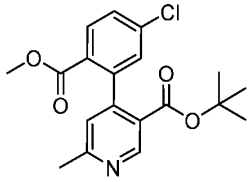
Step 2 tert-butyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate



To a stirred solution of tert-butyl 4-chloro-6-methylnicotinate (3.0 g, 13.18 mmol) in 1,4-Dioxane (50 mL) were added Bis(pinacolato)diboron (16.7 g, 65.90 mmol), AcOK (2.6 g, 26.40 mmol) and $Pd(dppf)Cl_2$ (1.1 g, 1.32 mmol) at 23 °C. The resulting solution was stirred at 100 °C for 16 h under nitrogen. The reaction mixture was diluted with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting

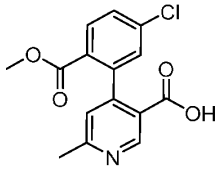
residue was purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~30% ethyl acetate in petroleum ether within 35 min to afford tert-butyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinate (4.6 g, 98%) as a colorless oil. MS (ESI) calc'd for ($C_{17}H_{26}BNO_4$) (M+1) $^+$, 320.2; found, 320.2.

Step 3 tert-butyl 4-(5-chloro-2-(methoxycarbonyl)phenyl)-6-methylnicotinate



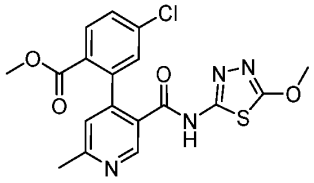
To a stirred solution of tert-butyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinate (2.0 g, 6.27 mmol) in 1,4-Dioxane (30 mL) were added methyl 4-chloro-2-iodobenzoate (1.8 g, 6.27 mmol), K_2CO_3 (2.6 g, 18.80 mmol) and Water (3 mL) at 23 °C. To the above solution was added Pd(dppf)Cl_2 (512.2 mg, 0.63 mmol) at 23 °C under nitrogen. The resulting mixture was stirred at 80 °C for 2 h under nitrogen. The reaction mixture was diluted with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 80 g silica gel column that was eluted with 0~40% ethyl acetate in petroleum ether within 25 min to afford tert-butyl 4-(5-chloro-2-(methoxycarbonyl)phenyl)-6-methylnicotinate (2.0 g, 86%) as a colorless oil MS (ESI) calc'd for ($C_{19}H_{20}ClNO_4$) $(M+1)^+$, 362.1, found 362.2.

Step 4 4-(5-chloro-2-(methoxycarbonyl)phenyl)-6-methylnicotinic acid



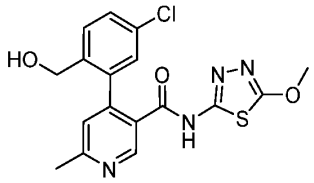
To a stirred solution of tert-butyl 4-(5-chloro-2-(methoxycarbonyl)phenyl)-6-methylnicotinate (500.0 mg, 1.38 mmol) in Dichloromethane (6 mL) was added TFA (3 mL) at 23 °C. The resulting solution was stirred at 23 °C for 16 h. The organic solvent was removed under vacuum to afford 4-(5-chloro-2-(methoxycarbonyl)phenyl)-6-methylnicotinic acid TFA salt (425.0 mg, 98%) as a yellow oil. MS (ESI) calc'd for ($C_{15}H_{12}ClNO_4$) (M+1) $^+$, 306.1, found 306.3.

Step 5 methyl 4-chloro-2-(5-((5-methoxy-1,3,4-thiadiazol-2-yl) carbamoyl)-2-methylpyridin-4-yl)benzoate



To a stirred solution of 4-(5-chloro-2-(methoxycarbonyl) phenyl)-6-methylnicotinic acid (420.0 mg, 1.37 mmol) in acetonitrile (5 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (180.0 mg, 1.37 mmol) and 1-methylimidazole (564.0 mg, 6.87 mmol). To the above solution was added a solution of TCFH (386.0 mg, 1.37 mmol) in acetonitrile (3 mL). The resulting mixture was stirred at 23 °C for 2 h. The suspension was filtered. The filter cake was collected, washed with acetonitrile and dried under vacuum to afford methyl 4-chloro-2-(5-((5-methoxy-1,3,4-thiadiazol-2-yl) carbamoyl)-2-methylpyridin-4-yl) benzoate (450.0 mg, 76%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{15}ClN_4O_4S$) (M+1) $^+$, 419.0, found 419.0.

Step 6 4-(5-chloro-2-(hydroxymethyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

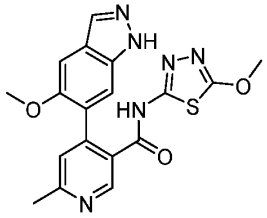


To a stirred solution of methyl 4-chloro-2-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)benzoate (70.0 mg, 0.17 mmol) in Tetrahydrofuran (1 mL) was added Lithium Aluminum Hydride (31.1 mg, 0.82 mmol) in portions at 0 °C. The resulting solution was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of water and acidified with citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 25 min to afford 4-(5-chloro-2-(hydroxymethyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (26.6 mg, 40%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{15}ClN_4O_3S$) $(M+1)^+$, 391.1; found 391.1. 1H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.82 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H),

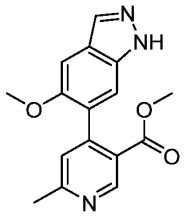
7.46 (dd, J = 8.4, 2.4 Hz, 1H), 7.30 (s, 1H), 7.15 (d, J = 2.4 Hz, 1H), 5.37 (br, 1H), 4.23 (s, 2H), 4.05 (s, 3H), 2.58 (s, 3H).

Example 67

N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinamide

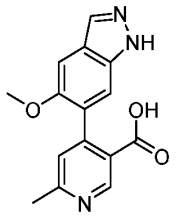


Step 1 methyl 4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinate



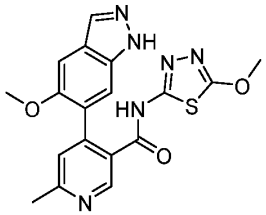
To a stirred solution of 6-bromo-5-methoxy-1H-indazole (500.0 mg, 2.20 mmol) in 1,4-Dioxane (5 mL) was added methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (915.1 mg, 3.30 mmol) at 20 °C. To the above solution were sequentially added K_2CO_3 (913.2 mg, 6.61 mmol), Water (1 mL) and $PdCl_2$(dtbpf) (143.2 mg, 0.22 mmol) at 20 °C. The resulting mixture was then stirred at 80 °C for 2 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~20% methanol in dichloromethane within 25 min to afford methyl 4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinate (341.0 mg, 51%) as a yellow solid. MS (ESI) calc'd for ($C_{16}H_{15}N_3O_3$) $(M+1)^+$, 298.1. found: 298.0.

Step 2 4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinate (300.0 mg, 1.00 mmol) in Tetrahydrofuran (THF) (1.5 mL) were added Water (1.5 mL) and LiOH (48.3 mg, 2.01 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 6 hr. The mixture was diluted with water (5 mL). The aqueous layer was acidified with citric acid to pH ~3. The suspension was filtered. The filter cake was washed with water, dried over vacuum to afford 4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinic acid (54.0 mg, crude) as a white solid. MS (ESI) calc'd for ($C_{15}H_{13}N_3O_3$) $(M+1)^+$, 284.1. found: 284.0.

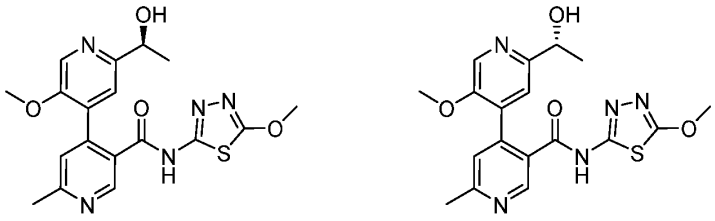
Step 3 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinamide



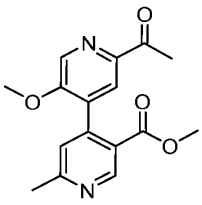
To a stirred solution of 4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinic acid (54.0 mg, 0.19 mmol) in Acetonitrile (2 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (25.0 mg, 0.19 mmol) and 1-methyl-1H-imidazole (78.0 mg, 0.95 mmol) at 20 °C. To the above solution was added a solution of TCFH (53.6 mg, 0.19 mmol) in Acetonitrile (2 mL) at 20 °C under nitrogen. The resulting mixture was then stirred at 20 °C for 2 hr under nitrogen. The mixture was diluted with acetonitrile (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~100% acetonitrile in water within 25 min to afford N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxy-1H-indazol-6-yl)-6-methylnicotinamide (68.6 mg, 88%) as a yellow solid. MS (ESI) calc'd for ($C_{18}H_{16}N_6O_3S$) $(M+1)^+$, 397.1 found: 397.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 12.70 (s, 1H), 8.73 (s, 1H), 8.00 (s, 1H), 7.50 – 7.45 (m, 2H), 7.18 (s, 1H), 4.06 (s, 3H), 3.49 (s, 3H) 2.62 (s, 3H).

Example 68 and 69

(*R*)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide and (S)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

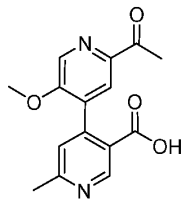


Step 1 methyl 2'-acetyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



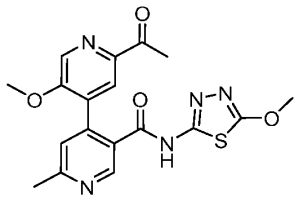
To a stirred solution of methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (1.5 g, 5.13 mmol) in Toluene (15 mL) were added bis(triphenylphosphine)palladium(II) chloride (3.6 g, 5.12 mmol) and tributyl(1-ethoxyvinyl)stannane (3.7 g, 10.26 mmol) at 25 °C. The resulting solution was stirred at 100 °C for 4 hr. The organic solvent was removed under vacuum. The residue was dissolved with Methanol (10 mL) and HCl (2 mL, conc.) at 25 °C. The resulting mixture was stirred at 25 °C for 1 hr. The residue was diluted with water. The aqueous layer was basified with sat. $NaHCO_3$ aqueous to pH 7~8 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (4 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~9% methanol in dichloromethane within 30 min to afford methyl 2'-acetyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (680.0 mg, 58%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{16}N_2O_4$) $(M+1)^+$, 301.1; found, 301.1

Step 2 2'-acetyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



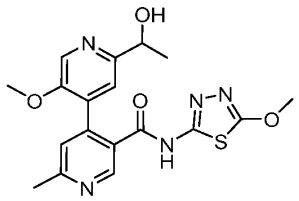
To a stirred solution of methyl 2'-acetyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (650.0 mg, 2.16 mmol) in Methanol (3 mL) were added NaOH (325.0 mg, 8.12 mmol) and Water (3 mL) at 25 °C. The resulting solution was stirred at 25 °C for 16 hr before diluted with water. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH 5~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-acetyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (550.0 mg, crude) as a white solid. MS (ESI) calc'd for ($C_{15}H_{14}N_2O_4$) $(M+1)^+$, 287.1; found, 287.1

Step 3 2'-acetyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



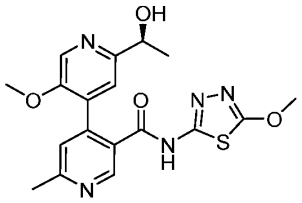
To a stirred solution of 2'-acetyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (530.0 mg, 1.82 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (241.0 mg, 1.82 mmol) in Acetonitrile (4 mL) was added 1-methyl-1H-imidazole (759.0 mg, 9.14 mmol) at 25 °C. To the above was added a solution of N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (518.0 mg, 1.82 mmol) in Acetonitrile (2 mL) at 25 °C under nitrogen. The resulting solution was stirred at 25 °C for 2 hr. NaOH (0.3 mL, 1 N) was added thereto at 25 °C. The resulting mixture was stirred at 25 °C for 10 min, and then acidified with citric acid to pH 5~6. The volatiles were removed under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 30 min to afford 2'-acetyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (450.0 mg, 40%) as a white solid .MS (ESI) calc'd for ($C_{18}H_{17}N_5O_4S$) $(M+1)^+$, 400.1; found, 400.1

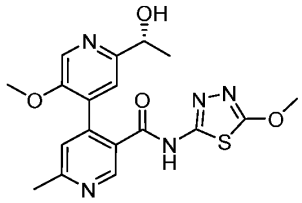
Step 4 2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 2'-acetyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (450.0 mg, 1.12 mmol) in Methanol (4 mL) was added $NaBH_4$ (85.0 mg, 2.25 mmol) at 25 °C. The resulting solution was stirred at 0 °C for 1 hr. The resulting mixture was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~20% acetonitrile in water within 45 min to afford 2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (150.0 mg, 32%) as a white solid. MS (ESI) calc'd for $(C_{18}H_{19}N_5O_4S)$ $(M+1)^+$, 402.1; found, 402.2

Step 5 (*R*)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide and (S)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide





The racemic compound (150.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: MtBE--HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 16 mL/min; Gradient: 10% B to 10% B in 23 min; Wave Length: 220/254 nm; RT1(min): 13.43; RT2(min): 19.75; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 1.1 mL; Number Of Runs: 3) to afford (*R*)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (56.6 mg, 37%) as a white solid with shorter retention time on chiral-HPLC and (*S*)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (58.0 mg, 38%) as a white solid with longer retention time on chiral-HPLC. The absolute stereochemistry was not determined and was arbitrarily assigned.

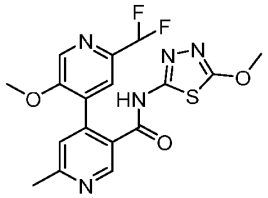
(*R*)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for $(C_{18}H_{19}N_5O_4S)$ $(M+1)^+$, 402.1; found,

402.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.76 (s, 1H), 8.23 (s, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 5.35 (d, J = 4.8 Hz, 1H), 4.81 – 4.71 (m, 1H), 4.08 (s, 3H), 3.62 (s, 3H), 2.60 (s, 3H), 1.40 (d, J = 6.4 Hz, 3H).

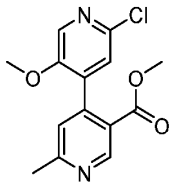
(*S*)-2'-(1-hydroxyethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{18}H_{19}N_5O_4S$) $(M+1)^+$, 402.1; found, 402.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.76 (s, 1H), 8.23 (s, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 5.34 (d, J = 4.8 Hz, 1H), 4.81 – 4.70 (m, 1H), 4.08 (s, 3H), 3.62 (s, 3H), 2.60 (s, 3H), 1.40 (d, J = 6.4 Hz, 3H).

Example 70

2'-(difluoromethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

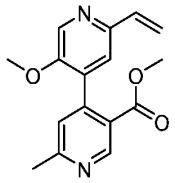


Step 1 methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



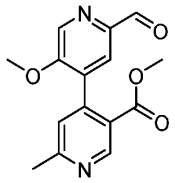
To a stirred solution of 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (3.0 g, 10.76 mmol) in dichloromethane (30 mL) were sequentially added methanol (3 mL) and (TriMethylsilyl) diazoMethane (2.5 g, 21.54 mmol) at 0 °C. The resulting solution was stirred at room temperature for 16 hr under nitrogen. The organic solvent was removed under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 80 g silica gel column and eluted with 0~65% ethyl acetate in petroleum ether within 40 min to afford methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (2.5 g, 78%) as a white solid. MS (ESI) calc'd for ($C_{14}H_{13}ClN_2O_3$) $(M+1)^+$, 293.1; found 293.2.

Step 2 methyl 5'-methoxy-6-methyl-2'-vinyl-(4,4'-bipyridine)-3-carboxylate



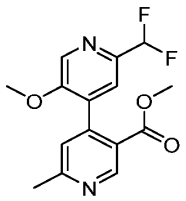
To a stirred solution of methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (500.0 mg, 1.71 mmol) in 1,4-dioxane (4.5 mL) were sequentially added water (1.5 mL), trifluoro(vinyl)-l4-borane, potassium salt (343.0 mg, 2.56 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (139.0 mg, 0.17 mmol) and K_2CO_3 (708.0 mg, 5.12 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in acetonitrile (4 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~35% acetonitrile in water within 30 min to afford methyl 5'-methoxy-6-methyl-2'-vinyl-(4,4'-bipyridine)-3-carboxylate (420.0 mg, 85%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{16}N_2O_3$) $(M+1)^+$, 285.1; found, 285.3.

Step 3 methyl 2'-formyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



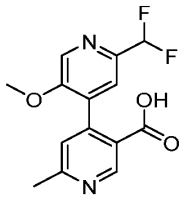
To a stirred solution of methyl 5'-methoxy-6-methyl-2'-vinyl-(4,4'-bipyridine)-3-carboxylate (370.0 mg, 1.30 mmol) in tetrahydrofuran (10 mL) were sequentially added water (10 mL), sodium periodate (1.1 g, 5.21 mmol) and osmium tetroxide (0.04 mL, 0.13 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 1 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in dichloromethane (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~71% ethyl acetate in petroleum ether within 30 min to afford methyl 2'-formyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (255.0 mg, 67%) as a white solid. MS (ESI) calc'd for ($C_{15}H_{14}N_2O_4$) $(M+1)^+$, 287.1, found 287.2.

Step 4 methyl 2'-(difluoromethyl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



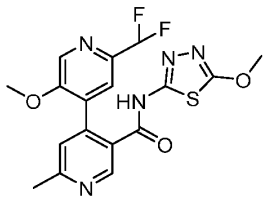
To a stirred solution of methyl 2'-formyl-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (230.0 mg, 0.80 mmol) in dichloromethane (2 mL) was added DAST (0.2 mL, 1.61 mmol) at 0 °C. The resulting solution was stirred at 20 °C for 48 hr under nitrogen. The reaction mixture was quenched by the additionof water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The resulting residue was dissolved in acetonitrile (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 30 min to afford methyl 2'-(difluoromethyl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (160.0 mg, 63%) as a brown oil. MS (ESI) calc'd for ($C_{15}H_{14}F_2N_2O_3$) $(M+1)^+$, 309.1, found 309.2.

Step 5 2'-(difluoromethyl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-(difluoromethyl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (160.0 mg, 0.52 mmol) in tetrahydrofuran (1.5 mL) were sequentially added water (0.5 mL) and lithium hydroxide (49.7 mg, 2.08 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid solution to pH 5~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-(difluoromethyl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (150.0 mg, 93%) as a yellow solid. MS (ESI) calc'd for ($C_{14}H_{12}F_2N_2O_3$) $(M+1)^+$, 295.1, found 295.2.

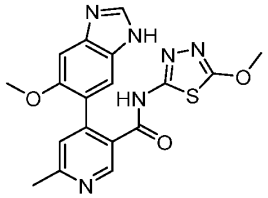
Step 6 2'-(difluoromethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



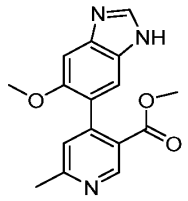
To a stirred solution of 2'-(difluoromethyl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (200.0 mg, 0.68 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (89.0 mg, 0.68 mmol) in acetonitrile (2 mL) was added 1-methylimidazole (0.2 mL, 2.72 mmol). Then a solution of TCFH (191.0 mg, 0.68 mmol) in acetonitrile (2 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 hr under nitrogen. The reaction mixture (2 mL) was purified by prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 27% B to 27% B in 8 min, 27% B to 95% B in 9.2 min, 95% B to 95% B in 10.5 min, 95% B to 5% B in 11 min, 5% B; Wave Length: 254 nm; RT1(min): 7; Injection Volume: 05 mL; Number Of Runs: 4) to afford 2'-(difluoromethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (78.5 mg, 27%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{15}F_2N_5O_3S$) $(M+1)^+$, 408.1; found 408.1. ^1H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.44 (s, 1H), 7.61 (s, 1H), 7.32 (s, 1H), 7.15 – 6.82 (m, 1H), 4.02 (s, 3H), 3.70 (s, 3H), 2.57 (s, 3H).

Example 71

N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinamide

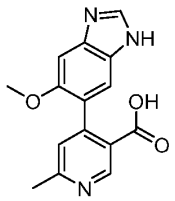


Step 1 methyl 4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinate



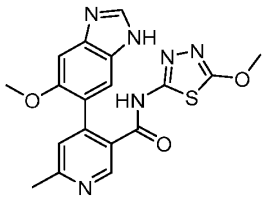
To a stirred solution of 6-bromo-5-methoxy-1H-benzo(d)imidazole (500.0 mg, 2.20 mmol) in 1,4-Dioxane (5 mL) was added methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinate (1.2 g, 4.40 mmol) at 23°C. To the above solution were added K_2CO_3 (913.0 mg, 6.61 mmol) in Water (1 mL) and Pd (dtbpf)Cl_2 (143.2 mg, 0.22 mmol) at 23 °C. The resulting mixture was then stirred at 80 °C for 2 hr under nitrogen. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~20% methanol in dichloromethane within 35 min to afford methyl 4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinate (142.0 mg, 20%) as a yellow oil. MS (ESI) calc'd for ($C_{16}H_{15}N_3O_3$) $(M+1)^+$, 298.1; found 298.1.

Step 2: 4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinate (140.0 mg, 0.47 mmol) in THF (1.5 mL) and Water (1.5 mL) was added LiOH (22.6 mg, 0.94 mmol) at 23 °C. The resulting solution was stirred at 50 °C for 2 hr. The reaction mixture was acidified with Citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinic acid (60.0 mg, crude) as a white solid. MS (ESI) calc'd for ($C_{15}H_{13}N_3O_3$) $(M+1)^+$,284.1; found, 284.1.

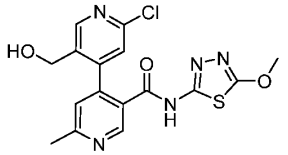
Step 3 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinamide



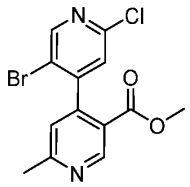
To a stirred solution of 4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinic acid (50.0 mg, 0.17 mmol), 5-methoxy-1,3,4-thiadiazol-2-amine (23.2 mg, 0.17 mmol) and 1-methylimidazole (72.5 mg, 0.88 mmol) in Acetonitrile (1 mL). To the above was added a solution of TCFH (49.6 mg, 0.17 mmol) in Acetonitrile (1 mL). The resulting mixture was stirred at 23°C for 2 hr. The mixture was dissolved in DMF (2 mL) and was purified by prep-HPLC with the following conditions: (Column: X Bridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 48% B to 48% B in 10 min, 48% B to 95% B in 11.2 min, 95% B to 95% B in 12.5 min, 95% B to 5% B in 13 min, 5% B; Wave Length: 254 nm; RT1(min): 7) to afford N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxy-1H-benzo(d)imidazol-6-yl)-6-methylnicotinamide (14.4 mg, 20%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{16}N_6O_3S$) $(M+1)^+$, 397.1, found 397.2. ^1H NMR (400 MHz, DMSO-d_6) δ 12.48 (br, 2H), 8.66 (s, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 7.33 (s, 1H), 7.06 (s, 1H), 4.04 (s, 3H), 3.53 (s, 3H), 2.57 (s, 3H).

Example 72

2'-chloro-5'-(hydroxymethyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



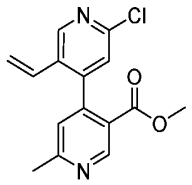
Step 1 methyl 5'-bromo-2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a solution of 5-bromo-2-chloro-4-iodopyridine (1.0 g, 3.24 mmol) and methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (2.7 g, 9.71 mmol) in 1,4-Dioxane (5 mL) and Water (1 mL) were added K_3PO_4 (0.9 g, 6.47 mmol) and $Pd(PPh_3)_2Cl_2$ (0.2 g, 0.32 mmol) at 20 °C under nitrogen. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi

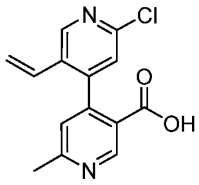
Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 35 min to afford methyl 5'-bromo-2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (770.0 mg, 51%) as a yellow solid. MS (ESI) calc'd for ($C_{13}H_{10}BrClN_2O_2$) $(M+1)^+$, 341.0, found 341.0.

Step 2: methyl 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylate



To a solution of methyl 5'-bromo-2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (770.0 mg, 2.25 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (347.0 mg, 2.25 mmol) in Toluene (4 mL) and Water (1 mL) were added potassium phosphate (393.0 mg, 2.25 mmol) and $Pd(dtbpf)Cl_2$ (1039.0 mg, 2.25 mmol) at 20 °C under nitrogen. The resulting solution was stirred at 100 °C for 2 hr under nitrogen. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~75% acetonitrile in water within 25 min to afford methyl 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylate (240.0 mg, 33%) as a yellow oil. MS (ESI) calc'd for ($C_{15}H_{13}ClN_2O_2$) $(M+1)^+$, 289.1; found 289.1.

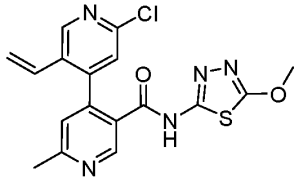
Step 3 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylate (30.0 mg, 0.11 mmol) in THF (1 mL) was added a solution of lithium hydroxide (3.0 mg, 0.11 mmol) in Water (0.2 mL) at 0 °C. The resulting solution was stirred at 20 °C for 1 hr. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to

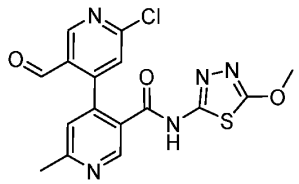
afford 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylic acid (40.0 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{14}H_{11}ClN_2O_2$) $(M+1)^+$, 275.1; found 275.1.

Step 4 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxamide



To a solution of 2'-chloro-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxylic acid (40.0 mg, 0.14 mmol) in Acetonitrile (0.5 mL) was added 5-methoxy-1,3,4-thiadiazol-2-amine (19.1 mg, 0.14 mmol) and 1-methylimidazole (59.6 mg, 0.73 mmol) at 20 °C under nitrogen. To the above solution was added TCFH (40.8 mg, 0.14 mmol) in Acetonitrile (0.5 mL) at 20 °C under nitrogen. The resulting mixture was then stirred at 20 °C for 1 hr. The suspension was filtered. The filter cake was collected and dried under vacuum to afford 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxamide (18.0 mg, 32%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{14}ClN_5O_2S$) (M+1)+, 388.1; found 388.1.

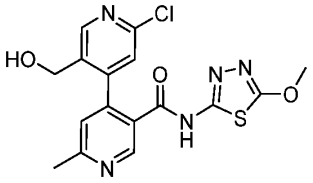
Step 5 2'-chloro-5'-formyl-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a solution of 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-5'-vinyl-(4,4'-bipyridine)-3-carboxamide (18.0 mg, 0.04 mmol) in Tetrahydrofuran (THF) (1 mL) and Water (0.3 mL) were added osmium tetroxide (11.2 mg, 0.04 mmol) and sodium periodate (9.9 mg, 0.04 mmol) at 20 °C under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-5'-formyl-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (34.0 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{16}H_{12}ClN_5O_5S$) $(M+1)^+$, 390.0; found 390.0.

Step 6 2'-chloro-5'-(hydroxymethyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-

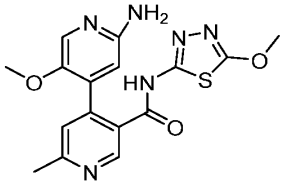
bipyridine)-3-carboxamide



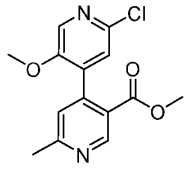
To a stirred solution of 2'-chloro-5'-formyl-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (34.0 mg, 0.08 mmol) in Methanol (1 mL) was added sodium borohydride (6.6 mg, 0.17 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 hr. The resulting mixture was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~55% acetonitrile in water within 35 min to afford 2'-chloro-5'-(hydroxymethyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (8.3 mg, 23%) as a white solid. MS (ESI) calc'd for $(C_{16}H_{14}ClN_5O_3S)$ $(M+1)^+$, 392.1; found 392.1. ^1H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.40 (s, 1H), 7.15 (s, 1H), 7.00 (s, 1H), 5.53 (s, 1H), 4.21 (s, 2H), 3.89 (s, 3H), 2.50 (s, 3H).

Example 73

2'-amino-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



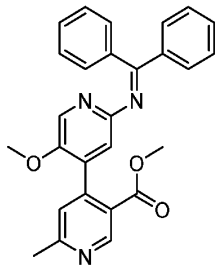
Step 1 methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (2.0 g, 7.18 mmol) in N,N-Dimethylformamide (20 mL) under nitrogen atmosphere were added K_2CO_3 (1.9 g, 14.35 mmol) and MeI (1.5 g, 10.76 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 16 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and

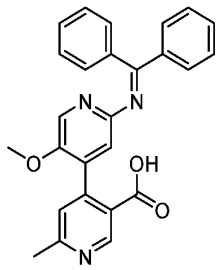
concentrated under vacuum. The residue was dissolved with DMF (8 mL), purified by Combi Flash (Biotage Isolera Prime), eluted with 5~48% acetonitrile in water within 40 min to afford methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (1.4 g, 67%) as a white solid. MS (ESI) calc'd for ($C_{14}H_{13}ClN_2O_3$) $(M+1)^+$, 293.0, found 293.1.

Step 2 methyl 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of methyl 2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (500.0 mg, 1.70 mmol) in 1,4-Dioxane (6 mL) were added diphenylmethanimine (464.0 mg, 2.56 mmol), Cs_2CO_3 (1670.0 mg, 5.12 mmol), $Pd(OAc)_2$ (38.3 mg, 0.17 mmol) and BINAP (213.0 mg, 0.34 mmol). The mixture was stirred at 80 °C under nitrogen atmosphere for 16 h. The mixture was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in DMF (5 mL), applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~51% acetonitrile in water within 30 min to afford methyl 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (600.0 mg, 79%) as a yellow solid. MS (ESI) calc'd for ($C_{27}H_{23}N_3O_3$) $(M+1)^+$, 438.1, found 438.1.

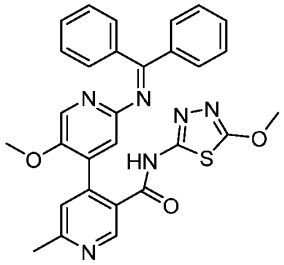
Step 3: 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylate (560.0 mg, 1.28 mmol) in Methanol (3 mL) and Water (3 mL) was

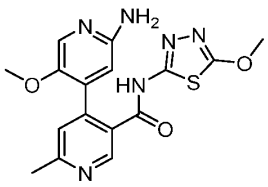
added NaOH (205.0 mg, 5.12 mmol). The resulting solution was stirred at 60 °C for 2 h. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~6 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (500.0 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{26}H_{21}N_3O_3$) $(M+1)^+$, 424.1, found 424.2.

Step 4 2'-((diphenylmethylene)amino)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 2'-((diphenylmethylene)amino)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (480.0 mg, 1.13 mmol) in Acetonitrile (5 mL) were sequentially added 5-methoxy-1,3,4-thiadiazol-2-amine (149.0 mg, 1.13 mmol) and 1-methyl-1H-imidazole (465.0 mg, 5.67 mmol) at 25 °C under nitrogen. To the above solution was added a solution of TCFH (318.0 mg, 1.133 mmol) in Acetonitrile (1 mL) at 25 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 2 h. The resulting solution (6 mL) was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 45 min to afford 2'-((diphenylmethylene)amino)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (320.0 mg, 50%) as a yellow solid. MS (ESI) calc'd for ($C_{29}H_{24}N_6O_3S$) $(M+1)^+$, 537.1, found 537.3.

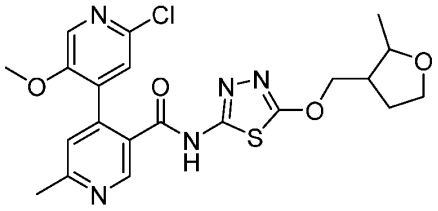
Step 5 2'-amino-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



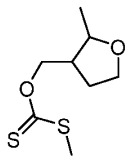
To a stirred solution of 2'-((diphenylmethylene)amino)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (300.0 mg, 0.55 mmol) in Tetrahydrofuran (3 mL) was added HCl (0.6 mL, 1.20 mmol, 2 N) at 25 °C. The resulting solution was stirred at 25 °C for 2 h and concentrated under vacuum. The resulting residue was dissolved in ACN (2 mL) and purified by purified by prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30 * 150mm 5 μm; Mobile Phase A: Water (0.1 % FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 6 % B to 13 % B in 8 min, 13 % B; Wave Length: 220 nm; RT1(min): 5.43.; Injection Volume: 0.6 mL; Number Of Runs: 4) to afford 2'-amino-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide (64.3 mg, 30%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{16}N_6O_3S$) $(M+1)^+$, 373.1, found 373.1. ^1H NMR (400 MHz, DMSO-d_6 + D_2O) δ 8.67 (s, 1H), 7.58 (s, 1H), 7.29 (s, 1H), 6.50 (s, 1H), 4.04 (s, 3H), 3.42 (s, 3H), 2.56 (s, 3H).

Example 74

2'-chloro-5'-methoxy-6-methyl-N-(5-((2-methyltetrahydrofuran-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



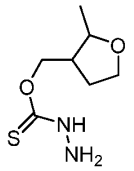
Step 1 S-methyl O-((2-methyltetrahydrofuran-3-yl)methyl) carbonodithioate



To a mixture of NaH (41.3 mg, 1.03 mmol, 60%) in THF (2 mL) was added (2-methyltetrahydrofuran-3-yl) methanol (100.0 mg, 0.86 mmol) in portions at 0 °C and stirred at 0 °C for 1 hr. Then CS_2 (98.1 mg, 1.29 mmol) was added to the above mixture and stirred at 0 °C for 10 min, and then MeI (183.1 mg, 1.29 mmol) was added to the above mixture at 5 °C. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and

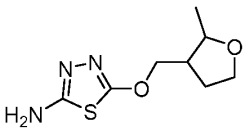
concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 20 g silica gel column that was eluted with 0~20% ethyl acetate in petroleum ether within 20 min. to afford S-methyl O-((2-methyltetrahydrofuran-3-yl)methyl) carbonodithioate (140.0 mg, 76%) as a colorless oil. MS (ESI) calc'd for ($C_8H_{14}O_2S_2$) $(M+1)^+$, 206.0.

Step 2 O-((2-methyltetrahydrofuran-3-yl)methyl) hydrazinecarbothioate



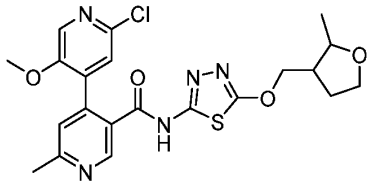
To a stirred solution of S-methyl O-((2-methyltetrahydrofuran-3-yl)methyl) carbonodithioate (140.0 mg, 0.68 mmol) in Methanol (1 mL) was added hydrazine (24.0 mg, 0.75 mmol, 80%) at 23 °C. The resulting solution was stirred at 23°C for 1 hr. The organic solvent was removed under vacuum to afford O-((2-methyltetrahydrofuran-3-yl)methyl) hydrazinecarbothioate (130.0 mg, crude) as a colorless oil. MS (ESI) calc'd for ($C_7H_{14}N_2O_2S$) $(M+1)^+$, 191.1.

Step 3 5-((2-methyltetrahydrofuran-3-yl)methoxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of O-((2-methyltetrahydrofuran-3-yl)methyl) hydrazinecarbothioate (130.0 mg, 0.68 mmol) in Methanol (1 mL) were added TEA (138.4 mg, 1.37 mmol) and cyanic bromide (80.0 mg, 0.75 mmol) at 23 °C. The resulting solution was stirred at 23 °C for 1 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 20 g silica gel column that was eluted with 0~10% methanol in dichloromethane within 25 min to afford 5-((2-methyltetrahydrofuran-3-yl)methoxy)-1,3,4-thiadiazol-2-amine (70.0 mg, 47%) as a yellow solid. MS (ESI) calc'd for ($C_8H_{13}N_3O_2S$) $(M+1)^+$,216.1 , found 216.1.

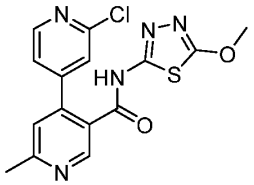
Step 4 2'-chloro-5'-methoxy-6-methyl-N-(5-((2-methyltetrahydrofuran-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



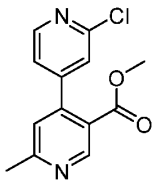
To a stirred solution of 5-((2-methyltetrahydrofuran-3-yl) methoxy)-1,3,4-thiadiazol-2-amine (60.0 mg, 0.28 mmol), Intermediate G (78.0 mg, 0.28 mmol) and 1-methylimidazole (114 mg, 1.39 mmol) in Acetonitrile (1.5 mL) and was added a solution of TCFH (78.0 mg, 0.28 mmol) in Acetonitrile (1.5 mL). The resulting mixture was stirred at 23 °C for 2 hr. The resulting mixture was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 25 min to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-((2-methyltetrahydrofuran-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (83.2 mg, 62%) as a white solid. MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1, found 476.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.49 – 4.41 (m, 1H), 4.40 – 4.26 (m, 1H), 4.03 – 3.96 (m, 1H), 3.90 – 3.79 (m, 1H), 3.72 – 3.54 (m, 4H), 2.65 – 2.52 (m, 4H), 2.15 – 1.97 (m, 1H), 1.80 – 1.74 (m, 1H), 1.20 (d, J = 6.4 Hz, 1H), 1.11 (d, J = 6.4 Hz, 2H).

Example 75

2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide



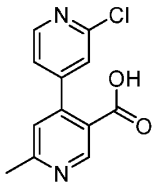
Step 1 methyl 2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of 4-bromo-2-chloropyridine (100.0 mg, 0.52 mmol) in 1,4-Dioxane (5 mL) and Water (1 mL) were sequentially added methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinate (288.0 mg, 1.04 mmol), K_2CO_3 (215.0 mg, 1.56 mmol) and Pd(dppf)Cl_2 (76.0 mg, 0.10 mmol) at 20 °C. The resulting solution was stirred at 100 °C under nitrogen atmosphere for 2 hr. The mixture was filtered. The filtrate was concentrated

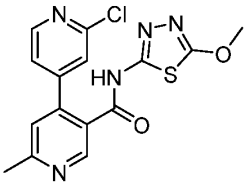
under vacuum. The resulting residue was dissolved in DMF (4 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 30 min to afford methyl 2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (120.0 mg, 83%) as a gray solid. MS (ESI) calculated for ($C_{13}H_{11}ClN_2O_2$) $(M+1)^+$, 263.0; found, 263.1.

Step 2 2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylic acid



To a solution of methyl 2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylate (340.0 mg, 1.29 mmol) in Tetrahydrofuran (2 mL) and Water (0.7 mL) was added lithium hydroxide (93.0 mg, 3.88 mmol) at 20 °C. The resulting solution was stirred at 40 °C for 2 hr. The aqueous layer was acidified with citric acid to pH ~4 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (150.0 mg, crude) as a brown solid. MS (ESI) calculated for ($C_{12}H_9ClN_2O_2$) $(M+1)^+$, 249.0; found, 249.0.

Step 3 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide

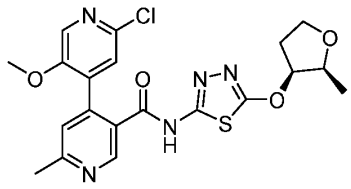
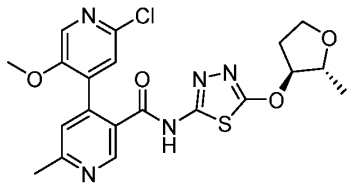


To a mixture of 5-methoxy-1,3,4-thiadiazol-2-amine (82.0 mg, 0.63 mmol) in acetonitrile (5 mL) were added 2'-chloro-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (130.0 mg, 0.52 mmol) and NMI (215.0 mg, 2.61 mmol). To the above was added a solution of TCFH (161.0 mg, 0.58 mmol) in acetonitrile (1 mL) under nitrogen. The resulting solution was stirred at 20 °C for 2 hr. The organic solvent was removed under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5%~ 40% acetonitrile in water within 40 min to afford 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-

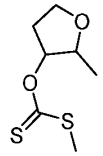
carboxamide (100.9 mg, 53%) as a white solid. MS (ESI) calculated for ($C_{15}H_{12}ClN_5O_2S$) $(M+1)^+$, 362.0; found, 362.1. ^1H NMR (400 MHz, DMSO-d_6), δ 13.03 (br, 1H), 8.85 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.51 (s, 1H), 7.36 (dd, J = 5.2, 1.6 Hz, 1H), 4.08 (s, 3H), 2.61 (s, 3H).

Example 76 and 77

2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3r)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide and 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3s)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

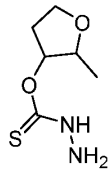



Step 1 S-methyl O-(2-methyltetrahydrofuran-3-yl) carbonodithioate



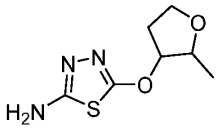
To a solution of 2-methyltetrahydrofuran-3-ol (300.0 mg, 2.94 mmol) in THF (10 mL) was added NaH (141.0 mg, 3.52 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 30 min. Then CS_2 (0.26 mL, 4.41 mmol) was added to the above mixture and stirred at 0 °C for 10 min. And then MeI (0.3 mL, 4.41 mmol) was added to the above mixture at 0 °C. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford S-methyl O-(2-methyltetrahydrofuran-3-yl) carbonodithioate (534.0 mg, crude) as a yellow oil. MS (ESI) calc'd for ($C_7H_{12}O_2S_2$) $(M+1)^+$, 193.0.

Step 2 O-(2-methyltetrahydrofuran-3-yl) hydrazinecarbothioate



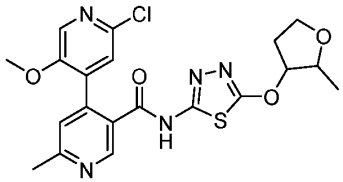
To a stirred solution of S-methyl O-(2-methyltetrahydrofuran-3-yl) carbonodithioate (530.0 mg, 2.76 mmol) in Methanol (5 mL) was added hydrazine (121.2 mg, 3.03 mmol, 80%) at 20 °C. The resulting solution was stirred at 20 °C for 30 min. The organic solvent was removed under vacuum to afford O-(2-methyltetrahydrofuran-3-yl) hydrazinecarbothioate (460.0 mg, crude) as a yellow oil. MS (ESI) calc'd for ($C_6H_{12}N_2O_2S$) $(M+1)^+$, 177.1; found 177.0

Step 3 5-((2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of O-(2-methyltetrahydrofuran-3-yl) hydrazinecarbothioate (460.0 mg, 2.61 mmol) in Methanol (2.5 mL) were added TEA (0.7 mL, 5.22 mmol) and BrCN (301.0 mg, 2.87 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 1 hr. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in MeOH/DCM (0.2/2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~20% methanol in dichloromethane within 30 min to afford 5-((2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine (144.0 mg, 27%) as a yellow solid. MS (ESI) calc'd for ($C_7H_{11}N_3O_2S$) $(M+1)^+$, 202.1; found 202.1.

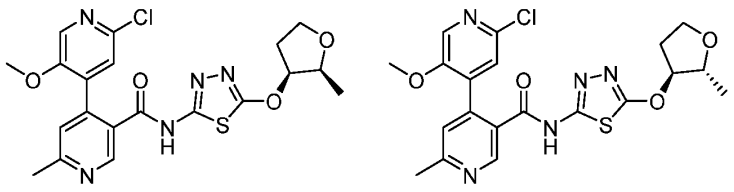
Step 4 2'-chloro-5'-methoxy-6-methyl-N-(5-((2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 5-((2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine (120.0 mg, 0.59 mmol) in Acetonitrile (1 mL) were added Intermediate G (166.0 mg, 0.59

mmol) and 1-methylimidazole (0.23 mL, 2.98 mmol) at 20 °C. To the above solution was added a solution of TCFH (168.0 mg, 0.59 mmol) in Acetonitrile (0.5 mL) at 20 °C under nitrogen. The resulting mixture was then stirred at 20 °C for 2 hr. The resulting mixture was dissolved in DMF (3 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~80% acetonitrile in water within 45 min to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-((2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (181.6 mg, 65%) as a white solid. MS (ESI) calc'd for $(C_{20}H_{20}ClN_5O_4S)$ $(M+1)^+$, 462.1; found, 462.2.

Step 5 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3r)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide and 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3s)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



A mixture of 2'-chloro-5'-methoxy-6-methyl-N-(5-((2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (181.6 mg) was sepatated by prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 32% B in 12 min, 32% B to 95% B in 12.2 min, 95% B to 95% B in 13.7 min, 95% B to 5% B in 15 min, 5% B; Wave Length: 220 nm; RT1(min): 8.92, 11.35(min): ; Injection Volume: 1.2 mL; Number Of Runs: 2) to afford 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3r)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (40.7 mg, 22%) as a white solid with shorter retention time on prep-HPLC and 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3s)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (51.6 mg, 28%) as a white solid with longer retention time on prep-HPLC. The absolute stereochemistry was not determined and was arbitrarily assigned.

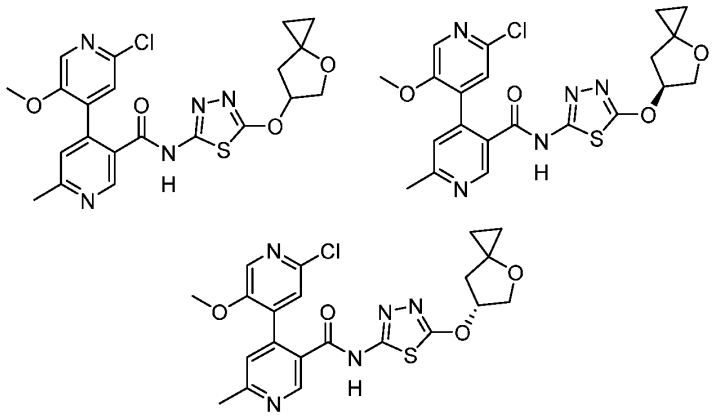
2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3r)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for $(C_{20}H_{20}ClN_5O_4S)$ $(M+1)^+$, 462.1; found, 462.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.82 (s, 1H),

8.17 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 5.40 (s, 1H), 3.98 – 3.87 (m, 2H), 3.70 – 3.34 (m, 4H), 2.58 (s, 3H), 2.47 – 2.34 (m, 1H), 2.15 – 2.04 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H).

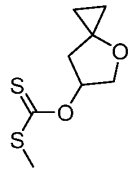
2'-chloro-5'-methoxy-6-methyl-N-(5-(((2r,3s)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 5.14 – 5.07 (m, 1H), 4.17 – 4.07 (m, 1H), 3.99 – 3.89 (m, 1H), 3.84 – 3.74 (m, 1H), 3.64 (s, 3H), 2.60 (s, 3H), 2.39 – 2.25 (m, 1H), 2.15 – 2.05 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H).

Example 95, 228 and 117

N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide, (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (R)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



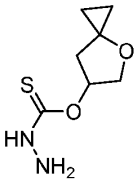
Step-1: S-methyl O-(4-oxaspiro(2.4)heptan-6-yl) carbonodithioate



To a stirred solution of 4-oxaspiro(2.4)heptan-6-ol (100.0 mg, 0.87 mmol) in Tetrahydrofuran (3 mL) was added NaH (42.0 mg, 1.05 mmol, 60%) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. Then CS_2 (100.0 mg, 1.31 mmol) was added to the above mixture at 0 °C. The resulting solution was then stirred at 0 °C for 0.5 h. Then MeI (187.0 mg, 1.31 mmol)

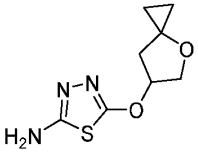
was added to the above mixture at 0 °C. The resulting solution was then stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford S-methyl O-(4-oxaspiro(2.4)heptan-6-yl) carbonodithioate (150.0 mg, crude) as yellow oil. The crude product was used in next step without further purification.

Step-2: O-(4-oxaspiro(2.4)heptan-6-yl) hydrazinecarbothioate



To a stirred solution of S-methyl O-(4-oxaspiro(2.4)heptan-6-yl) carbonodithioate (150.0 mg, 0.73 mmol) in Methanol (3 mL) was added hydrazine (47.1 mg, 0.73 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. The organic solvent was removed under vacuum to afford O-(4-oxaspiro(2.4)heptan-6-yl) hydrazinecarbothioate (130.0 mg, crude) as yellow oil, which was used in the next step without further purification.

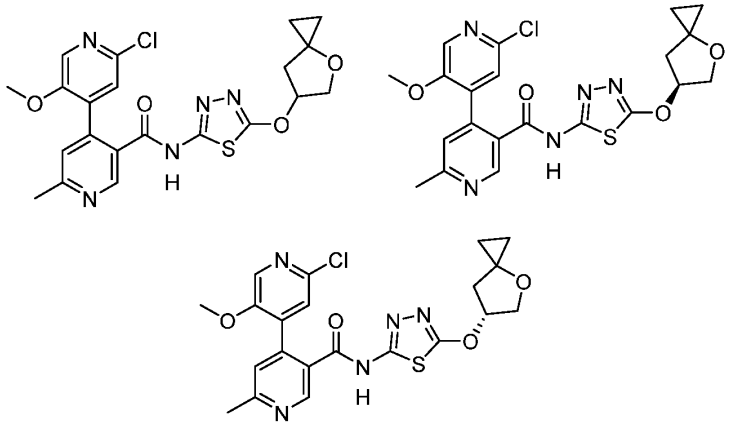
Step-3: 5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of O-(4-oxaspiro(2.4)heptan-6-yl) hydrazinecarbothioate (130.0 mg, 0.69 mmol), cyanic bromide (110.0 mg, 1.03 mmol) and Et_3N (175.0 mg, 1.72 mmol) in Methanol (3 mL) was stirred at 25 °C for 2 h under nitrogen atmosphere. The organic solvent was removed under vacuum. The resulting residue was dissolved in MeOH (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~17% acetonitrile in water within 20 min to afford 5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (80.0 mg, 43% over three steps) as a white solid. MS (ESI) calc'd for ($C_8H_{11}N_3O_2S$) $(M+1)^+$, 214.1, found 214.1.

Step-4: (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (R)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-

carboxamide



To a stirred solution of Intermediate G (92.0 mg, 0.33 mmol) in Acetonitrile (5 mL) were sequentially added 5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (70.4 mg, 0.33 mmol), 1-methyl-1H-imidazole (136.0 mg, 1.65 mmol) and N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (93.0 mg, 0.33 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The organic solvent was removed under vacuum. The resulting residue was dissolved in ACN (2 mL) was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 35 min to afford racemic N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (65.0 mg, 38%) as a yellow solid. The racemic compound was separated by prep-chiral HPLC with the following conditions: (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 16 min; Wave Length: 220/254 nm; RT1(min): 12.80; RT2(min): 14.92; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.3 mL; Number Of Runs: 8) to afford (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (14.3 mg, 21%) as a white solid with the first peak on chiral HPLC and (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (21.1 mg, 32%) as a yellow solid with the second peak on chiral HPLC. The absolute stereochemistry was determined using vibrational circular dichroism (VCD) and ab initio calculations.

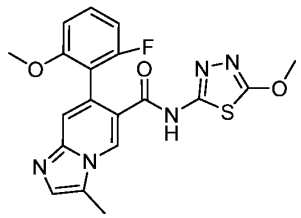
(S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_4S$) $(M+1)^+$,

474.1; found, 474.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 5.62 – 5.54 (m, 1H), 4.10 – 3.94 (m, 2H), 3.64 (s, 3H), 2.58 (s, 3H), 2.50 – 2.42 (m, 1H), 2.19 – 2.11 (m, 1H), 0.87 – 0.77 (m, 1H), 0.77 – 0.68 (m, 1H), 0.66 – 0.56 (m, 1H), 0.56 – 0.46 (m, 1H).

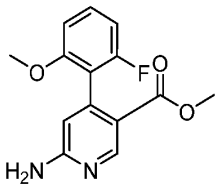
(R)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_4S$) $(M+1)^+$, 474.1; found, 474.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 5.62 – 5.55 (m, 1H), 4.09 – 3.93 (m, 2H), 3.63 (s, 3H), 2.58 (s, 3H), 2.51 – 2.42 (m, 1H), 2.19 – 2.10 (m, 1H), 0.88 – 0.78 (m, 1H), 0.77 – 0.70 (m, 1H), 0.66 – 0.56 (m, 1H), 0.56 – 0.46 (m, 1H).

Example 120

7-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-3-methylimidazo(1,2-a)pyridine-6-carboxamide

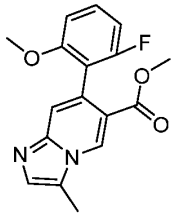


Step-1: methyl 6-amino-4-(2-fluoro-6-methoxyphenyl)nicotinate



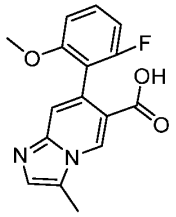
To a solution of methyl 6-amino-4-bromonicotinate (200.0 mg, 0.86 mmol) in 1,4-Dioxane (5 mL) and water (1 mL) were added (2-fluoro-6-methoxyphenyl)boronic acid (177.0 mg, 1.03 mmol), Pd(dtbpf)Cl_2 (56.4 mg, 0.087 mmol) and potassium phosphate (367.0 mg, 1.73 mmol) at 20 °C under nitrogen. The resulting solution was stirred at 90 °C for 2 h under nitrogen. The solvent was removed under vacuum, the residue was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 40 min to afford methyl 6-amino-4-(2-fluoro-6-methoxyphenyl)nicotinate (180.0 mg, 62%) as a brown solid. MS (ESI) calc'd for ($C_{14}H_{13}FN_2O_3$) $(M+1)^+$, 277.1, found 277.1.

Step-2: methyl 7-(2-fluoro-6-methoxyphenyl)-3-methylimidazo(1,2-a)pyridine-6-carboxylate



A mixture of methyl 6-amino-4-(2-fluoro-6-methoxyphenyl)nicotinate (230.0 mg, 0.66 mmol) and 1-bromopropan-2-one (109.0 mg, 0.79 mmol) in Ethanol (4 mL) was stirred at 60 °C for 16 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~45% acetonitrile in water within 40 min to afford methyl 7-(2-fluoro-6-methoxyphenyl)-3-methylimidazo(1,2-a)pyridine-6-carboxylate (100.0 mg, 46%) as a red solid. MS (ESI) calc'd for ($C_{17}H_{15}FN_2O_3$) $(M+1)^+$, 315.3, found 315.2.

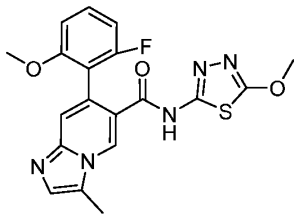
Step-3: 7-(2-fluoro-6-methoxyphenyl)-3-methylimidazo(1,2-a)pyridine-6-carboxylic acid



To a solution of methyl 7-(2-fluoro-6-methoxyphenyl)-3-methylimidazo(1,2-a)pyridine-6-carboxylate (100.0 mg, 0.32 mmol) in Methanol (1 mL) was added NaOH (38.2 mg, 0.95 mmol) in Water (1 mL). The resulting solution was stirred at 50 °C for 3 h. The aqueous layer was acidified with Citric acid to pH ~4 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude residue was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~14% acetonitrile in water within 30 min to afford 7-(2-fluoro-6-methoxyphenyl)-3-methylimidazo(1,2-a)pyridine-6-carboxylic acid (50.0 mg, 52%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{13}FN_2O_3$) $(M+1)^+$, 301.1, found 301.1.

Step-4: 7-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-3-

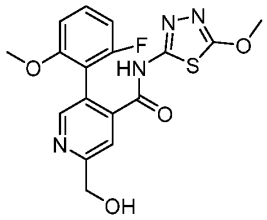
methylimidazo(1,2-a)pyridine-6-carboxamide



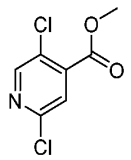
To a stirred solution of 7-(2-fluoro-6-methoxyphenyl)-3-methylimidazo(1,2-a)pyridine-6-carboxylic acid (20.0 mg, 0.067 mmol) in DMF (1 mL) was added HATU (38.0 mg, 0.10 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 10 min. To the above solution was added 5-methoxy-1,3,4-thiadiazol-2-amine (8.8 mg, 0.067 mmol) and N,N-diisopropylethylamine (17.2 mg, 0.13 mmol). The resulting solution was stirred at 20 °C for 1 h. The resulting residue was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~80% acetonitrile in water within 30 min to afford 7-(2-fluoro-6-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-3-methylimidazo(1,2-a)pyridine-6-carboxamide (4.8 mg, 17%) as a white solid. MS (ESI) calc'd for ($C_{19}H_{16}FN_5O_3S$) $(M+1)^+$, 414.1; found, 414.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 9.35 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.54 – 7.44 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.99 – 6.90 (m, 1H), 4.10 (s, 3H), 3.72 (s, 3H), 2.31 (s, 3H).

Example 121

5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)isonicotinamide

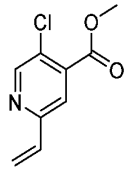


Step-1: methyl 2,5-dichloroisonicotinate



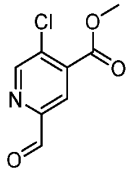
To a stirred solution of 2,5-dichloroisonicotinic acid (10.0 g, 52.00 mmol) in Dichloromethane (100.0 mL) were added Methanol (10.0 mL) and (diazomethyl)trimethylsilane (52 mL, 104.20 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2 h. The organic solvent was removed under vacuum. The resulting residue was dissolved in Dichloromethane (10 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 330 g silica gel column that was eluted with 0~38% ethyl acetate in petroleum ether within 40 min to afford methyl 2,5-dichloroisonicotinate (9.3 g, 83%) as colorless oil. MS (ESI) calc'd for ($C_7H_5ClNO_2$) $(M+1)^+$, 206.0; found 206.0.

Step-2: methyl 5-chloro-2-vinylisonicotinate



To a stirred solution of methyl 2,5-dichloroisonicotinate (4.8 g, 23.35 mmol) and trifluoro(vinyl)-l4-borane, potassium salt (3.1 g, 23.35 mmol) in 1,4-Dioxane (50.0 mL) were added K_2CO_3 (9.7 g, 70.00 mmol) in Water (5.0 mL) and $PdCl_2$(dppf) (1.7 g, 2.35 mmol) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in Dichloromethane (9.0 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~35% ethyl acetate in petroleum ether within 40 min to afford methyl 5-chloro-2-vinylisonicotinate (3.4 g, 73%) as colorless oil. MS (ESI) calc'd for ($C_9H_8ClNO_2$) (M+1)+, 198.0; found 198.0.

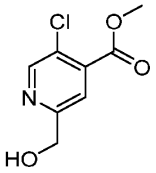
Step-3: methyl 5-chloro-2-formylisonicotinate



To a stirred solution of methyl 5-chloro-2-vinylisonicotinate (2.7 g, 13.66 mmol) in Tetrahydrofuran (15.0 mL) and Water (15.0 mL) were added osmium tetroxide (0.9 mL, 2.73 mmol) and sodium periodate (6.9 g, 27.3 mmol) at 25 °C. The resulting solution was stirred at

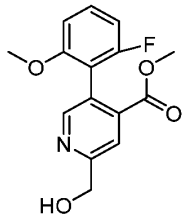
25 °C for 2 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in Dichloromethane (10.0 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 120 g silica gel column that was eluted with 0~35% ethyl acetate in petroleum ether within 40 min to afford methyl 5-chloro-2-formylisonicotinate (1.6 g, 56%) as colorless oil. MS (ESI) calc'd for ($C_8H_6ClNO_3$) $(M+1)^+$,200.0; found 200.0.

Step-4: methyl 5-chloro-2-(hydroxymethyl)isonicotinate



To a stirred solution of methyl 5-chloro-2-formylisonicotinate (1.2 g, 6.01 mmol) in Methanol (10.0 mL) was added $NaBH_4$ (0.1 g, 3.01 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 15 min. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford methyl 5-chloro-2-(hydroxymethyl)isonicotinate (840 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_8H_8ClNO_3$) $(M+1)^+$, 202.0; found 202.0.

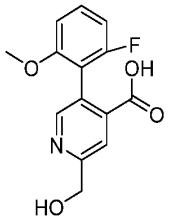
Step-5: methyl 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)isonicotinate



To a degassed solution of methyl 5-chloro-2-(hydroxymethyl)isonicotinate (1.0 g, 5.16 mmol) in 1,4-Dioxane (8.0 mL) and Water (1.6 mL) were added (2-fluoro-6-methoxyphenyl)boronic acid (1.7 g, 10.32 mmol) and K_2CO_3 (2.2 g, 15.48 mmol), 1,1'-Bis (di-t-butylphosphino)ferrocene palladium dichloride (1.0 g, 1.55 mmol) at 23 °C under nitrogen. The resulting solution was stirred at 80 °C for 2 h under nitrogen. The suspension was filtered with diatomite. The filtrate was collected and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 80 g

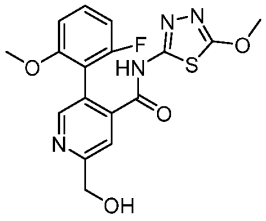
silica gel column and eluted with 0~75% ethyl acetate in petroleum ether within 45 min to afford methyl 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)isonicotinate (950 mg, 61%) as a white solid. MS (ESI) calc'd for ($C_{15}H_{14}FNO_4$) $(M+1)^+$, 292.1; found 292.1.

Step-6: 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)isonicotinic acid



To a stirred solution of methyl 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)isonicotinate (500.0 mg, 1.71 mmol) in Tetrahydrofuran (3.0 mL) were added LiOH (164.0 mg, 6.87 mmol) and Water (1.0 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~4 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)isonicotinic acid (250 mg, crude) as a white solid. MS (ESI) calc'd for ($C_{14}H_{12}FNO_4$) $(M+1)^+$, 278.1; found 278.1.

Step-7: 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)isonicotinamide

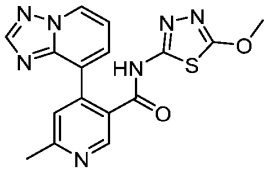


To a stirred solution of 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)isonicotinic acid (100 mg, 0.36 mmol) in Acetonitrile (1 mL) were sequentially added 5-methoxy-1,3,4-thiadiazol-2-amine (47 mg, 0.36 mmol) and 1-methyl-1H-imidazole (148 mg, 1.80 mmol) at 23 °C. Then N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (101 mg, 0.36 mmol) in acetonitrile (1 mL) was added to the above mixture at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The reaction mixture (2 mL) was purified by prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 19*150 mm, 5μm;

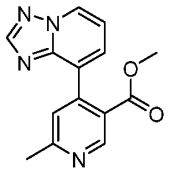
Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15% B to 35% B in 8 min, 35% B; Wave Length: 254 nm) to afford 5-(2-fluoro-6-methoxyphenyl)-2-(hydroxymethyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)isonicotinamide (43.7 mg, 30%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_4S$) $(M+1)^+$, 391.1; found 391.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.99 (br, 1H), 8.49 (s, 1H), 7.81 (s, 1H), 7.44 – 7.34 (m, 1H), 6.96 – 6.85 (m, 2H), 5.60 (t, J = 5.6 Hz, 1H), 4.68 (d, J = 5.6 Hz, 2H), 4.06 (s, 3H), 3.58 (s, 3H).

Example 123

4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

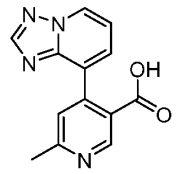


Step-1: methyl 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-6-methylnicotinate



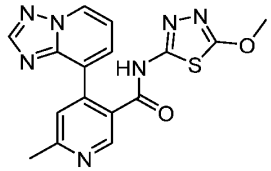
To a stirred solution of methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (1.0 g, 3.79 mmol) in 1,4-Dioxane (10 mL) were added 8-bromo-(1,2,4)triazolo(1,5-a)pyridine (500.0 mg, 2.52 mmol), K_2CO_3 (1.0 g, 7.57 mmol) in Water (2 mL) and Pd(dtbpf)Cl_2 (164.0 mg, 0.25 mmol) at 20 °C. The resulting solution was stirred at 80 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~100% ethyl acetate in petroleum ether within 30 min to afford methyl 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-6-methylnicotinate (500.0 mg, 70%) as a yellow solid. MS (ESI) calc'd for ($C_{14}H_{12}N_4O_2$) $(M+1)^+$, 269.1, found, 269.1.

Step-2: 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-6-methylnicotinic acid



To a stirred solution of methyl 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-6-methylnicotinate (380.0 mg, 1.41 mmol) in Tetrahydrofuran (2 mL) and Water (2 mL) was added LiOH (67.8 mg, 2.83 mmol) at 20 °C. The resulting solution was stirred at 25 °C for 1 h. The mixture was acidified with citric acid to pH ~3. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~30% acetonitrile in water within 20 min to afford 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-6-methylnicotinic acid (256.0 mg, 70%) as a white solid. MS (ESI) calc'd for ($C_{13}H_{10}N_4O_2$) $(M+1)^+$, 255.1, found, 255.1.

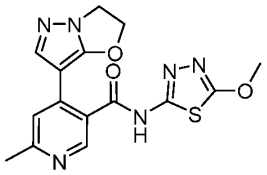
Step-3: 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



To a stirred solution of 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-6-methylnicotinic acid (100.0 mg, 0.39 mmol) in Ethyl acetate (2 mL) was added 5-methoxy-1,3,4-thiadiazol-2-amine (51.6 mg, 0.39 mmol) at 20 °C. To the above solution were added pyridine (0.06 mL, 0.78 mmol) and T_3P (501.0 mg, 0.78 mmol, 50% in EtOAc) at 0 °C under nitrogen. The resulting solution was stirred at 80 °C for 3 h. The reaction mixture was concentrated under vacuum. The resulting residue was dissolved in DMSO (1.5 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~100% acetonitrile in water within 25 min to afford 4-((1,2,4)triazolo(1,5-a)pyridin-8-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (48.8 mg, 33%) as a light brown solid. MS (ESI) calc'd for ($C_{16}H_{13}N_7O_2S$) $(M+1)^+$, 368.1; found, 368.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 9.01 (d, J = 4.0 Hz, 1H), 8.88 (s, 1H), 8.39 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.33 (t, J = 8.0 Hz, 1H), 4.04 (s, 3H), 2.63 (s, 3H).

Example 126

4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

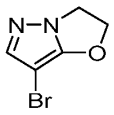


Step-1: 2,3-dihydropyrazolo(5,1-b)oxazole



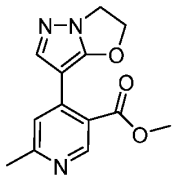
To a solution of 1,2-dihydro-3H-pyrazol-3-one (5.0 g, 59.50 mmol) in Acetonitrile (80 mL) were added 1,2-dibromoethane (33.5 g, 178.50 mmol) and K_2CO_3 (24.6 g, 178.50 mmol). The above solution was stirred at 90 °C for 16 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 120 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~90% acetonitrile in water within 35 min to afford 2,3-dihydropyrazolo(5,1-b)oxazole (1.2 g, 14%) as a white solid. MS (ESI) calc'd for ($C_5H_6N_2O$) $(M+1)^+$, 111.0; found, 111.0.

Step-2: 7-bromo-2,3-dihydropyrazolo(5,1-b)oxazole



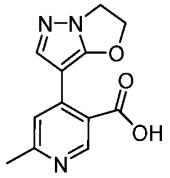
To a stirred solution of 2,3-dihydropyrazolo(5,1-b)oxazole (1.2 g, 8.50 mmol) in Acetonitrile (15 mL) was added NBS (1.8 g, 10.11 mmol) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 2 hr under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 40 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~85% acetonitrile in water within 30 min to afford 7-bromo-2,3-dihydropyrazolo(5,1-b)oxazole (840.0 mg, 47%) as a brown solid. MS (ESI) calc'd for ($C_5H_5BrN_2O$) $(M+1)^+$, 189.0; found, 189.0.

Step-3: methyl 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-6-methylnicotinate



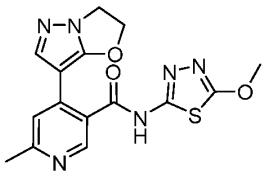
To a stirred solution of methyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (440.0 mg, 1.59 mmol) in 1,4-Dioxane (3 mL) were sequentially added 7-bromo-2,3-dihydropyrazolo(5,1-b)oxazole (300.0 mg, 1.59 mmol), K_2CO_3 (439.0 mg, 3.17 mmol) and $Pd(dppf)Cl_2$ (116.0 mg, 0.16 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 2 hr under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 25 min to afford methyl 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-6-methylnicotinate (210.0 mg, 50 %) as a yellow solid. MS (ESI) calc'd for ($C_{13}H_{13}N_3O_3$) $(M+1)^+$, 260.1; found, 260.1.

Step-4: 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-6-methylnicotinic acid



To a stirred solution of methyl 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-6-methylnicotinate (200.0 mg, 0.77 mmol) in Water (0.3 mL) and THF (1 mL) was added LiOH (162.0 mg, 3.86 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 16 h under nitrogen atmosphere. The resulting residue was acidified to pH ~5 with formic acid, and then diluted with DMF (1 mL) which was applied to a 25 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~30% acetonitrile in water within 20 min to afford 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-6-methylnicotinic acid (90.0 mg, 40 %) as a yellow solid. MS (ESI) calc'd for ($C_{12}H_{11}N_3O_3$) $(M+1)^+$, 246.1; found, 246.1.

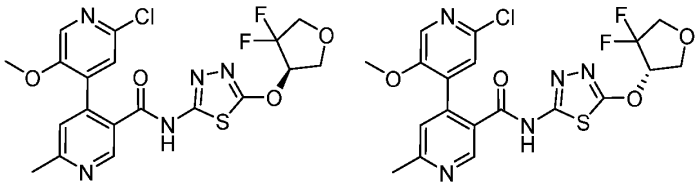
Step-5: 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



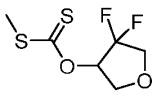
To a stirred solution of 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-6-methylnicotinic acid (85.0 mg, 0.35 mmol) in Acetonitrile (4 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (68.0 mg, 0.52 mmol) and NMI (285.0 mg, 3.47 mmol). To the above solution was added TCFH (97.0 mg, 0.35 mmol) in MeCN (0.5 mL) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 25 °C for 1 hr under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (0.5 mL) which was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~80% acetonitrile in water within 30 min to afford 4-(2,3-dihydropyrazolo(5,1-b)oxazol-7-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (64.7 mg, 50%) as a yellow solid. MS (ESI) calc'd for ($C_{15}H_{14}N_6O_3S$) $(M+1)^+$, 359.1; found, 359.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.49 (s, 1H), 7.57 (s, 1H), 7.38 (s, 1H), 5.17 – 5.06 (m, 2H), 4.37 – 4.24 (m, 2H), 4.10 (s, 3H), 2.51 (s, 3H).

Example 127 and 128

(R)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (S)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

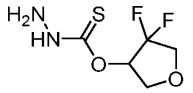


Step-1: O-(4,4-difluorotetrahydrofuran-3-yl) S-methyl carbonodithioate



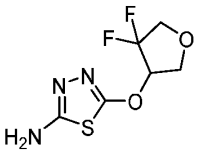
To a solution of NaH (38.7 mg, 0.97 mmol, 60%) in THF (2 mL) was added a solution of 4,4-difluorotetrahydrofuran-3-ol (100.0 mg, 0.81 mmol) in THF (2 mL) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. To the above mixture was added CS_2 (92.0 mg, 1.21 mmol) dropwise at 0 °C and stirred at 0 °C for 20 min. Then MeI (172.0 mg, 1.21 mmol) was added to the above mixture dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h under nitrogen. The resulting mixture was quenched with water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford O-(4,4-difluorotetrahydrofuran-3-yl) S-methyl carbonodithioate (180.0 mg, crude) as yellow oil. MS (ESI) calculated for ($C_6H_8F_2O_2S_2$) $(M+1)^+$, 215.0.

Step-2: O-(4,4-difluorotetrahydrofuran-3-yl) hydrazinecarbothioate



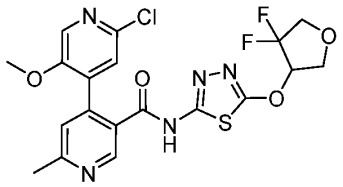
To a mixture of O-(4,4-difluorotetrahydrofuran-3-yl) S-methyl carbonodithioate (180.0 mg, 0.84 mmol) in methanol (3 mL) was added hydrazine hydrate (52.56 mg, 0.84 mmol, 80%). The resulting solution was stirred at 23 °C for 1 h. The solvents were removed under vacuum to afford O-(4,4-difluorotetrahydrofuran-3-yl) hydrazinecarbothioate (160.0 mg, crude) as yellow oil. MS (ESI) calculated for (C_5H_8 $F_2N_2O_2S$) $(M+1)^+$, 199.0.

Step-3: 5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine



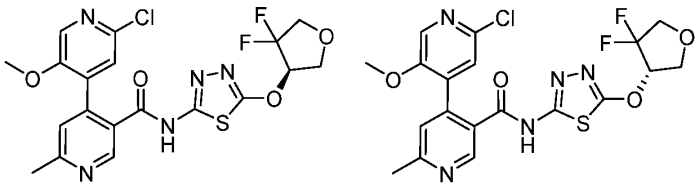
To a mixture of O-(4,4-difluorotetrahydrofuran-3-yl) hydrazinecarbothioate (160.0 mg, 0.81 mmol) in methanol (3 mL) were sequentially added TEA (163.0 mg, 1.62 mmol) and BrCN (94.0 mg, 0.89 mmol). The mixture was stirred at 23 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 20 g silica gel column and eluted with 0~80% ethyl acetate in petroleum ether within 30 min to afford 5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine (75.0 mg, 39% over three steps) as a yellow solid. MS (ESI) calculated for ($C_6H_7F_2N_3O_2S$) $(M+1)^+$, 224.0; found, 224.0.

Step-4: 2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of Intermediate G (74.9 mg, 0.27 mmol) in acetonitrile (2 mL) was added 1-methylimidazole (0.1 mL, 1.34 mmol) and 5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine (60.0 mg, 0.27 mmol). Then TCFH (75.0 mg, 0.27 mmol) in acetonitrile (0.5 mL) was added to the above mixture at 23 °C. The resulting solution was stirred at 23 °C for 2 h under nitrogen. The resulting residue was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~45% acetonitrile in water within 30 min to afford 2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (60.0 mg, 46%) as a white solid. MS (ESI) calculated for ($C_{19}H_{16}ClF_2N_5O_4S$) $(M+1)^+$, 484.1; found, 484.1.

Step-5: (R)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (S)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



2'-Chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (60.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.2% FA)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 15 mL/min; Gradient: 80% B to 80% B in 24 min; Wave Length: 220/254 nm; RT1(min): 13.10; RT2(min): 19.39; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 1.5 mL; Number Of Runs: 2) to afford (R)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (23.5 mg, 39%) as a white solid with the first peak on chiral HPLC and (S)-2'-chloro-N-(5-((4,4-

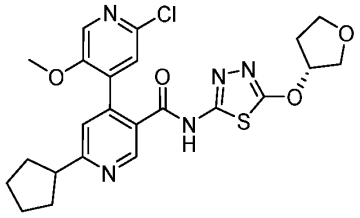
difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (23.2 mg, 38%) as a white solid with the second peak on chiral HPLC. The absolute stereochemistry was not determined.

(R)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{19}H_{16}ClF_2N_5O_4S$) $(M+1)^+$, 484.1; found, 484.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.64 – 5.60 (m, 1H), 4.44 – 4.33 (m, 1H), 4.15 – 3.97 (m, 3H), 3.63 (s, 3H), 2.60 (s, 3H).

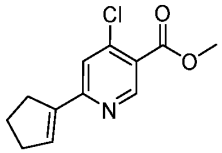
(S)-2'-chloro-N-(5-((4,4-difluorotetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{19}H_{16}ClF_2N_5O_4S$) $(M+1)^+$, 484.1; found, 484.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.64 – 5.60 (m, 1H), 4.39 – 4.33 (m, 1H), 4.14 – 3.97 (m, 3H), 3.63 (s, 3H), 2.60 (s, 3H).

Example 134

(R)-2'-chloro-6-cyclopentyl-5'-methoxy-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



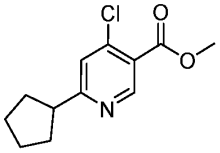
Step-1: methyl 4-chloro-6-(cyclopent-1-en-1-yl)nicotinate



To a stirred solution of methyl 6-bromo-4-chloronicotinate (1.0 g, 3.99 mmol) in Water (6 mL) and 1,4-Dioxane (20 mL) were sequentially added 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.6 g, 3.19 mmol), $Pd(PPh_3)_2Cl_2$ (0.3 g, 0.43 mmol) and K_2CO_3 (1.1 g, 7.96 mmol). The resulting solution was stirred at 60 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous

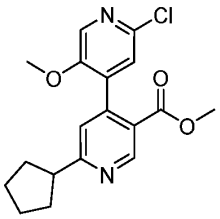
sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 40 g silica gel column and eluted with 0~50% ethyl acetate in petroleum ether within 20 min to afford methyl 4-chloro-6-(cyclopent-1-en-1-yl)nicotinate (360.0 mg, 34%) as a white solid. MS (ESI) calc'd for ($C_{12}H_{12}ClNO_2$) $(M+1)^+$, 238.1; found, 238.1.

Step-2: methyl 4-chloro-6-cyclopentylnicotinate



To a stirred solution of methyl 4-chloro-6-(cyclopent-1-en-1-yl)nicotinate (200.0 mg, 0.72 mmol) in Methanol (5 mL) was added Raney nickel (900.0 mg, 15.33 mmol) at 30 °C under nitrogen atmosphere. The resulting solution was stirred at 30 °C for 5 min under hydrogen (20 atm). The suspension was filtered. The filtrate was collected and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 10~90% acetonitrile in water within 20 min to afford methyl 4-chloro-6-cyclopentylnicotinate (150.0 mg, 80%) as yellow oil. MS (ESI) calc'd for ($C_{12}H_{14}ClNO_2$) $(M+1)^+$, 240.1; found, 240.1.

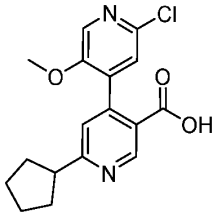
Step-3: methyl 2'-chloro-6-cyclopentyl-5'-methoxy-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of methyl 4-chloro-6-cyclopentylnicotinate (140.0 mg, 0.58 mmol) in 1,4-Dioxane (2 mL) and Water (0.2 mL) were sequentially added (2-chloro-5-methoxypyridin-4-yl)boronic acid (109.0 mg, 0.58 mmol), $Pd(dtbpf)Cl_2$ (38.1 mg, 0.06 mmol) and K_2CO_3 (161.0 mg, 1.17 mmol). The resulting solution was stirred at 80 °C for 16 h under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 25 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 10~100% acetonitrile in water within 20

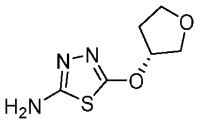
min to afford methyl 2'-chloro-6-cyclopentyl-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (120.0 mg, 50%) as yellow oil. MS (ESI) calc'd for ($C_{18}H_{19}ClN_2O_3$) $(M+1)^+$, 347.1; found, 347.1.

Step-4: 2'-chloro-6-cyclopentyl-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of methyl 2'-chloro-6-cyclopentyl-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (110.0 mg, 0.32 mmol) in Tetrahydrofuran (1mL) and Water (1 mL) was added lithium hydroxide (38.0 mg, 1.59 mmol). The resulting solution was stirred at room temperature for 2 h. The aqueous layer was acidified with HCl (1 *N*) to pH ~3 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 30~80% acetonitrile in water within 15 min to afford 2'-chloro-6-cyclopentyl-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (80.0 mg, 74%) as a white solid. MS (ESI) calc'd for ($C_{17}H_{17}ClN_2O_3$) $(M+1)^+$, 333.1; found, 333.1.

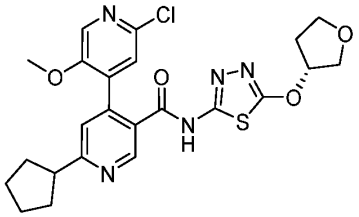
Step-5: (R)-5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine



To a solution of (R)-tetrahydrofuran-3-ol (1.0 g, 11.35 mmol) in Tetrahydrofuran (10 mL) was added NaH (460 mg, 13.50 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 1 h under nitrogen atmosphere. To the above mixture was added 5-bromo-1,3,4-thiadiazol-2-amine (2.0 g, 11.35 mmol) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 2 h. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (4 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~15% acetonitrile in water within 25 mins

to afford (R)-5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine (330 mg, 14%) as a white solid. MS (ESI) calc'd for ($C_6H_9N_3O_2S$) $(M+1)^+$, 188.0; found, 188.1.

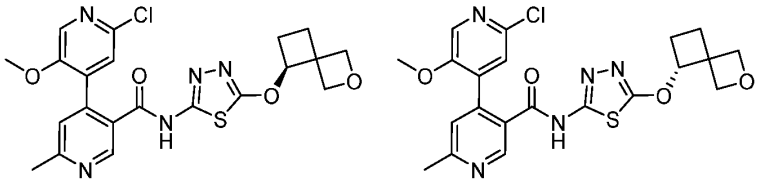
Step-6: (R)-2'-chloro-6-cyclopentyl-5'-methoxy-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



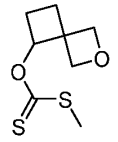
To a stirred solution of 2'-chloro-6-cyclopentyl-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (30.0 mg, 0.09 mmol) in acetonitrile (1 mL) were added (R)-5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-amine (16.9 mg, 0.09 mmol) and 1-methyl-1H-imidazole (37.0 mg, 0.45 mmol). To the above solution was added TCFH (25.3 mg, 0.09 mmol) in acetonitrile (1 mL). The resulting solution was stirred at 25 °C for 1 h under nitrogen. The organic solvent was removed under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 40~70% acetonitrile in water within 35 min to afford (R)-2'-chloro-6-cyclopentyl-5'-methoxy-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (30.3 mg, 66%) as a white solid. MS (ESI) calc'd for ($C_{23}H_{24}ClN_5O_4S$) $(M+1)^+$, 502.1; found, 502.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 7.58 (s, 1H), 7.43 (s, 1H), 5.55 – 5.48 (m, 1H), 4.02 – 3.76 (m, 4H), 3.63 (s, 3H), 3.22 – 3.20 (m, 1H), 2.32 – 2.22 (m, 1H), 2.18 – 2.00 (m, 3H), 1.81 – 1.68 (m, 6H).

Example 136 and 137

(S)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (R)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

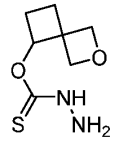


Step-1: S-methyl O-(2-oxaspiro(3.3)heptan-5-yl) carbonodithioate



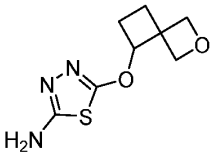
To a stirred solution of 2-oxaspiro(3.3)heptan-5-ol (500.0 mg, 4.38 mmol) in THF (10 mL) was added NaH (350.0 mg, 8.75 mmol, 60%) in portions at 0 °C. The resulting solution was stirred at 0 °C for 0.5 h under nitrogen atmosphere. To the above solution was added CS_2 (500.0 mg, 6.57 mmol) at 0 °C. The resulting mixture was then stirred at 0 °C for 0.5 h. To the above solution was added MeI (935.0 mg, 6.59 mmol) at 0 °C. The resulting mixture was then stirred at 0 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford S-methyl O-(2-oxaspiro(3.3)heptan-5-yl) carbonodithioate (620.0 mg, crude) as yellow oil, the crude product was used in the next step without further purification.

Step-2: O-(2-oxaspiro(3.3)heptan-5-yl) hydrazinecarbothioate



To a stirred solution of S-methyl O-(2-oxaspiro(3.3)heptan-5-yl) carbonodithioate (620.0 mg, 3.03 mmol) in Methanol (8 mL) was added hydrazine hydrate (190.0 mg, 3.03 mmol, 80%) at 25 °C. The resulting solution was stirred at 25 °C for 0.5 h under nitrogen atmosphere. The solvents were removed under vacuum to afford O-(2-oxaspiro(3.3)heptan-5-yl) hydrazinecarbothioate (450.0 mg, crude) as a yellow oil, which was used in the next step without further purification.

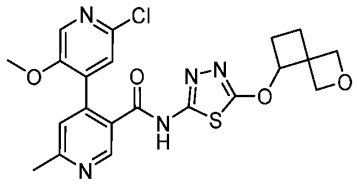
Step-3: 5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of O-(2-oxaspiro(3.3)heptan-5-yl) hydrazinecarbothioate (450.0 mg, 2.39 mmol) in Methanol (8 mL) was added BrCN (279.0 mg, 2.63 mmol) and TEA (483.0 mg, 4.78 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 h under nitrogen

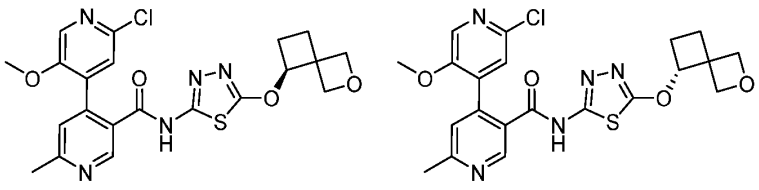
atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~10% methanol in dichloromethane within 35 min to afford 5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-amine (280.0 mg, 51%) as a yellow solid. MS (ESI) calc'd for ($C_8H_{11}N_3O_2S$) $(M+1)^+$,214.1; found, 214.1.

Step-4: N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-amine (280.0 mg, 1.22 mmol) in Acetonitrile (5 mL) was added Intermediate G (340.0 mg, 1.22 mmol) and NMI (501.0 mg, 6.11 mmol). To the above solution was added TCFH (343.0 mg, 1.22 mmol) in MeCN (0.5 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h under nitrogen atmosphere. The solvents were removed under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 25 g C18 column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~80% acetonitrile in water within 30 min to afford N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (170.0 mg, 27%) as a white solid. MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_4S$) $(M+1)^+$, 474.1; found, 474.1.

Step-5: (S)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (R)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



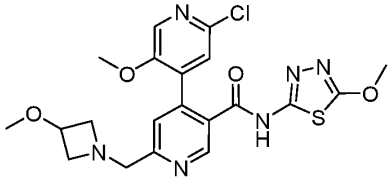
N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (170.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.1% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 18 mL/min; Gradient: 50% B to 50% B in 20 min; Wave Length: 220/254 nm; RT1(min): 12.21; RT2(min): 15.93; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 4) to afford (S)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (40.9 mg, 24%) as a white solid with the first peak on chiral HPLC and (R)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (34.0 mg, 19%) as a white solid with the second peak on chiral HPLC. The absolute stereochemistry was not determined.

(S)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for $(C_{21}H_{20}ClN_5O_4S)$ $(M+1)^+$, 474.1; found, 474.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 5.24 – 5.15 (m, 1H), 4.87 (d, J = 6.4 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.53 (d, J = 6.4 Hz, 1H), 4.46 (d, J = 6.8 Hz, 1H), 3.65 (s, 3H), 2.60 (s, 3H), 2.32 – 2.21 (m, 1H), 2.19 – 2.06 (m, 1H), 1.94 – 1.79 (m, 2H).

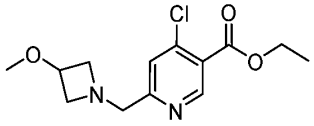
(R)-N-(5-((2-oxaspiro(3.3)heptan-5-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for $(C_{21}H_{22}ClN_5O_4S)$ $(M+1)^+$, 474.1; found, 474.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.23 – 5.15 (m, 1H), 4.87 (d, J = 6.4 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.53 (d, J = 6.4 Hz, 1H), 4.46 (d, J = 6.8 Hz, 1H), 3.65 (s, 3H), 2.60 (s, 3H), 2.32 – 2.21 (m, 1H), 2.19 – 2.06 (m, 1H), 1.94 – 1.82 (m, 2H).

Example 144

2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxamide

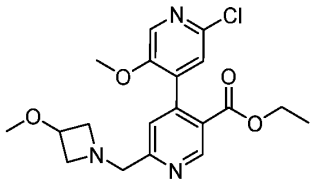


Step-1: ethyl 4-chloro-6-((3-methoxyazetidin-1-yl)methyl)nicotinate



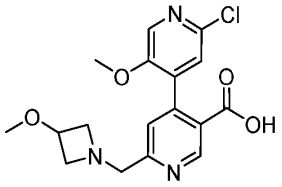
To a degassed solution of ethyl 4-chloro-6-(chloromethyl)nicotinate (500.0 mg, 2.14 mmol) in dry Ethanol (5 mL) were added 3-methoxyazetidine (149.0 mg, 1.71 mmol) and TEA (432.0 mg, 4.27 mmol) dropwise at 25 °C and stirred at 25 °C for 1 hr under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (2 mL) and purified by Combi Flash which applied to a 40 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 25 min to afford ethyl 4-chloro-6-((3-methoxyazetidin-1-yl)methyl)nicotinate (460.0 mg, 56%) as yellow oil. MS (ESI) calculated for ($C_{13}H_{17}ClN_2O_3$) $(M+1)^+$, 285.1; found, 285.1.

Step-2: ethyl 2'-chloro-5'-methoxy-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxylate



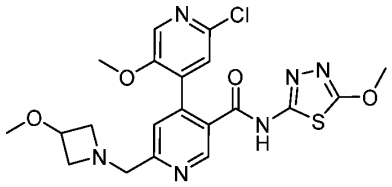
To a stirred solution of ethyl 4-chloro-6-((3-methoxyazetidin-1-yl)methyl)nicotinate (460.0 mg, 1.62 mmol) in dioxane (5 ml) were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (908.0 mg, 4.85 mmol), K_2CO_3 (447.0 mg, 3.23 mmol) and $Pd(dppf)Cl_2$ (119.0 mg, 0.16 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash which applied to 40 g silica gel column and eluted with 0~50% ethyl acetate in petroleum ether within 25 min to afford ethyl 2'-chloro-5'-methoxy-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxylate (250.0 mg, 23%) as a white solid. MS (ESI) calculated for ($C_{19}H_{22}ClN_3O_4$) $(M+1)^+$, 392.1; found, 392.1.

Step-3: 2'-chloro-5'-methoxy-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of ethyl 2'-chloro-5'-methoxy-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxylate (250.0 mg, 0.64 mmol) in Tetrahydrofuran (THF) (2 mL) and Water (2 mL) was added LiOH (134.0 mg, 3.19 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The organic solvent was removed under vacuum. The aqueous layer was acidified with Citric acid to pH ~2 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 25 g C18 column and purified by Combi Flash, eluted with 5~30% acetonitrile in water within 20 min to afford 2'-chloro-5'-methoxy-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxylic acid (90.0 mg, 36%) as a white solid. MS (ESI) calculated for ($C_{17}H_{18}ClN_3O_4$) $(M+1)^+$, 364.1; found, 364.1.

Step-4: 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxamide

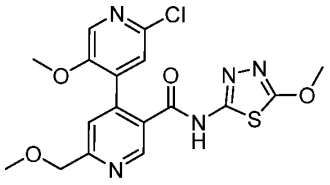


To a stirred solution of 2'-chloro-5'-methoxy-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-carboxylic acid (100.0 mg, 0.28 mmol) in acetonitrile (2 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (36.1 mg, 0.28 mmol) and NMI (113.0 mg, 1.37 mmol). To the above solution was added TCFH (77.0 mg, 0.28 mmol) in acetonitrile (1 mL). The resulting solution was stirred at 25 °C under nitrogen for 1 h. The solvents were removed under vacuum. The resulting residue was dissolved in DMF (2 mL) and was purified by prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 30% B in 10 min, 30% B; Wave Length: 220 nm; RT1(min): 8.25; Injection Volume: 1.2 mL; Number Of Runs: 3) to afford 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-((3-methoxyazetidin-1-yl)methyl)-(4,4'-bipyridine)-3-

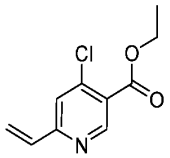
carboxamide (15.1 mg, 11%) as a white solid. MS (ESI) calculated for ($C_{20}H_{21}ClN_6O_4S$) $(M+1)^+$, 477.1; found, 477.2. ^1H NMR(400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.27 (s, 1H), 8.12 (s, 1H), 7.20 (s, 1H), 6.40 (s, 1H), 4.32 – 4.22 (m, 1H), 4.18 – 4.06 (m, 5H), 3.98 – 3.92 (m, 2H), 3.90 (s, 3H), 3.74 – 3.68 (m, 2H), 3.21 (s, 3H).

Example 158

2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxamide

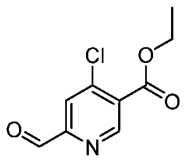


Step-1: ethyl 4-chloro-6-vinylnicotinate



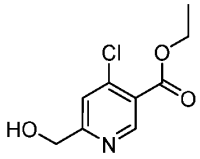
To a stirred solution of ethyl 4,6-dichloronicotinate (10.0 g, 45.40 mmol) in 1,4-Dioxane (60 mL) and water (6 mL)were added trifluoro(vinyl)-l4-borane, potassium salt (6.1 g, 45.40 mmol), K_2CO_3 (12.5 g, 91.00 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.7 g, 4.54 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 1.5 hr under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 120 g silica gel column and eluted with 0~50% ethyl acetate in petroleum ether within 35 min to afford ethyl 4-chloro-6-vinylnicotinate (9.0 g, 75%) as a yellow solid. MS (ESI) calc'd for ($C_{10}H_{10}ClNO_2$) $(M+1)^+$, 212.0; found, 212.0.

Step-2: ethyl 4-chloro-6-formylnicotinate



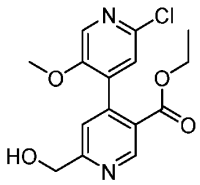
To a stirred solution of ethyl 4-chloro-6-vinylnicotinate (9.0 g, 42.50 mmol) in Tetrahydrofuran (210 mL) and Water (70 mL) were added osmium tetroxide (2.1 g, 8.50 mmol) and sodium periodate (18.2 g, 85.00 mmol) at 20 °C. The resulting solution was stirred at 20 °C for 16 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (8 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 330 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 25 min to afford ethyl 4-chloro-6-formylnicotinate (3.1 g, 31%) as a yellow solid. MS (ESI) calc'd for ($C_9H_8ClNO_3$) $(M+1)^+$, 214.0; found, 214.0.

Step-3: ethyl 4-chloro-6-(hydroxymethyl)nicotinate



To a stirred solution of ethyl 4-chloro-6-formylnicotinate (2.0 g, 9.36 mmol) in Ethanol (20 mL) was added $NaBH_4$ (0.4 g, 9.34 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford ethyl 4-chloro-6-(hydroxymethyl)nicotinate (2.0 g, crude) as a yellow oil. MS (ESI) calc'd for ($C_9H_{10}ClNO_3$) $(M+1)^+$,216.0; found, 216.0.

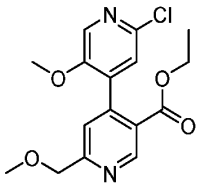
Step-4: ethyl 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of ethyl 4-chloro-6-(hydroxymethyl)nicotinate (2.0 g, 9.28 mmol) in 1,4-Dioxane (20 mL) were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (2.4 g, 12.99 mmol), K_2CO_3 (3.9 g, 27.80 mmol) in Water (4 mL) and $Pd(dtbpf)Cl_2$ (604.0 mg, 0.93 mmol) at 20 °C. The resulting solution was stirred at 80 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was collected and washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under

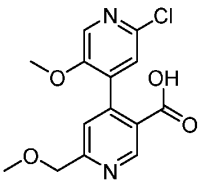
vacuum. The resulting residue was dissolved in DCM (8 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to an 80 g silica gel column that was eluted with 0~90% ethyl acetate in petroleum ether within 30 min to afford ethyl 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (1.1 g, 30%) as a brown oil. MS (ESI) calculated for ($C_{15}H_{15}ClN_2O_4$) $(M+1)^+$, 323.1; found, 323.1.

Step-5: ethyl 2'-chloro-5'-methoxy-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxylate



To a stirred solution of NaH (109.1 mg, 2.73 mmol, 60%) in N,N-Dimethylformamide (2 ml) were added a solution of ethyl 2'-chloro-6-(hydroxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (600.0 mg, 1.86 mmol) in N,N-Dimethylformamide (2 ml) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. To the above solution was added dimethyl sulfate (251.0 mg, 1.99 mmol) at 0 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 3 hr. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~30% acetonitrile in water within 30 min to afford ethyl 2'-chloro-5'-methoxy-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxylate (210.0 mg, 34%) as a brown oil. MS (ESI) calculated for ($C_{16}H_{17}ClN_2O_4$) $(M+1)^+$, 337.1; found, 337.1.

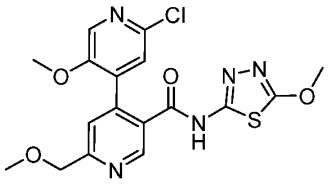
Step-6: 2'-chloro-5'-methoxy-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of ethyl 2'-chloro-5'-methoxy-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxylate (180.0 mg, 0.53 mmol) in Tetrahydrofuran (THF) (1 mL) was added LiOH (38.4 mg, 1.60 mmol) in Water (0.3 mL) at 25 °C. The resulting solution was stirred at 25 °C for 16 h. The reaction mixture was acidified with citric acid to pH 4~5 and purified directly. The resulting residue was diluted with acetonitrile (2 mL) which was applied to a 40 g C18

column, purified by Combi Flash (Biotage Isolera Prime) and eluted with 5~30% acetonitrile in water (0.05% FA) within 30 min to afford 2'-chloro-5'-methoxy-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxylic acid (120.0 mg, 70%) as a white solid. MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_4$) $(M+1)^+$, 309.1; found, 309.1.

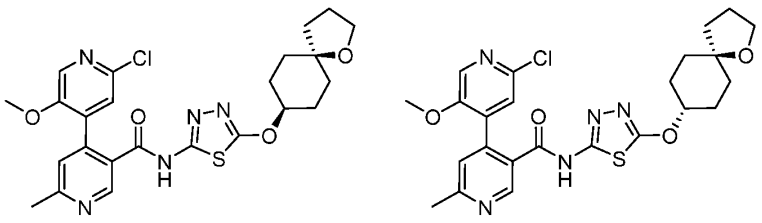
Step-7: 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxamide



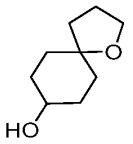
To a stirred solution of 2'-chloro-5'-methoxy-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxylic acid (60.0 mg, 0.19 mmol) in Acetonitrile (1 mL) were added 1-methyl-1H-imidazole (80.0 mg, 0.97 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (25.5 mg, 0.19 mmol) at 25 °C. To the above solution was added TCFH (54.5 mg, 0.19 mmol) in MeCN (0.5 mL) at 25 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 2 hr. The residue was dissolved in DMF (1 mL) and purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 26% B in 8 min, 26% B; Wave Length: 254 nm; RT1(min): 7) to afford 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-(methoxymethyl)-(4,4'-bipyridine)-3-carboxamide (19.1 mg, 23%) as a white solid. MS (ESI) calculated for ($C_{17}H_{16}ClN_5O_4S$) $(M+1)^+$, 422.1; found, 422.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.91 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 4.62 (s, 2H), 4.07 (s, 3H), 3.64 (s, 3H), 3.42 (s, 3H).

Example 173 and 174

N-(5-(((5s,8r)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((5r,8s)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

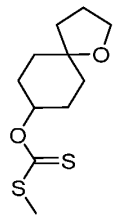


Step-1: 1-oxaspiro(4.5)decan-8-ol



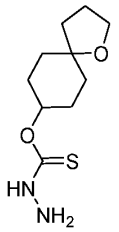
To a stirred solution of 1-oxaspiro(4.5)decan-8-one (100.0 mg, 0.64 mmol) in Methanol (1 mL) was added $NaBH_4$ (50.0 mg, 1.32 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 25 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 20 g silica gel column that was eluted with 0~50% ethyl acetate in petroleum ether within 35 min to afford 1-oxaspiro(4.5)decan-8-ol (80.0 mg, 71%) as colorless oil.

Step-2: S-methyl O-(1-oxaspiro(4.5)decan-8-yl) carbonodithioate



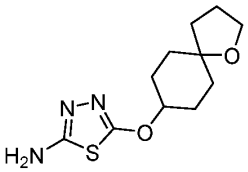
To a mixture of NaH (41.0 mg, 1.02 mmol, 60%) in THF (5 mL) was added 1-oxaspiro(4.5)decan-8-ol (80.0 mg, 0.51 mmol) in portions at 0 °C and stirred at 0 °C for 1 h under nitrogen. Then CS_2 (58.0 mg, 0.76 mmol) was added to the above mixture and stirred at 0 °C for 20 min, and then MeI (109.0 mg, 0.76 mmol) was added to the above mixture at 5 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford S-methyl O-(1-oxaspiro(4.5)decan-8-yl) carbonodithioate (100.0 mg, crude) as yellow oil, which was used in the next step without further purification.

Step-3: O-(1-oxaspiro(4.5)decan-8-yl) hydrazinecarbothioate



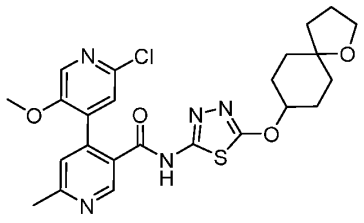
To a stirred solution of S-methyl O-(1-oxaspiro(4.5)decan-8-yl) carbonodithioate (100.0 mg, 0.40 mmol) in Methanol (4 mL) was added hydrazine hydrate (20.0 mg, 0.49 mmol, 80%) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 25 °C for 0.5 h. The solvents were removed under vacuum to afford O-(1-oxaspiro(4.5)decan-8-yl) hydrazinecarbothioate (120.0 mg, crude) as yellow oil, which was used in the next step without further purification.

Step-4: 5-((1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-amine



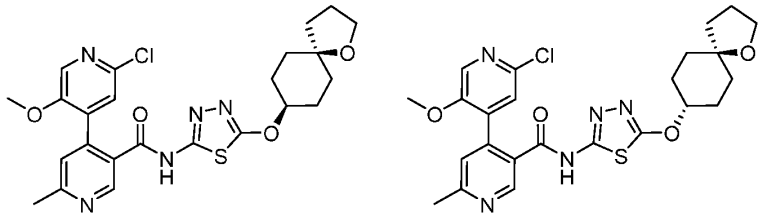
To a stirred solution of O-(1-oxaspiro(4.5)decan-8-yl) hydrazinecarbothioate (120.0 mg, 0.38 mmol) and TEA (76.0 mg, 0.76 mmol) in Methanol (4 mL) was added BrCN (45.0 mg, 0.42 mmol) at 25 °C under nitrogen atmosphere. The resulting solution was stirred at 25 °C for 1 h under nitrogen atmosphere. The solvents were removed under vacuum. The resulting residue was dissolved in DCM (1 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 20 g silica gel column that was eluted with 0~10% methanol in dichloromethane within 30 min to afford 5-((1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-amine (80.0 mg, 81%) as a yellow solid. MS (ESI) calc'd for $(C_{11}H_{17}N_3O_2S)$ $(M+1)^+$, 256.1; found, 256.1.

Step-5: N-(5-((1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 5-((1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-amine (80.0 mg, 0.31 mmol) in acetonitrile (1 mL) were added Intermediate G (87.0 mg, 0.31 mmol) and 1-methyl-1H-imidazole (129.0 mg, 1.56 mmol). To the above solution was added TCFH (88.0 mg, 0.31 mmol) in MeCN (0.5 mL). The resulting solution was stirred at 25 °C under nitrogen for 1 hr. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash, eluted with 5~80% acetonitrile in water within 25 min to afford N-(5-((1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (97.0 mg, 42%) as a white solid. MS (ESI) calc'd for ($C_{24}H_{26}ClN_5O_4S$) $(M+1)^+$, 516.1; found, 516.2.

Step-6: N-(5-(((5s,8r)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((5r,8s)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



N-(5-((1-Oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (90.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.2% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 9.02; RT2(min): 11.22; Sample Solvent: MeOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 5) to afford N-(5-(((5s,8r)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (42.6 mg, 47%) as a white solid with the first peak on chiral HPLC and N-(5-(((5r,8s)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (22.7 mg, 25%) as a white solid with the second peak on chiral HPLC. The relative stereochemistry was not determined.

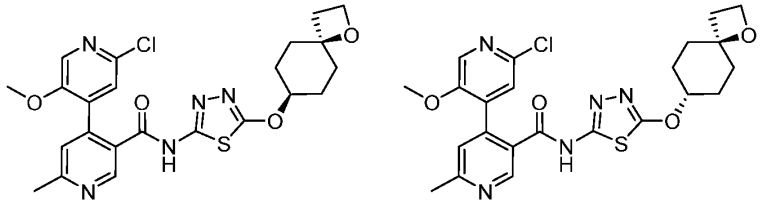
N-(5-(((5s,8r)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{24}H_{26}ClN_5O_4S$) $(M+1)^+$, 516.1; found, 516.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.81 (s, 1H), 8.18 (s,

1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.95 – 4.85 (m, 1H), 3.80 – 3.56 (m, 5H), 2.60 (s, 3H), 2.13 – 1.75 (m, 6H), 1.74 – 1.58 (m, 4H), 1.56 – 1.40 (m, 2H).

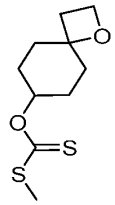
N-(5-(((5r,8s)-1-oxaspiro(4.5)decan-8-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{24}H_{26}ClN_5O_4S$) $(M+1)^+$, 516.1; found, 516.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.04 – 4.98 (m, 1H), 3.76 – 3.68 (m, 2H), 3.64 (s, 3H), 2.59 (s, 3H), 2.04 – 1.94 (m, 2H), 1.94 – 1.81 (m, 2H), 1.81 – 1.73 (m, 2H), 1.72 – 1.58 (m, 4H), 1.55 – 1.45 (m, 2H).

Example 185 and 186

N-(5-(((4s,7s)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((4r,7r)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

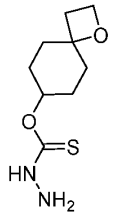


Step-1: S-methyl O-(1-oxaspiro(3.5)nonan-7-yl) carbonodithioate



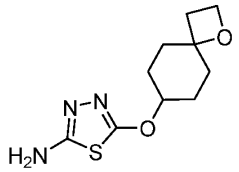
To a stirred solution of 1-oxaspiro(3.5)nonan-7-ol (100.0 mg, 0.70 mmol) in Tetrahydrofuran (THF) (3 mL) was added NaH (33.8 mg, 0.84 mmol, 60%) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. To the above solution was added CS_2 (80.0 mg, 1.05 mmol) at 0 °C under nitrogen. The resulting mixture was then stirred at 0 °C for 20 min. To the above solution was added MeI (150.0 mg, 1.05 mmol) at 0 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford S-methyl O-(1-oxaspiro(3.5)nonan-7-yl) carbonodithioate (160.0 mg, crude) as yellow oil.

Step-2: O-(1-oxaspiro(3.5)nonan-7-yl) hydrazinecarbothioate



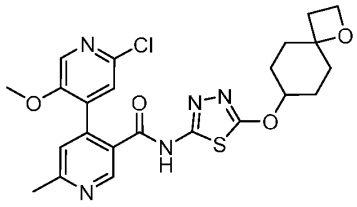
A mixture of S-methyl O-(1-oxaspiro(3.5)nonan-7-yl) carbonodithioate (160.0 mg, 0.69 mmol), hydrazinium hydroxide (43.1 mg, 0.69 mmol) in Methanol (3 mL) was stirred at 25 °C for 2 h under nitrogen. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-(1-oxaspiro(3.5)nonan-7-yl) hydrazinecarbothioate (170.0 mg, crude) as yellow oil. MS (ESI) calc'd for ($C_9H_{16}N_2O_2S$) $(M+1)^+$, 217.1; found 217.1.

Step-3: 5-((1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-amine



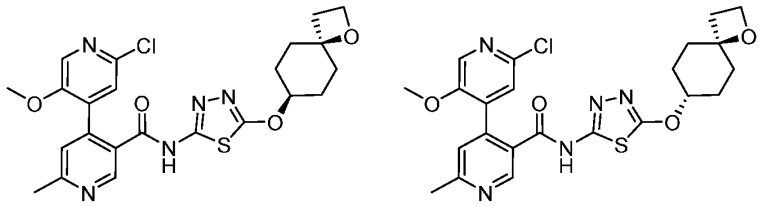
To a mixture of O-(1-oxaspiro(3.5)nonan-7-yl) hydrazinecarbothioate (170.0 mg, 0.78 mmol) in Methanol (3 mL) were added TEA (159.0 mg, 1.57 mmol) and cyanic bromide (100.0 mg, 0.94 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 h under nitrogen before concentrated under vacuum. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~30% acetonitrile in water within 20 min to afford 5-((1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-amine (89.0 mg, 45% over three steps) as a yellow solid. MS (ESI) calc'd for ($C_{10}H_{15}N_3O_2S$) $(M+1)^+$, 242.2; found 242.2.

Step-4: N-(5-((1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of Intermediate G (81.0 mg, 0.29 mmol), 5-((1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-amine (70.0 mg, 0.29 mmol) and 1-methylimidazole (119.0 mg, 1.45 mmol) in Acetonitrile (1 mL). To the above was added a solution of N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (90.0 mg, 0.32 mmol) in acetonitrile (1 mL) at 25 °C under nitrogen. The resulting mixture was stirred at 25 °C for 2 h. The resulting residue was dissolved in DMF (1 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 30 min to afford N-(5-((1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (80.0 mg, 52%) as a yellow solid. MS (ESI) calc'd for ($C_{23}H_{24}ClN_5O_4S$) $(M+1)^+$, 502.1; found 502.1.

Step-5: N-(5-(((4s,7s)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((4r,7r)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



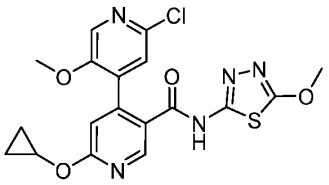
The racemic compound of N-(5-((1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (80 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.2% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 17 mL/min; Gradient: 70% B to 70% B in 18 min; Wave Length: 220/254 nm; RT1(min): 9.42; RT2(min): 15.47; Sample Solvent: MeOH: DCM=1: 1--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 3) to afford N-(5-(((4s,7s)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (40.2 mg, 49%) as a white solid with shorter retention time on chiral HPLC and N-(5-(((4r,7r)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (15.0 mg, 18%) as a white solid with longer retention time on chiral HPLC. The stereochemistry was not determined.

N-(5-(((4s,7s)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{23}H_{24}ClN_5O_4S$) $(M+1)^+$, 502.2; found,502.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 4.95 – 4.850 (m, 1H), 4.37 (t, J = 7.6 Hz, 2H), 3.64 (s, 3H), 2.59 (s, 3H), 2.34 (t, J = 7.6 Hz, 2H), , 2.01 – 1.64 (m, 8H).

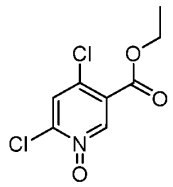
N-(5-(((4r,7r)-1-oxaspiro(3.5)nonan-7-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calc'd for ($C_{23}H_{24}ClN_5O_4S$) $(M+1)^+$, 502.2; found,502.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.96 – 4.89 (m, 1H), 4.38 (t, J = 7.6 Hz, 2H), 3.64 (s, 3H), 2.59 (s, 3H), 2.36 (t, J = 7.6 Hz, 2H), 2.14 – 1.86 (m, 4H), 1.76 – 1.66 (m, 4H).

Example 196

2'-chloro-6-cyclopropoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

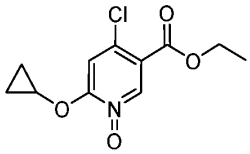


Step-1: 2,4-dichloro-5-(ethoxycarbonyl)pyridine 1-oxide



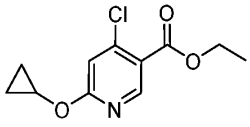
To a stirred solution of ethyl 4,6-dichloronicotinate (10.0 g, 45.66 mmol) in DCM (100 mL) were added TFAA (19.2 g, 90.89 mmol) and urea·H_2O_2 (8.6 g, 90.89 mmol) at 25 °C under nitrogen. The mixture was stirred at 25 °C for 2 h. The resulting mixture was diluted with DCM (100 mL). The combined organic layers were washed with sat. Na_2CO_3 aqueous solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 120 g silica gel column and eluted with 0~48% ethyl acetate in petroleum ether within 30 min to afford 2,4-dichloro-5-(ethoxycarbonyl)pyridine 1-oxide (8.9 g, 75%) as a white solid. MS (ESI) calculated for ($C_8H_7Cl_2NO_3$) $(M+1)^+$, 236.0; found, 236.0.

Step-2: 4-chloro-2-cyclopropoxy-5-(ethoxycarbonyl)pyridine 1-oxide



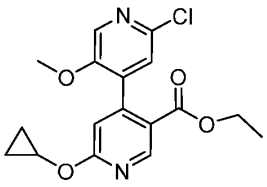
To a stirred solution of 2,4-dichloro-5-(ethoxycarbonyl)pyridine 1-oxide (5.0 g, 21.18 mmol) in THF (50 mL) was added NaH (1.0 g, 25.00 mmol, 60%) in portions at 0 °C. The resulting solution was stirred at 0 °C for 40 min. To the above solution was added cyclopropanol (1.4 g, 24.14 mmol) at 0 °C under nitrogen. The resulting solution was stirred at 25 °C for 2 h. The reaction mixture was quenched by water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (5 mL) which was applied to a 120 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~55% acetonitrile in water within 30 min to afford 4-chloro-2-cyclopropoxy-5-(ethoxycarbonyl)pyridine 1-oxide (2.9 g, 53%) as a white solid. MS (ESI) calculated for ($C_{11}H_{12}ClNO_4$) $(M+1)^+$, 258.0; found, 258.0.

Step-3: ethyl 4-chloro-6-cyclopropoxynicotinate



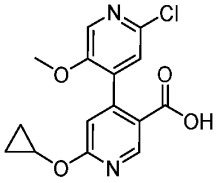
To a stirred solution of 4-chloro-2-cyclopropoxy-5-(ethoxycarbonyl)pyridine 1-oxide (2.9 g, 112.84 mmol) in HOAc (30 mL) was added Fe (2.5 g, 446.42 mmol) at 25 °C. The resulting solution was stirred at 60 °C for 16 hr under nitrogen. The suspension was filtered. The filter cake was washed with ethyl acetate. The filtrate was collected and dried under vacuum. The resulting residue was dissolved in DMF (5 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 15~85% acetonitrile in water within 30 min to afford ethyl 4-chloro-6-cyclopropoxynicotinate (1.5 g, 55%) as a yellow solid. MS (ESI) calculated for ($C_{11}H_{12}ClNO_3$) $(M+1)^+$, 242.1; found, 242.0.

Step-4: ethyl 2'-chloro-6-cyclopropoxy-5'-methoxy-(4,4'-bipyridine)-3-carboxylate



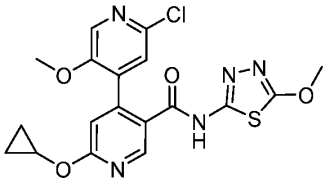
To a solution of ethyl 4-chloro-6-cyclopropoxynicotinate (1.0 g, 4.15 mmol) in dioxane (5 mL) were added Pd(dtbpf)Cl_2 (269.7 mg, 0.41 mmol), K_2CO_3 (1.7 g, 12.32 mmol) and (2-chloro-5-methoxypyridin-4-yl)boronic acid (1.2 g, 6.41 mmol) at 25 °C. The resulting solution was stirred at 80 °C for 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (3 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~80% acetonitrile in water within 30 min to afford ethyl 2'-chloro-6-cyclopropoxy-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (500.0 mg, 34%) as a yellow solid. MS (ESI) calculated for ($C_{17}H_{17}ClN_2O_4$) $(M+1)^+$, 349.1; found, 349.1.

Step-5: 2'-chloro-6-cyclopropoxy-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of ethyl 2'-chloro-6-cyclopropoxy-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (200.0 mg, 0.57 mmol) in Tetrahydrofuran (THF) (1 mL) was added LiOH (27.5 mg, 1.14 mmol) in Water (1 mL) at 0 °C. The resulting solution was stirred at room temperature for 1 h. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~5 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 2'-chloro-6-cyclopropoxy-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (173 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{15}H_{13}ClN_2O_4$) $(M+1)^+$, 321.1; found 321.1.

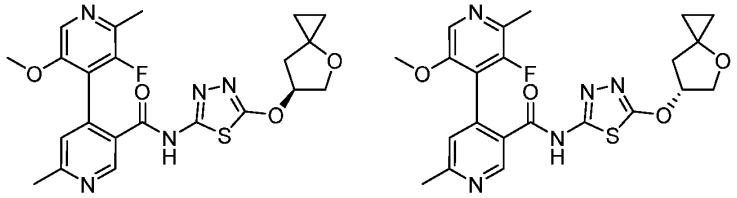
Step-6: 2'-chloro-6-cyclopropoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



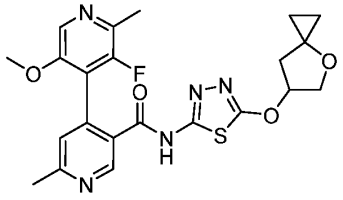
To a solution of 2'-chloro-6-cyclopropoxy-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (120.0 mg, 0.37 mmol) in Acetonitrile (0.5 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (49.1 mg, 0.37 mmol) and NMI (153.0 mg, 1.87 mmol) at 20 °C under nitrogen. To the above solution was added TCFH (105.0 mg, 0.37 mmol) in Acetonitrile (0.5 mL) at 25 °C under nitrogen. The resulting mixture was then stirred at 25 °C for 1 hour. The resulting residue was dissolved in DMF (2 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~75% acetonitrile in water within 25 min to afford 2'-chloro-6-cyclopropoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (62.3 mg, 37%) as a white solid. MS (ESI) calc'd for ($C_{18}H_{16}ClN_5O_4S$) $(M+1)^+$, 434.1; found 434.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.62 (s, 1H), 8.16 (s, 1H), 7.54 (s, 1H), 6.99 (s, 1H), 4.41 – 4.31 (m, 1H), 4.08 (s, 3H), 3.64 (s, 3H), 0.89 – 0.77 (m, 2H), 0.80 – 0.70 (m, 2H).

Example 207 and 208

N-(5-(((S)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((R)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

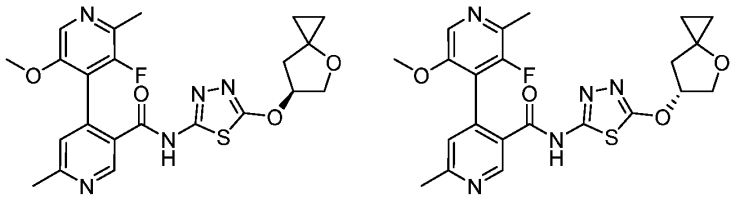


Step-1: N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (259.0 mg, 0.94 mmol, Example 61, Step 2) in acetonitrile (2 mL) were sequentially added 5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (200.0 mg, 0.94 mmol, Example 95 and 107, Step 3) and 1-methyl-1H-imidazole (385.0 mg, 4.69 mmol) at 25 °C. Then N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (263.0 mg, 0.94 mmol) in acetonitrile (1 mL) was added to the above mixture at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The resulting residue was dissolved in acetonitrile (3 mL) which was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~42% acetonitrile in water within 30 min to afford N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (290.0 mg, 63%) as a white solid. MS (ESI) calculated for ($C_{22}H_{22}FN_5O_4S$) $(M+1)^+$, 472.1; found, 472.2.

Step-2: N-(5-(((S)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((R)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



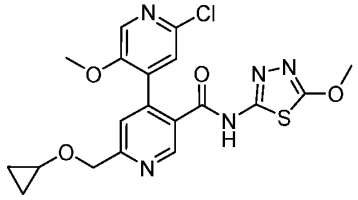
N-(5-((4-Oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (200.0 mg) was separated by prep-chiral HPLC with the following conditions: (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.2% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 10 min; Wave Length: 220/254 nm; RT1(min): 7.86; RT2(min): 9.68; Sample Solvent: MeOH: DCM=2: 1(0.1% FA); Injection Volume: 0.8 mL; Number Of Runs: 14) to afford N-(5-(((S)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (87.3 mg, 43.3%) as a white solid with the first peak on chiral HPLC and N-(5-(((R)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (81.6 mg, 40%) as a white solid with the second peak on chiral HPLC. The absolute stereochemistry was not determined.

N-(5-(((S)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{22}H_{22}FN_5O_4S$) $(M+1)^+$, 472.1; found, 472.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.91 (s, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 5.59 – 5.56 (m, 1H), 4.02 – 4.00 (m, 2H), 3.69 (s, 3H), 2.59 (s, 3H), 2.49 – 2.44 (m, 1H), 2.43 (s, 3H), 2.15 – 2.14 (m, 1H), 0.82 – 0.51 (m, 4H).

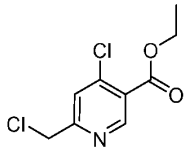
N-(5-(((R)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{22}H_{22}FN_5O_4S$) $(M+1)^+$, 472.1; found, 472.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ13.00 (s, 1H), 8.91 (s, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 5.59 – 5.56 (m, 1H), 4.02 – 4.00 (m, 2H), 3.69 (s, 3H), 2.59 (s, 3H), 2.49 – 2.44 (m, 1H), 2.43 (s, 3H), 2.15 – 2.14 (m, 1H), 0.82 – 0.53 (m, 4H).

Example 215

2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide

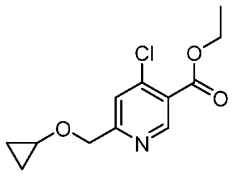


Step-1: ethyl 4-chloro-6-(chloromethyl)nicotinate



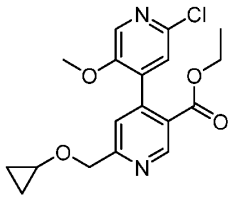
To a stirred solution of ethyl 4-chloro-6-(hydroxymethyl)nicotinate (2.0 g, 9.28 mmol) in Dichloromethane (30 mL) was added $SOCl_2$ (1.6 g, 13.91 mmol) at 0 °C. The resulting solution was then stirred at 25 °C for 2 h. The reaction mixture was quenched by the addition of saturated sodium bicarbonate solution and extracted with Dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford ethyl 4-chloro-6-(chloromethyl)nicotinate (1.8 g, crude) as yellow oil, which was used in the next step without further purification. MS (ESI) calc'd for ($C_9H_9Cl_2NO_2$) $(M+1)^+$, 234.0, found 234.1.

Step-2: ethyl 4-chloro-6-(cyclopropoxymethyl)nicotinate



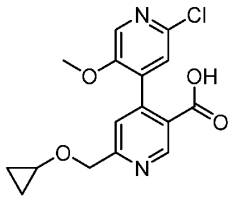
To a stirred solution of cyclopropanol (223.0 mg, 3.84 mmol) in Tetrahydrofuran (20 mL) was added NaH (185.0 mg, 4.61 mmol, 60%) in portions at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. Then ethyl 4-chloro-6-(chloromethyl)nicotinate (900.0 mg, 3.84 mmol) in Tetrahydrofuran (20 mL) was added to the above mixture at 0 °C. The resulting solution was then stirred at 25 °C for 1.5 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DMF (6 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 25 min to afford ethyl 4-chloro-6-(cyclopropoxymethyl)nicotinate (330.0 mg, 30%) as a yellow solid. MS (ESI) calc'd for ($C_{12}H_{14}ClNO_3$) $(M+1)^+$, 256.0, found 256.1.

Step-3: ethyl 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate



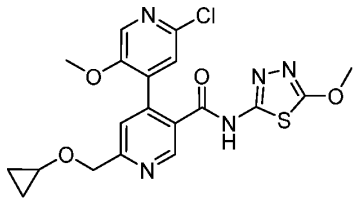
To a stirred solution of ethyl 4-chloro-6-(cyclopropoxymethyl)nicotinate (220.0 mg, 0.86 mmol) in 1,4-Dioxane (2 mL) and Water (0.4 mL) were sequentially added (2-chloro-5-methoxypyridin-4-yl)boronic acid (484.0 mg, 2.58 mmol), K_2CO_3 (357.0 mg, 2.58 mmol) and 1,1'-Bis (di-t-butylphosphino)ferrocene palladium dichloride (56.1 mg, 0.08 mmol) at 25 °C. The resulting solution was stirred at 80 °C for 16 h under nitrogen atmosphere. The suspension was filtered. The filtrate was concentrated under vacuum. The residue was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~43% acetonitrile in water within 30 min to afford ethyl 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (110.0 mg, 30%) as a yellow solid. MS (ESI) calc'd for ($C_{18}H_{19}ClN_2O_4$) $(M+1)^+$, 363.1, found 363.0.

Step-4: 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid



To a stirred solution of ethyl 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylate (189.0 mg, 0.52 mmol) in Tetrahydrofuran (1.5 mL) and Water (0.5 mL) was added LiOH (37.4 mg, 1.56 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The organic solvent was acidified with citric acid to pH 5~6. The organic solvent was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~40% acetonitrile in water within 30 min to afford 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (80.0 mg, 8%) as a white solid. MS (ESI) calc'd for ($C_{16}H_{15}ClN_2O_4$) $(M+1)^+$, 335.0, found 335.0.

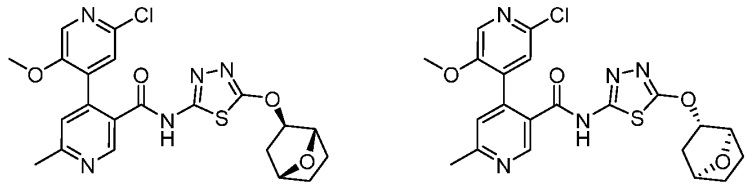
Step-5: 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide



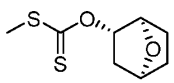
To a stirred solution of 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-(4,4'-bipyridine)-3-carboxylic acid (30.0 mg, 0.09 mmol) in Acetonitrile (1 mL) were sequentially added 1-methyl-1H-imidazole (36.8 mg, 0.44 mmol), 5-methoxy-1,3,4-thiadiazol-2-amine (14.1 mg, 0.10 mmol) and TCFH (25.1 mg, 0.09 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 2 h. The organic solvent was acidified with citric acid to pH ~6. The organic solvent (2 mL) was applied to a 20 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 30 min to afford 2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (20.5 mg, 50%) as a white solid. MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.0, found 448.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.52 (s, 1H), 8.15 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 4.20 – 4.00 (m, 6H), 3.90 (s, 3H), 0.92 – 0.78 (m, 4H).

Example 216 and 217

N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide

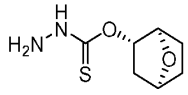


Step-1: *rac*-O-((1R,2S,4S)-7-oxabicyclo(2.2.1) heptan-2-yl) S-methyl carbonodithioate



To a stirred solution of *rac*-(1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-ol (750 mg, 6.57 mmol) in Tetrahydrofuran (15 mL) under nitrogen at 0 °C was added sodium hydride (315 mg, 13.14 mmol) portionwise during 5 min. After addition reaction mixture was stirred at room temperature for 30 min. After 30 min to the above reaction mixture were added carbon disulfide (0.792 mL, 13.14 mmol) followed by methyl iodide (0.411 mL, 6.57 mmol)) at room temperature. Then the reaction mixture was stirred at room temperature for additional 30 min. The reaction was quenched with cold water extracted with ethyl acetate (2 x 40 mL).The combined organic layers were dried over sodium sulphate, filtered and concentrated under vacuum to afford *rac*-O-((1R,2S,4S)-7-oxabicyclo(2.2.1) heptan-2-yl) S-methyl carbonodithioate (1.3 g, 6.29 mmol, 96 % yield) as yellow liquid. MS (ESI) calculated for ($C_8H_{12}O_2S_2$) $(M+1)^+$, 205.04, found, 205.0

Step-2: *rac*-O-((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl) hydrazinecarbothioate

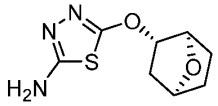


To a stirred solution of *rac*-O-((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl) S-methyl carbonodithioate (1.3 g, 6.24 mmol) in Methanol (5mL) was added hydrazine monohydrate (0.343 g, 6.86 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hr. The organic solvent was removed under vacuum. The resulting residue was diluted with water (40 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was dried over anhydrous sodium sulphate, filtered concentrated under reduced pressure

to afford *rac*-O-((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl) hydrazinecarbothioate (1 g, 5.29 mmol, 85 % yield) as pale yellow solid.

MS (ESI) calculated for ($C_7H_{12}N_2O_2S$) $(M+1)^+$, 189.07; found, 189.2.

Step-3: *rac*-5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-amine

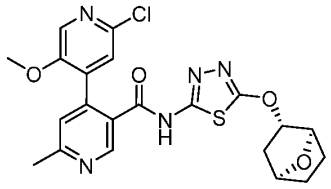


To a stirred solution of rac-O-((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl) hydrazinecarbothioate (1 g, 5.31 mmol) in Ethanol (5 mL) were added triethylamine (0.740 mL, 5.31 mmol) followed by cyanogen bromide (0.563 g, 5.31 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 mins. The organic solvent was removed under vacuum. The resulting residue was diluted with water (30 mL) and extracted with 10% MeOH in ethyl acetate (2 x 50 mL). The organic layer dried over anhydrous sodium sulphate, filtered concentrated under vacuum to get the crude product as a brown gum.

The resulting residue was dissolved in ACN (4 mL) and THF (2 mL) and liquid injected to a 100 g C18 column and purified by GRACE revelleris X2, eluted with 0~100% acetonitrile in water within 40 min to afford *rac*-5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-amine (500 mg, 2.258 mmol, 42.5 % yield) as a brown solid.

MS (ESI) calculated for ($C_8H_{11}N_3O_2S$) $(M+1)^+$, 214.07; found, 214.2

Step-4: *rac*-N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



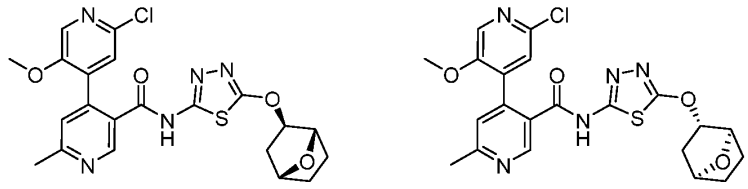
To a stirred solution of Intermediate G (200 mg, 0.718 mmol) in Acetonitrile (3 mL) and N,N-Dimethylformamide (0.6 mL) were added 1-methyl-1H-imidazole (177 mg, 2.153 mmol), Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (221 mg, 0.789 mmol) and *rac*-5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-amine (153 mg, 0.718 mmol) at room temperature. The reaction mixture was stirred at room

temperature for 3h. The reaction mixture was quenched with cold water and extracted with ethyl acetate (2 X 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to get the crude product as a brown gum.

The resulting residue was dissolved in ACN (4 mL) and THF (2 mL) and liquid injected to a 100 g C18 column and purified by GRACE revelleris X2, eluted with 0~100% acetonitrile in water within 40 min to afford *rac*-N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (200 mg, 58%) as a white solid.

MS (ESI) calculated for ($C_{21}H_{20}ClN_5O_4S$) $(M+1)^+$, 474.1; found, 474.2.

Step-5: N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



The *rac*-N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (200 mg) was separated by prep-chiral SFC with the following conditions: (Column: YMC Cellulose SZ (250*30)mm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: 0.5% Isopropyl Amine in Methanol; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.42; RT2(min): 4.03; Sample Solvent: DCM/MeOH-HPLC; Injection Volume: 0.9 mL/Injection; Cycle time: 7.5 min) to afford N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (50 mg, 0.105 mmol, 14.67 % yield) as a pale brown solid with the first peak on chiral SFC with shorter retention time and N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (52 mg, 0.110 mmol, 15.26 % yield) as a pale brown solid

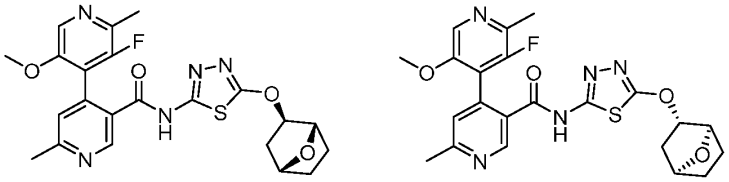
with the second peak on chiral SFC with longer retention time. The absolute stereochemistry was not determined.

N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{21}H_{20}ClN_5O_4S$) $(M+1)^+$, 474.1; found, 474.0. 1H-NMR (400 MHz, DMSO-d^6): δ 12.92 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.00 (dd, J = 2.4 Hz, 7.2 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.62 (t, J = 5.2 Hz, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.12-2.05 (m, 1H), 1.72-1.69 (m, 1H), 1.61-1.58 (m, 1H), 1.53-1.38 (m, 3H).

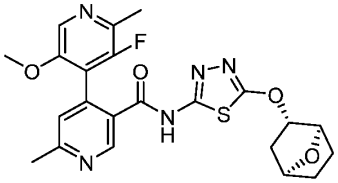
N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{21}H_{20}ClN_5O_4S$) $(M+1)^+$, 474.1; found, 474.0. 1H-NMR (400 MHz, DMSO-d^6): δ 12.92 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.42 (s, 1H), 5.00 (dd, J = 2.0 Hz, 6.8 Hz, 1H), 4.66 (d, J = 6.0 Hz, 1H), 4.62 (t, J = 4.8 Hz, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.12-2.05 (m, 1H), 1.72-1.69 (m, 1H), 1.61-1.58 (m, 1H), 1.53-1.38 (m, 3H).

Example 218 and 219

N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide



Step 1: *rac*-N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

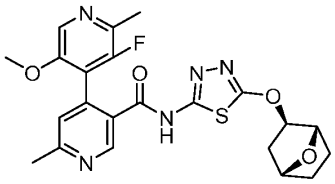
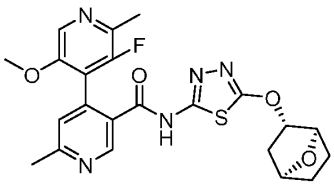


To a stirred solution of 3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxylic acid (80 mg, 0.290 mmol, Example 61, Step 2) in Acetonitrile (3 mL) and N,N-

Dimethylformamide (0.6 mL) were added 1-methyl-1H-imidazole (71.3 mg, 0.869 mmol), Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (89 mg, 0.319 mmol) and *rac*-5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-amine (61.8 mg, 0.290 mmol, Example 216 and 217, Step 3) at room temperature. The reaction mixture was stirred at room temperature for 3h. The reaction mixture was quenched with cold water and extracted with ethyl acetate (2 X 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to get the crude product as a brown gum.

The resulting residue was dissolved in ACN (4 mL) and liquid injected to a 100 g C18 column and purified by GRACE revelleris X2, eluted with 0~100% acetonitrile in (0.1 M formic acid) water within 40 min to afford *rac*-N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (60 mg, 44%) as a white solid. MS (ESI) calculated for ($C_{22}H_{22}FN_5O_4S$) $(M+1)^+$, 472.15; found, 472.2.

Step-2: N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide and N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide

The *rac*-N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (combined 2 batches 90 mg) was separated by prep-chiral SFC with the following conditions: (Column: Lux Amylose-1 (250*30)mm, 5µm; Mobile Phase A: CO_2, Mobile Phase B: 0.5% Isopropyl Amine in Methanol; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Total flow: 100g/mL; Wave Length: 210 nm; RT1(min): 2.29; RT2(min): 3.65; Sample Solvent: MeOH-HPLC; Injection Volume: 0.6 mL/Injection; Cycle time: 6 min) to afford N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (22 mg, 0.046 mmol,

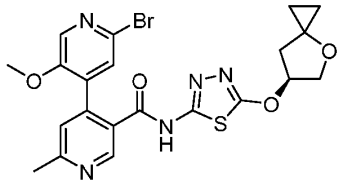
15.95% yield) as a white solid with the first peak on chiral SFC with shorter retention time and N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide (25 mg, 0.052 mmol, 17.85 % yield) as a light brown solid with the second peak on chiral SFC with longer retention time. The absolute stereochemistry was not determined.

N-(5-(((1S,2R,4R)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{22}H_{22}FN_5O_4S$) $(M+1)^+$, 472.15; found, 472.2. 1H-NMR (400 MHz, DMSO-d^6): δ 13.0 (s, 1H), 8.90 (s, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 4.99 (dd, J = 2.00 Hz, 7.2 Hz, 1H), 4.65 (d, J = 5.6 Hz, 1H), 4.62 (t, J = 5.2 Hz, 1H), 3.68 (d, J = 2.0 Hz, 3H), 2.59 (s, 3H), 2.42 (d, J = 2.8 Hz, 3H), 2.11-2.03 (m, 1H), 1.73-1.56 (m, 2H), 1.55-1.36 (m, 3H).

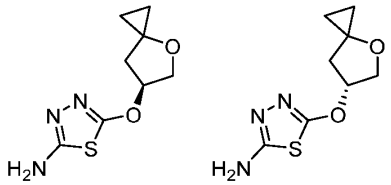
N-(5-(((1R,2S,4S)-7-oxabicyclo(2.2.1)heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-3'-fluoro-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{22}H_{22}FN_5O_4S$) $(M+1)^+$, 472.15; found, 472.0. 1H-NMR (400 MHz, DMSO-d^6): δ 13.0 (s, 1H), 8.92 (s, 1H), 8.17 (s, 1H), 7.38 (s, 1H), 4.98 (dd, J = 2.00 Hz, 6.80 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.61 (t, J = 4.8 Hz, 1H), 3.68 (s, 3H), 2.58 (s, 3H), 2.42 (d, J = 3.2 Hz, 3H), 2.11-2.03 (m, 1H), 1.73-1.56 (m, 2H), 1.55-1.35 (m, 3H).

Example 226

(S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



Step-1: (S)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine and (R)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine



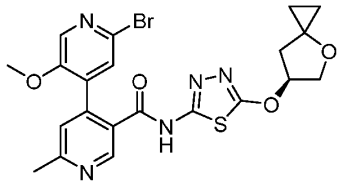
The racemic 5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (1.8 g, 8.44 mmol, Example 95 and 107, Step 3) was separated by prep-chiral SFC with the following

conditions: (Column: Lux A1 (250*30)mm, 5µm; Mobile Phase A: CO_2, Mobile Phase B: Methanol; Gradient: isocratic 30% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 254 nm; RT1(min): 2.59; RT2(min): 3.24; Sample Solvent: MeOH-HPLC (100 mL); Injection Volume: 1 mL/Injection; Cycle time: 5 min) to afford (S)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (0.750 g, 3.51 mmol, 41.6 % yield) as pale brown solid with the first peak on chiral SFC with shorter retention time and (R)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (0.650 g, 3.02 mmol, 35.8 % yield) as pale brown solid with the second peak on chiral SFC with longer retention time. The absolute stereochemistry was not determined.

(S)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine: MS (ESI) calculated for ($C_8H_{11}N_3O_2S$) (M+1)+, 214.07; found, 214.0. 1H-NMR (400 MHz, DMSO-d^6): δ 6.79 (s, 2H), 5.49-5.40 (m, 1H), 4.01-3.89 (m, 2H), 2.41 (q, J = 6.80 Hz, 1H), 2.08 (d, J = 14.0 Hz, 1H), 0.85-0.76 (m, 1H), 0.75-0.68 (m, 1H), 0.62-0.55 (m, 1H), 0.54-0.45 (m, 1H),

(R)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine: MS (ESI) calculated for ($C_8H_{11}N_3O_2S$) (M+1)+, 214.07; found, 214.0. 1H-NMR (400 MHz, DMSO-d^6): δ 6.79 (s, 2H), 5.49-5.40 (m, 1H), 4.01-3.89 (m, 2H), 2.41 (q, J = 6.80 Hz, 1H), 2.08 (d, J = 14.00 Hz, 1H), 0.85-0.76 (m, 1H), 0.75-0.68 (m, 1H), 0.62-0.55 (m, 1H), 0.54-0.45 (m, 1H),

Step-2: (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



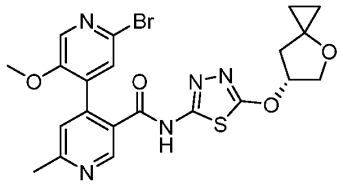
To a stirred solution of 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (150 mg, 0.464 mmol, Example 63, Step 3), in Acetonitrile (3 mL) and N,N-Dimethylformamide (0.5 mL)were added Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (143 mg, 0.511 mmol), 1-methylimidazole (0.148 mL, 1.857 mmol), and (S)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (99 mg, 0.464 mmol) at room temperature. The reaction mixture was stirred at same temperature for 3 h. The reaction mixture was diluted with water, extracted with ethyl acetate (2 X 20 mL). The combined organic layer dried over anhydrous sodium sulphate, filtered concentrated under vacuum to afford crude product as yellow gum.

The crude product was purified by prep-HPLC with the following conditions: (Column: X-SELECT C18(19*250) MM 5 MICRON; Mobile Phase A: 10mM ABC in Milli Q Water 80%, Mobile Phase B: Acetonitrile 20%; Flow rate: 12 mL/min; Run time: 21 min; (Sample Solvent: THF:ACN; Injection Volume: 200 µL; number of injections: 38) to afford (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (110 mg, 0.209 mmol, 45.1 % yield) as an off white solid. The absolute stereochemistry was not determined.

MS (ESI) calculated for ($C_{21}H_{20}BrN_5O_4S$) $(M+1)^+$, 518.05; found, 518.0. 1H-NMR (400 MHz, DMSO-d^6): δ 12.93 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 5.63-5.58 (m, 1H), 4.08-3.95 (m, 2H), 3.63 (s, 3H), 2.59 (s, 3H), 2.50-2.45 (m, 1H), 2.15 (d, J = 13.60 Hz, 1H), 0.88-0.78 (m, 1H), 0.77-0.69 (m, 1H), 0.68-0.57 (m, 1H), 0.56-0.46 (m, 1H).

Example 227

(R)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



To a stirred solution of 2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxylic acid (150 mg, 0.464 mmol, Example 63, Step 3), in Acetonitrile (3 mL) and N,N-Dimethylformamide (0.5 mL)were added Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (195 mg, 0.696 mmol), 1-methylimidazole (0.148 mL, 1.857 mmol), and (R)-5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-amine (99 mg, 0.464 mmol, Example 226, Step 1) at room temperature. The reaction mixture was stirred at room temperature for 3 h. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate (2 X 20 mL). The combined organic layer dried over anhydrous sodium sulphate, filtered concentrated under vacuum to afford the crude product as yellow gum.

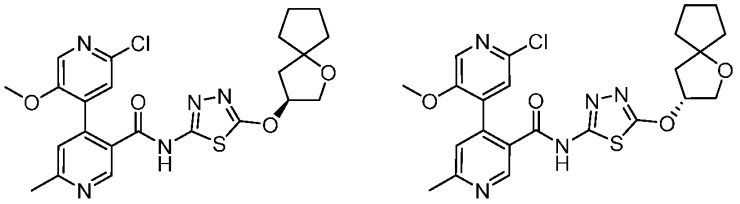
The crude product was purified by prep-HPLC with the following conditions: (Column: X-SELECT C18(19*250 MM) 5 MICRON; Mobile Phase A: 10mM ABC in Milli Q Water 80%, Mobile Phase B: Acetonitrile 20%; Flow rate: 10 mL/min; Run time: 21 min; (Sample Solvent: THF:ACN; Injection Volume: 200 µL; number of injections: 24) to afford (R)-N-(5-

((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-bromo-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (75 mg, 0.144 mmol, 31.1 % yield) as an off white solid. The absolute stereochemistry was not determined.

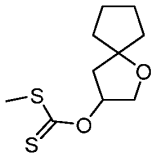
MS (ESI) calculated for ($C_{21}H_{20}BrN_5O_4S$) $(M+1)^+$, 518.05; found, 518.0. 1H-NMR (400 MHz, DMSO-d^6): δ 12.93 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.63 (s, 1H), 7.42 (s, 1H), 5.63-5.58 (m, 1H), 4.09-3.96 (m, 2H), 3.63 (s, 3H), 2.59 (s, 3H), 2.50-2.40 (m, 1H), 2.15 (d, J = 14.40 Hz, 1H), 0.88-0.78 (m, 1H), 0.77-0.69 (m, 1H), 0.67-0.57 (m, 1H), 0.56-0.46 (m, 1H).

Example 229 and 230

(S)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (R)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



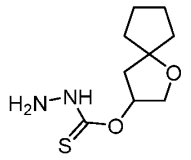
Step-1: S-methyl O-(1-oxaspiro(4.4)nonan-3-yl) carbonodithioate:



To a stirred solution of 1-oxaspiro(4.4)nonan-3-ol (0.7 g, 4.92 mmol) in Tetrahydrofuran (10 mL) under nitrogen at 0 °C was added sodium hydride (0.394 g, 9.85 mmol) portionwise over 5 min. After addition reaction mixture was stirred at room temperature for 30 min. After 30 min to the above reaction mixture were added carbon disulfide (0.593 mL, 9.85 mmol) and followed by methyl iodide (0.308 mL, 4.92 mmol) at room temperature. The reaction mixture was stirred at room temperature for additional 30 mins. After 30 mins the reaction was quenched with cold water and extracted with ethyl acetate (20 mL x3). The combine organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to afford S-methyl O-(1-oxaspiro(4.4)nonan-3-yl) carbonodithioate (0.95 g, 3.90 mmol, 79 % yield) as orange oil.

MS (ESI) calculated for (C10H16O2S2) $(M+H)^+$, 233.07; found, 233.0

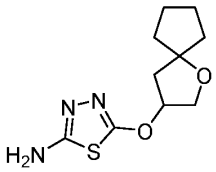
Step-2: O-(1-oxaspiro(4.4)nonan-3-yl) hydrazinecarbothioate



To a stirred solution of S-methyl O-(1-oxaspiro(4.4)nonan-3-yl) carbonodithioate (1.1 g, 4.73 mmol) in Methanol (10 mL) was added hydrazine hydrate (0.237 g, 4.73 mmol) at rt under nitrogen. The reaction mixture was stirred for 2h at rt. The organic solvent was removed under vacuum. The residue was diluted with water. The aqueous layer was extracted with ethyl acetate (20 mL X 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford O-(1-oxaspiro(4.4)nonan-3-yl) hydrazinecarbothioate (0.68 g, 2.69 mmol, 56.8 % yield) as orange liquid.

MS (ESI) calculated for ($C_9H_{16}N_2O_2S$) $(M+1)^+$, 217.1; found, 217.2.

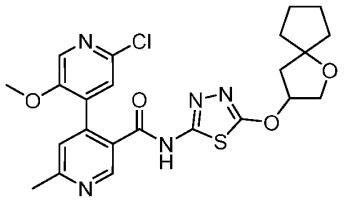
Step-3: 5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-amine



To a stirred solution of O-(1-oxaspiro(4.4)nonan-3-yl) hydrazinecarbothioate (0.68 g, 3.14 mmol), in Ethanol (10 mL) were added triethylamine (0.438 mL, 3.14 mmol) followed by Cyanogen bromide (0.333 g, 3.14 mmol) at room temperature . The reaction mixture was stirred at room temperature for 1h. The organic solvent was removed under vacuum. The residue was diluted with water. The aqueous layer was extracted with ethyl acetate (30 mL X 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to get the crude product as orange solid. The crude product was pre-absorbed on silica (using 10 mL DCM, 10g of silica (60-120 mesh), loaded on the biotage 40g snap, and eluted with 7-9% of methanol in dichloromethane for 30 mins with flow rate 30 ml/min. The appropriate fractions were collected and concentrated under vacuum to afford 5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-amine (0.24 g, 0.733 mmol, 23.31 % yield) as yellow solid

MS (ESI) calculated for ($C_{10}H_{15}N_3O_2S$) $(M+1)^+$, 242.1; found, 242.1

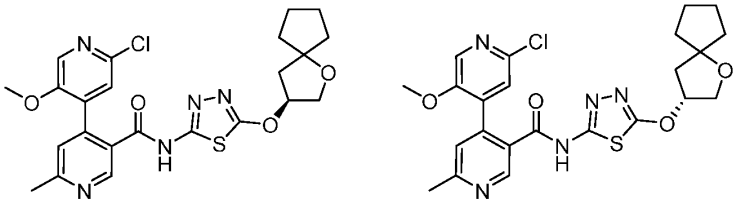
Step-4: N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide.



To a stirred solution of Intermediate G (200 mg, 0.718 mmol) and 5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-amine (237 mg, 0.718 mmol) in Acetonitrile (2 mL) and N,N-Dimethylformamide (1.2 mL) was added 1-methylimidazole (0.286 mL, 3.59 mmol) and Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (221 mg, 0.789 mmol) at rt under nitrogen. The reaction mixture was stirred for 1h. The reaction mixture was quenched with cold water and extracted with ethyl acetate (10 mL X 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the crude product as orange oil.

The crude product was purified by prep-HPLC with the following conditions: (Column: YMC C8(20x250) MM 5 MICRON; Mobile Phase A: 10mM ABC in MQ WATER 80%, Mobile Phase B: acetonitrile 20%; Flow rate: 12 mL/min; Run time: 25 min; (Sample Solvent: THF:ACN; Injection Volume: 200 µL; number of injections: 18) to afford *rac*-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (35 mg, 0.068 mmol, 9.42 % yield) as white solid.

Step-5: (S)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide and (R)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide



Racemic compound N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (35 mg) was purified by Chiral SFC by using following method with the following conditions: Column: YMC Cellulose SC

(250*30)mm, 5µm, Mobile Phase : CO2: 0.5% Isopropyl Amine in IPA (60:40)%, Total Flow : 100 g/min, Back pressure : 100 bar, Wave length : 220 nm ,Cycle time: 10 min, a sample was dissolved in 2.0 mL of MeOH /Acetonitrile and injected 800 µl/injection

After SFC purification, the two appropriate fractions were collected.

Fraction-1 was concentrated and lyophilized to afford (S)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (12 mg) as an off-white solid.

^{1}H NMR in DMSO-d_6 showed the required protons of the desired compound along with trapped isopropyl amine.

To remove the isopropyl amine, (S)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (12 mg) was washed MTBE & hexane and lyophillized to afford (S)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (8 mg, 0.016 mmol, 23.04 % yield) as an off-white solid. The absolute stereochemistry was not determined.

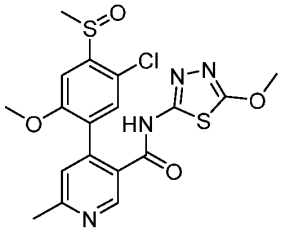
(S)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{23}H_{24}ClN_5O_4S$) $(M+1)^+$, 502.13; found, 502.1. 1H-NMR (400 MHz, CD_3OD): δ 8.81 (s, 1H), 8.10 (s, 1H), 7.50 (s, 1H), 7.44 (s, 1H), 5.54-5.49 (m, 1H), 4.13 (dd, J = 4.8 Hz, 10.8 Hz, 1H), 4.04 (d, J = 10.8 Hz, 1H), 3.74 (s, 3H), 2.69 (s, 3H), 2.40 (dd, J = 6.4 Hz, 14.4 Hz, 1H), 2.25 (d, J = 14.8 Hz, 1H), 1.96-1.81 (m, 2H), 1.80-1.60 (m, 6H).

Fraction-2 was concentrated and lyophilized to afford (R)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (4 mg, 7.49 µmol, 11.08 % yield) as an off-white solid. The absolute stereochemistry was not determined.

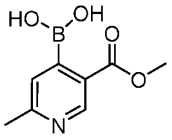
(R)-N-(5-((1-oxaspiro(4.4)nonan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide: MS (ESI) calculated for ($C_{23}H_{24}ClN_5O_4S$) $(M+1)^+$, 502.13; found, 502.1. 1H-NMR (400 MHz, CD_3OD): δ 8.81 (s, 1H), 8.10 (s, 1H), 7.50 (s, 1H), 7.43 (s, 1H), 5.54-5.49 (m, 1H), 4.13 (dd, J = 4.8 Hz, 10.8 Hz, 1H), 4.04 (d, J = 10.8 Hz, 1H), 3.74 (s, 3H), 2.68 (s, 3H), 2.40 (dd, J = 6.4 Hz, 14.4 Hz, 1H), 2.25 (d, J = 14.4 Hz, 1H), 1.96-1.81 (m, 2H), 1.80-1.60 (m, 6H).

Example 231

4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



Step-1: (5-(methoxycarbonyl)-2-methylpyridin-4-yl)boronic acid:

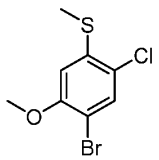


To a stirred solution of methyl 4-chloro-6-methylnicotinate (1g, 5.39 mmol) in 1,4-Dioxane (10 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.052 g, 8.08 mmol), and potassium acetate (1.586 g, 16.16 mmol) at room temperature and degassed with nitrogen for 20 minutes. After 20 minutes PdCl2(dppf)-CH2Cl2adduct (0.308 g, 0.377 mmol) was added and again degassed with nitrogen for 5 minutes. The reaction mixture was stirred at 90 °C for 16 hours. The reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad and washed with ethyl acetate (200 mL). The filtrate was concentrated under vacuum to afford crude product as brown oil.

The crude product was purified by reverse-phase chromatography with the following conditions: (Column: 40 g Reveleris column, C18; Mobile Phase A: 0.1% FA in water, Mobile Phase B: acetonitrile,0-100 %) to afford (5-(methoxycarbonyl)-2-methylpyridin-4-yl)boronic acid (250 mg, 1.281 mmol, 23.77 % yield) as an off white solid.

MS (ESI) calculated for ($C_8H_{10}BNO_4$) $(M+1)^+$, 196.08; found, 196.2

Step-2: (4-bromo-2-chloro-5-methoxyphenyl)(methyl)sulfane:



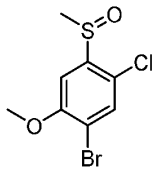
A solution of 4-bromo-2-chloro-5-methoxyaniline (500 mg, 2.114 mmol) in 2N HCl (15.86 mL, 31.7 mmol), was heated to 50 °C for 30 min, then the reaction mixture was cooled to 0

°C, and added sodium nitrite (160 mg, 2.326 mmol) in water (10 mL) dropwise. The resulting reaction mixture was stirred for 40 min at 0°C, then sodium thiomethoxide (296 mg, 4.23 mmol) in water (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred again for 18h at room temperature. After completion of the reaction, The reaction mixtures was diluted with 10% NaOH aq. solution (15 mL) and extracted with EtOAc (2 x 50 mL). The separated organic layer was dried over anhydrous Na2SO4 and concentrated under vacuum to afford crude product as light yellow oil.

The crude product was pre-absorbed on silica (using 5 mL DCM, 3 g of silica (60-120 mesh), loaded on the pre-packed Orochem 40 g column and eluted at 0-30 % of ethyl acetate in PET ether for 45 minutes with flow rate 20 ml/min. The appropriate fractions were collected and concentrated reduced pressure to afford (4-bromo-2-chloro-5-ethoxyphenyl)(methyl)sulfane (420 mg, 1.428 mmol, 67.6 % yield) as yellow solid.

GCMS calculated for ($C_8H_8BrClOS$) $(M)^+$, 267.91; found, (m/z) 267.9

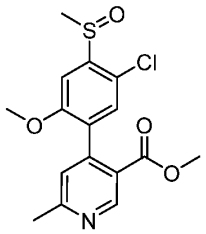
Step-3: 1-bromo-5-chloro-2-methoxy-4-(methylsulfinyl)benzene:



To a stirred solution of (4-bromo-2-chloro-5-methoxyphenyl)(methyl)sulfane (500 mg, 1.869 mmol) in Dichloromethane (10mL) was added *m*CPBA (355 mg, 2.056 mmol) portion wise at 0 °C, under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction mixtures was diluted with 10% Na2CO3 aq. solution (30 mL) and extracted with EtOAc (2 x 50 mL), washed with brine. The organic layer was separated and dried over anhydrous Na2SO4, concentrated under vacuum to afford crude product as light yellow oil. The crude product was pre-absorbed on silica (using 5 mL DCM, 2 g of silica (60-120 mesh), loaded on the pre-packed Orochem 40 g column and eluted at 0-60 % of ethyl acetate in PET ether for 60 minutes with flow rate 15 ml/min. The appropriate fractions were collected and concentrated reduced pressure to afford 1-bromo-5-chloro-2-methoxy-4-(methylsulfinyl)benzene (200 mg, 0.684 mmol, 36.6 % yield) as brown solid.

MS (ESI) calculated for ($C_8H_8BrClO_2S$) $(M+1)^+$, 282.92; found, 282.8

Step-4: methyl 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate:

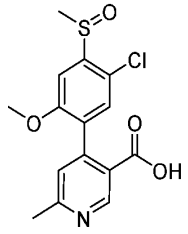


To a stirred solution of 1-bromo-5-chloro-2-methoxy-4-(methylsulfinyl)benzene (200 mg, 0.705 mmol) in 1,4-Dioxane (10 mL) were added methyl (5-(methoxycarbonyl)-2-methylpyridin-4-yl)boronic acid (275 mg, 1.411 mmol) and potassium carbonate (292 mg, 2.116 mmol) at room temperature and degassed with nitrogen for 10 minutes. To the resulting reaction mixture was added PdCl2(dppf) (103 mg, 0.141 mmol). The reaction mixture was stirred at 100 °C for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad and washed with ethyl acetate (100 mL). The filtrate was washed with water (50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to afford crude product as light brown oil.

The crude product was pre-absorbed on silica (using 10 mL DCM, 3 g of silica (60-120 mesh), loaded on the pre-pack orochem 40 g column and eluted at 0-80 % of ethyla acetate in PET ether for 45 minutes with flow rate 15 ml/min. The appropriate fractions were collected and concentrated reduced pressure to afford methyl 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate (120 mg, 0.326 mmol, 46.2 % yield) as an light brown oil

MS (ESI) calculated for ($C_{16}H_{16}ClNO_4S$) $(M+1)^+$, 354.06; found, 354.0

Step-5: 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid:

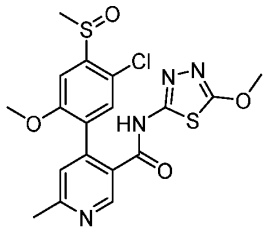


To a stirred solution of methyl 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate (120 mg, 0.339 mmol) in a mixture of Tetrahydrofuran (2 mL), Methanol (2 mL) and Water (2 mL) was added lithiumhydroxide.monohydrate (40.6 mg, 1.696 mmol) at

room temperature. The reaction mixture was stirred at room temperature for 2.5 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum. The resulting residue diluted with water (3 mL), the aqueous layer was acidified with 1.5 N HCl upto pH-6 and extracted with ethyl acetate (3 X 20 mL). The combined organic layer dried over anhydrous sodium sulphate, filtered concentrated under reduced pressure to afford 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (60 mg, 0.155 mmol, 45.8 % yield) as light brown solid.

MS (ESI) calculated for ($C_{15}H_{14}ClNO_4S$) $(M+1)^+$, 340.04; found, 340.0

Step-6: 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.



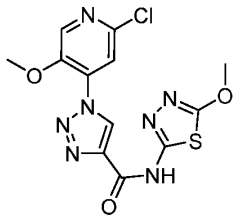
To a stirred solution of 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (30 mg, 0.088 mmol), in Acetonitrile (2 mL) were added Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (27.2 mg, 0.097 mmol), and 1-methylimidazole (0.028 mL, 0.353 mmol) the reaction mixture was stirred at room temperature for 30 min under nitrogen , then 5-methoxy-1,3,4-thiadiazol-2-amine (13.90 mg, 0.106 mmol)) was added. The reaction mixture was stirred at same temperature for 16 h. The reaction mixture was diluted with water, extracted with ethyl acetate (2 X 10 mL). The combined organic layer dried over anhydrous sodium sulphate, filtered concentrated under vacuum to afford crude product as brown oil.

The crude product was purified by prep-HPLC with the following conditions: (Column: X-select C18 (19*150) MM 5 MICRON; Mobile Phase A: 10mM ABC in Milli Q Water 90%, Mobile Phase B: Acetonitrile 10%; Flow rate: 8 mL/min; Run time: 18 min; (Sample Solvent: THF:ACN; Injection Volume: 200 µL; number of injections: 12) to afford 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (4.5 mg, 9.06 µmol, 10.26 % yield) as a white solid. MS (ESI) calculated for ($C_{18}H_{17}ClN_4O_4S_2$) $(M+1)^+$, 453.05; found, 453.0.

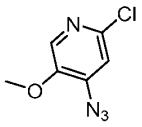
1H-NMR (400 MHz, DMSO-d^6): δ 12.85 (s, 1H), 8.77 (s, 1H), 7.60 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 4.06 (s, 3H), 3.61 (s, 3H), 2.86 (s, 3H), 2.58 (s, 3H).

Example 234

1-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-1,2,3-triazole-4-carboxamide

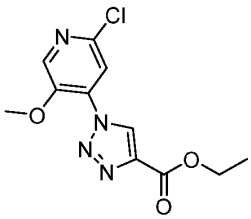


Step-1: 4-azido-2-chloro-5-methoxypyridine



To a degassed solution of (2-chloro-5-methoxypyridin-4-yl)boronic acid (4.0 g, 21.35 mmol) in Methanol (5 mL) were added $CuSO_4$ (171.0 mg, 1.06 mmol) and sodium azide (0.7 g, 10.67 mmol) at 23 °C. The resulting solution was stirred at 80 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was dissolved in DCM (5 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column that was eluted with 0~80% ethyl acetate in petroleum ether within 25 min to afford 4-azido-2-chloro-5-methoxypyridine (570 mg, 13%) as a white solid. MS (ESI) calc'd for ($C_6H_5ClN_4O$) $(M+1)^+$, 185.0; found 185.0.

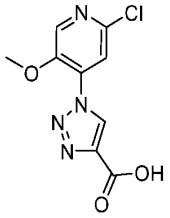
Step-2: ethyl 1-(2-chloro-5-methoxypyridin-4-yl)-1H-1,2,3-triazole-4-carboxylate



To a stirred solution of 4-azido-2-chloro-5-methoxypyridine (570.0 mg, 3.09 mmol) in Toluene (1 mL) was added ethyl propiolate (218.0 mg, 2.22 mmol) at 23 °C. The resulting

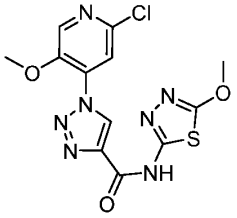
solution was stirred at 80 °C for 1 h. The solvents were removed under vacuum to afford ethyl 1-(2-chloro-5-methoxypyridin-4-yl)-1H-1,2,3-triazole-4-carboxylate (800.0 mg, crude) as a yellow solid. MS (ESI) calc'd for ($C_{11}H_{11}ClN_4O_3$) $(M+1)^+$, 283.1; found, 283.1.

Step-3: 1-(2-chloro-5-methoxypyridin-4-yl)-1H-1,2,3-triazole-4-carboxylic acid



To a stirred solution of ethyl 1-(2-chloro-5-methoxypyridin-4-yl)-1H-1,2,3-triazole-4-carboxylate (400.0 mg, 1.41 mmol) in THF (5 mL) and Water (5 mL) was added LiOH (67.8 mg, 2.83 mmol). The resulting solution was stirred at 23 °C for 1 h. The organic solvent was removed under vacuum. The aqueous layer was acidified with citric acid to pH ~3. The resulting residue was dissolved in DMF (1 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 20 min to afford 1-(2-chloro-5-methoxypyridin-4-yl)-1H-1,2,3-triazole-4-carboxylic acid (160.0 mg, 44%) as a white solid MS (ESI) calc'd for ($C_9H_7ClN_4O_3$) $(M+1)^+$, 255.0; found, 255.0.

Step-4: 1-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-1,2,3-triazole-4-carboxamide

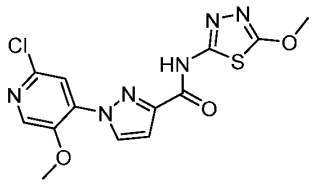


To a stirred solution of 1-(2-chloro-5-methoxypyridin-4-yl)-1H-1,2,3-triazole-4-carboxylic acid (100 mg, 0.39 mmol), 5-methoxy-1,3,4-thiadiazol-2-amine (51.5 mg, 0.39 mmol) in Acetonitrile (0.2 mL) were added 1-methylimidazole (161.0 mg, 1.96 mmol) and TCFH (110.0 mg, 0.39 mmol). The resulting mixture was then stirred at 23 °C for 1 h. The suspension was filtered. The filter cake was collected and dried under vacuum to afford 1-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-1,2,3-triazole-4-carboxamide (69.2 mg, 47%) as a white solid. MS (ESI) calc'd for ($C_{12}H_{10}ClN_7O_3S$) $(M+1)^+$,

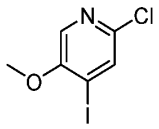
368.0, found 368.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 9.42 (s, 1H), 8.59 (s, 1H), 8.06 (s, 1H), 4.10 (s, 6H).

Example 235

1-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide

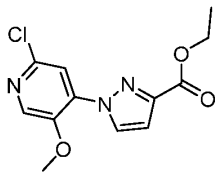


Step-1: 2-chloro-4-iodo-5-methoxypyridine



To a degassed solution of 6-chloro-4-iodopyridin-3-ol (5.0 g, 19.57 mmol) in N,N-Dimethylformamide (20 mL) was added NaH (939.0 mg, 23.49 mmol, 60%) in portions at 0 °C and stirred at 0 °C for 40 min. To the above solution was added MeI (4.1 g, 29.40 mmol) at 0 °C under nitrogen. The resulting solution was then stirred at 25 ° C for 16 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by Combi Flash (Biotage Isolera Prime) which applied to 120 g silica gel column and eluted with 0~50% ethyl acetate in petroleum ether within 45 min to afford 2-chloro-4-iodo-5-methoxypyridine (3.1 g, 51%) as a white solid. MS (ESI) calc'd for (C_6H_5ClINO) $(M+1)^+$, 269.9; found 269.9.

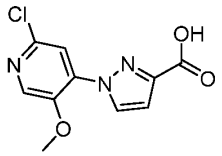
Step-2: ethyl 1-(2-chloro-5-methoxypyridin-4-yl)-1H-pyrazole-3-carboxylate



To a degassed solution of 2-chloro-4-iodo-5-methoxypyridine (1.0 g, 3.71 mmol) in N,N-Dimethylformamide (10 mL) were added Cs_2CO_3 (2.4 g, 7.42 mmol), ethyl 1H-pyrazole-5-carboxylate (728.0 mg, 5.20 mmol) and copper(I) iodide (141.0 mg, 0.74 mmol). The resulting solution was stirred at 25 °C for 30 min under nitrogen, then the solution was heated

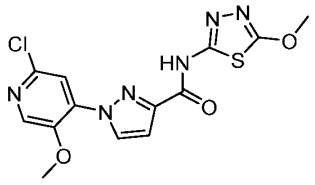
to 100 °C stirred for additional 1 h. The suspension was filtered. The filtrate was collected and concentrated under vacuum. The mixture was dissolved in DMF (3 mL) which was applied to a 80 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~60% acetonitrile in water within 25 min to afford ethyl 1-(2-chloro-5-methoxypyridin-4-yl)-1H-pyrazole-3-carboxylate (690.1 mg, 59%) as a white solid. MS (ESI) calc'd for ($C_{12}H_{12}ClN_3O_3$) $(M+1)^+$, 282.1; found, 282.1.

Step-3: 1-(2-chloro-5-methoxypyridin-4-yl)-1H-pyrazole-3-carboxylic acid



To a solution of ethyl 1-(2-chloro-5-methoxypyridin-4-yl)-1H-pyrazole-3-carboxylate (300.0 mg, 1.07 mmol) in Tetrahydrofuran (3 mL) and Water (1 mL) was added LiOH (25.5 mg, 1.06 mmol). The resulting solution was stirred at 25 ° C for 2 h. The organic solvent was removed under vacuum. The aqueous layer was acidified with Formic acid to pH ~3 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum The mixture was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera Prime), eluted with 5~50% acetonitrile in water within 20 min to afford 1-(2-chloro-5-methoxypyridin-4-yl)-1H-pyrazole-3-carboxylic acid (270.2 mg, 90%) as a white solid. MS (ESI) calc'd for ($C_{10}H_8ClN_3O_3$) $(M+1)^+$, 254.0.1; found, 254.0.

Step-4: 1-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide

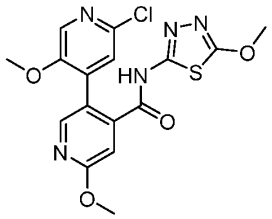


To a solution of 1-(2-chloro-5-methoxypyridin-4-yl)-1H-pyrazole-3-carboxylic acid (100.0 mg, 0.39 mmol) in Acetonitrile (1 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (51.7 mg, 0.39 mmol) and 1-methyl-1H-imidazole (162.2 mg, 1.97 mmol). To the above was added a solution of TCFH (111.1 mg, 0.39 mmol) in Acetonitrile (1 mL) at 25 °C. The resulting solution was stirred at 25 °C for 2 h under nitrogen. The mixture was dissolved in DMF (2 mL) which was applied to a 40 g C18 column and purified by Combi Flash (Biotage Isolera

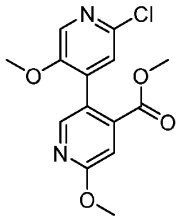
Prime), eluted with 5~50% acetonitrile in water within 20 min to afford 1-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (53.1 mg, 36 %) as a white solid. MS (ESI) calc'd for ($C_{13}H_{11}ClN_6O_3S$) $(M+1)^+$, 367.0; found, 367.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.47 (s, 1H), 8.36 (s, 1H), 7.15 (d, J = 2.4 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H).

Example 242

2'-chloro-5',6-dimethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide



Step-1: Synthesis of methyl 2'-chloro-5',6-dimethoxy-[3,4'-bipyridine]-4-carboxylate:



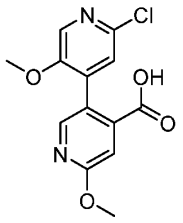
To a stirred solution of methyl 5-bromo-2-methoxyisonicotinate (1 g, 4.06 mmol) in dioxane (15 ml) and H_2O (1.5 ml) was added potassium carbonate (0.674 g, 4.88 mmol), Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.178 g, 0.244 mmol) and (2-chloro-5-methoxypyridin-4-yl)boronic acid (0.838 g, 4.47 mmol). The reaction mixture was stirred at 85 °C for 8 hours. After completion, the reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as a brown solid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Biotage (12 g) column and eluted with 20 % of ethyl acetate in pet ether for 20 minutes with flow rate 30 ml/min. The appropriate fractions were collected and concentrated vacuum to afford methyl

2'-chloro-5',6-dimethoxy-[3,4'-bipyridine]-4-carboxylate (680 mg, 2.203 mmol, 54.2 % yield) as a white solid.

MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_4$) $(M+1)^+$, 309.07; found, 309.0

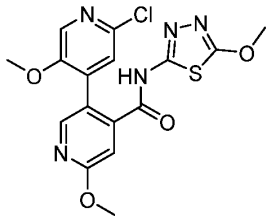
Step-2: Synthesis of 2'-chloro-5',6-dimethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of methyl 2'-chloro-5',6-dimethoxy-[3,4'-bipyridine]-4-carboxylate (680 mg, 2.203 mmol) in tetrahydrofuran (6 mL), methanol (3 mL) and water (3 mL) was added lithium hydroxide monohydrate (92 mg, 2.203 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After completion, reaction mixture was concentrated under vacuum, residue was acidified with 1.5 N HCl up to pH-3 to give off-white precipitate. The obtained precipitate was filtered and dried under vacuum to afford 2'-chloro-5',6-dimethoxy-[3,4'-bipyridine]-4-carboxylic acid (440 mg, 1.380 mmol, 62.6 % yield) as a white solid.

MS (ESI) calculated for ($C_{13}H_{11}ClN_2O_4$) $(M+1)^+$, 295.05; found, 295.0

Step-3: Synthesis of 2'-chloro-5',6-dimethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of 2'-chloro-5',6-dimethoxy-[3,4'-bipyridine]-4-carboxylic acid (50 mg, 0.170 mmol) in acetonitrile (3 mL) and N,N-dimethylformamide (0.6 mL) were added chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (52.4 mg, 0.187 mmol), 1-methyl-1H-imidazole (41.8 mg, 0.509 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine

(22.25 mg, 0.170 mmol) at room temperature. The reaction mixture was stirred at room temperature for 8 hours. After completion, the reaction mixture was quenched with cold water (10 mL) and extracted by ethyl acetate (2 x 20 mL). The combined organic layer dried over anhydrous sodium sulfate, filtered, concentrated under vacuum to afford crude product as a yellow semi solid.

The crude product (200 mg) of this batch was mixed crude product (170 mg) of another batch and combined two batches were purified together using prep-HPLC.

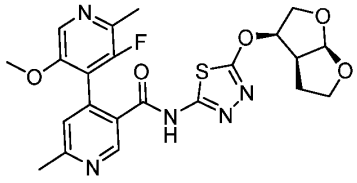
The crude product was purified by prep-HPLC with the following conditions: (X-select (19*250 mm) 5 MICRON; Mobile Phase A: 10mM ABC in Milli Q Water 80%, Mobile Phase B: Acetonitrile 20% Flow rate: 12 mL/min; Run time: 17 min; (Sample Solvent: THF:ACN; Injection Volume: 400 µL; number of injections: 25) to afford 2'-chloro-5',6-dimethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide (52 mg, 0.125 mmol, 73.4 % yield) as an off-white solid.

MS (ESI) calculated for ($C_{16}H_{14}ClN_5O_4S$) $(M+1)^+$, 408.06; found, 408.0

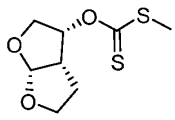
1H-NMR (400 MHz, DMSO-d^6): δ 12.98 (brs, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 7.53 (s, 1H), 7.20 (s, 1H), 4.08 (s, 3H), 3.97 (s, 3H), 3.60 (s, 3H)

Example 243

3'-fluoro-N-(5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



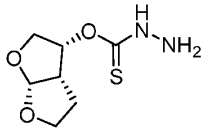
Step-1. O-((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) S-methyl carbonodithioate



To a solution of ((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol (3.7 g, 28.4 mmol) in tetrahydrofuran (THF) (100 mL) was added NaH (60%, 1.478 g, 37.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min before the dropwise addition of carbon disulfide (2.60 mL, 31.3 mmol) followed by methyl iodide (1.955 mL, 31.3 mmol). The mixture was

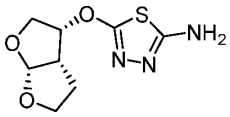
allowed to stir for 10 min before quenching with saturated aq. NH_4Cl (5 mL) and brine (10 mL). The mixture was diluted with EtOAc (30 mL) and the layers were separated. The aq. layer was washed with EtOAc (2x20mL). The combined organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel (0-100% EtOAc/heptane, 80g column) to give the desired product as a yellow oil. LCMS (ES) = 221.2 $[M+H]^+$ ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.91 (dt, *J* = 8.3, 6.4 Hz, 1H), 5.76 (d, *J* = 4.9 Hz, 1H), 4.17 (dd, *J* = 10.3, 6.4 Hz, 1H), 4.04 – 3.88 (m, 3H), 3.28 – 3.17 (m, 1H), 2.59 (s, 3H), 2.08 – 2.00 (m, 1H), 1.98 – 1.87 (m, 1H).

Step-2. O-((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) hydrazinecarbothioate



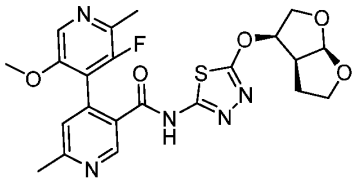
To a solution of (O-((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) S-methyl carbonodithioate (5.8g, 26.3 mmol) in methanol (100 mL) at 0 °C was added hydrazine hydrate solution (1.136 mL, 29.0 mmol) dropwise. The mixture was stirred at 0 °C for 2 h. Upon completion, the reaction was concentrated under vacuum. The residue was azeotroped in a mixture of MeOH/toluene (1mL/10mL) to give the crude product O-((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) hydrazinecarbothioate (5.38 g, 26.3 mmol, 100 % yield). LCMS (ES) = 205.2 $[M+H]^{+\cdot}$

Step-3. 5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-amine



To a solution of (O-((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) hydrazinecarbothioate (5.3 g, 25.9 mmol) in methanol (100 mL) at 0 °C was added triethylamine (7.96 mL, 57.1 mmol) followed by cyanic bromide (3M in DCM) (10.38 mL, 31.1 mmol) dropwise. The mixture was stirred at 0 °C for 2 h. Upon completion, the reaction was concentrated under vacuum and the residue was purified by silicagel chromatography (0-5% MeOH/DCM, 80g column) to give the desired product as a brown solid. LCMS (ES) = 230.2 $[M+H]^{+\cdot}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (s, 2H), 5.64 (d, *J* = 5.4 Hz, 1H), 5.24 (dt, *J* = 8.3, 6.4 Hz, 1H), 4.06 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.87 (td, *J* = 8.1, 2.4 Hz, 1H), 3.79 – 3.70 (m, 2H), 3.21 – 3.10 (m, 1H), 2.04 – 1.93 (m, 1H), 1.88 – 1.73 (m, 1H).

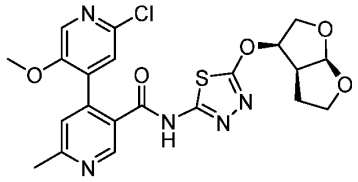
Step-4. 3'-fluoro-N-(5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide



To a solution of 3'-fluoro-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxylic acid (100 mg, 0.362 mmol, Example 61, Step 2) in acetonitrile (10 mL) at 23 °C were added N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (112 mg, 0.398 mmol) and 1-methyl-1H-imidazole (62.4 mg, 0.760 mmol). The reation was allowed to stir for 5 min before adding 5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-amine (91 mg, 0.398 mmol) after which the reaction was allowed to stir at 23 °C for 1.5 h. The reaction was concentrated under vacuum, taken up in EtOAc and washed with saturated aq. NH4Cl. The EtOAc layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column (0-100% (3:1)(EtOAc/EtOH)/heptane, 40g column) to give the desired product 3'-fluoro-N-(5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (122 mg, 0.250 mmol, 69.1 % yield) as a light brown solid. MS (ESI) calc'd for ($C_{22}H_{22}FN_5O_5S$) (M+1)+, 488.0, found 488.3. ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.89 (s, 1H), 8.09 (s, 1H), 7.46 (s, 1H), 5.74 (d, J = 5.4 Hz, 1H), 5.46 (dt, J = 7.9, 6.1 Hz, 1H), 4.20 (dd, J= 9.8, 6.4 Hz, 1H), 4.01 – 3.88 (m, 3H), 3.77 (d, J = 1.5 Hz, 3H), 3.32 – 3.25 (m, 1H), 2.68 (s, 3H), 2.50 (d, J = 2.9 Hz, 3H), 2.23 – 2.08 (m, 1H), 2.03 – 1.84 (m, 1H).

Example 262

2'-chloro-N-(5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide

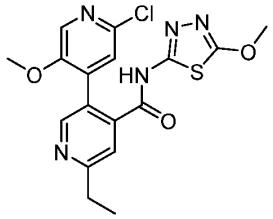


To a solution of Intermediate G (498 mg, 1.788 mmol), 5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-amine (410 mg, 1.788 mmol), and 1-methyl-1H-

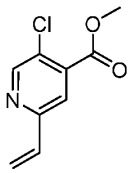
imidazole (147 mg, 1.788 mmol, Example 243, Step 3) in acetonitrile (10 mL) at 0 °C was added N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (552 mg, 1.967 mmol). The mixture was allowed to stir at 0 °C for 1 h. The reaction mixture was concentrated under vacuum and purified by silica gel column (0-100% (3:1)(EtOAc/EtOH)/Heptane, 40g column, 20mins) to give the desired product 2'-chloro-N-(5-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (326 mg, 0.665 mmol, 37.2 % yield) as a light pink solid. MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_5S$) $(M+1)^+$, 490.0, found 490.2. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 12.98 – 12.59 (m, 1H), 9.08 (s, 1H), 8.05 (s, 1H), 7.26 (s, 1H), 7.21 (s, 1H), 5.81 (d, J = 5.4 Hz, 1H), 5.42 – 5.33 (m, 1H), 4.21 (dd, J = 9.8, 6.8 Hz, 1H), 4.08 – 3.93 (m, 2H), 3.88 (dd, J = 9.8, 7.3 Hz, 1H), 3.74 (s, 3H), 3.34 – 3.23 (m, 1H), 2.70 (s, 3H), 2.23 – 2.11 (m, 1H), 2.03 – 1.87 (m, 1H).

Example 270

2'-chloro-6-ethyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide



Step-1: Synthesis of methyl 5-chloro-2-vinylisonicotinate:



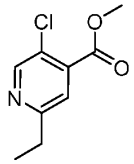
A solution of methyl 2,5-dichloroisonicotinate (1 g, 4.85 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.822 g, 5.34 mmol) and potassium carbonate (1.342 g, 9.71 mmol) in acetonitrile (15 mL) and methanol (2 mL) was degassed with nitrogen for 15 minutes followed by addition of palladium (II) acetate (54 mg, 0.243 mmol) and triphenylphosphine (0.127 g, 0.485 mmol). The reaction mixture was heated to 40°C and stirred for 16 hours. The reaction mixture was quenched with water and extracted with ethyl acetate (2 x 200 mL). The

combine organic layer was dried over sodium sulfate, filtered and concentrated to give crude product as yellow liquid.

The crude was pre-absorbed on silica, loaded on pre-packed biotage column (25 g), and then eluted 2-10% of ethyl acetate in pet ether for 40 mins with flow rate 25 ml/min. The fractions were collected and concentrated under reduced pressure to afford methyl 5-chloro-2-vinylisonicotinate (730 mg, 3.66 mmol, 75 % yield) as colourless liquid.

MS (ESI) calculated for ($C_9H_8ClNO_2$) $(M+1)^+$, 198.03; found, 198.0

Step-2: Synthesis of methyl 5-chloro-2-ethylisonicotinate:

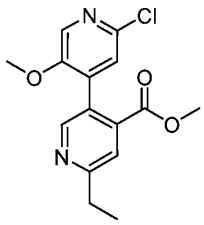


To a solution of methyl 5-chloro-2-vinylisonicotinate (0.62 g, 3.14 mmol) in ethyl acetate (25 mL) stirred under nitrogen at room temp was added palladium, (5 wt % on calcium carbonate, poisoned with lead, 1.669 g, 0.784 mmol) in one charge. The reaction mixture was stirred at room temperature under hydrogen atmosphere for 2 hours. After completion, the reaction mixture was filtered through celite bed and washed with ethyl acetate (100mL). The filtrate was concentrated under reduced pressure to give crude product as brown liquid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem 25 g column and eluted at 5-15 % of ethyl acetate in PET ether for 20 minutes with flow rate 25 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 5-chloro-2-ethylisonicotinate (530 mg, 2.56 mmol, 81% yield) as brown oil.

LCMS calculated for ($C_9H_{10}ClNO_2$) $(M+1)^+$, 200.05; found, 200.2

Step-3: Synthesis of methyl 2'-chloro-6-ethyl-5'-methoxy-[3,4'-bipyridine]-4-carboxylate:

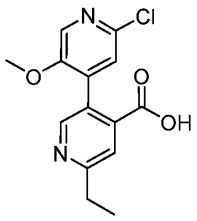


To a solution of methyl 5-chloro-2-ethylisonicotinate (530 mg, 2.65 mmol) and (2-chloro-5-methoxypyridin-4-yl)boronic acid (497 mg, 2.65 mmol) in 1,4-Dioxane (15 mL) was added a solution of potassium carbonate (734 mg, 5.31 mmol) in water (3.00 mL) in one charge under nitrogen at room temperature. The reaction mixture was degassed for 10 min with nitrogen followed by addition of [1,1′-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (173 mg, 0.265 mmol) at room temperature. The resulting reaction mixture was stirred at 80 °C for 16 hours. After completion, the reaction mixture was cooled to room temperature and filtered through celite bed, washed with ethyl acetate (25 mL). The filtrate was washed with water (20 mL) and brine solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product as brown liquid.

The crude product was pre-absorbed on silica, loaded on the pre-packed orochem 40 g column and eluted at 25-30 % of ethyl acetate in PET ether for 30 minutes with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2'-chloro-6-ethyl-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (500 mg, 1.508 mmol, 56.8 % yield) as brown solid.

MS (ESI) calculated for ($C_{15}H_{15}ClN_2O_3$) $(M+1)^+$, 307.09; found, 307.2

Step-4: Synthesis of 2'-chloro-6-ethyl-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid:

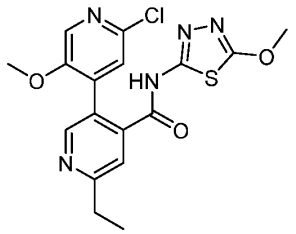


To a stirred solution of methyl 2'-chloro-6-ethyl-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (500 mg, 1.630 mmol) in tetrahydrofuran (10 mL) and water (2.000 mL) was added lithiumhydroxide monohydrate (342 mg, 8.15 mmol) at room temperature. The reaction was stirred at room temperature for 5 hours. After completion, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with water (10 mL) and washed with ethyl acetate (40 mL). The aqueous part was acidified by 1.5N HCl (~pH 2) and extracted with 20% MeOH in DCM (60 mL). The organic phases were combined and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to

afford 2'-chloro-6-ethyl-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (400 mg, 1.306 mmol, 80% yield ; LCMS purity 80%) as white solid.

MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_3$) $(M+1)^+$, 293.07; found, 293.0

Step-5: Synthesis of 2'-chloro-6-ethyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of 2'-chloro-6-ethyl-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (70 mg, 0.239 mmol) in acetonitrile (5 mL) and N, N-Dimethylformamide (0.5 mL) was added Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (81 mg, 0.287 mmol), 1-methyl-1H-imidazole (0.057 mL, 0.717 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (31.4 mg, 0.239 mmol) at room temperature. The reaction was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was diluted with water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (5 X 10 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product as yellow viscous liquid.

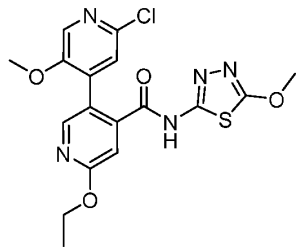
The crude product was purified by GRACE revelleris X2 (reverse phase) with the following conditions: (Column: 40 g Grace C18 catriage; Mobile Phase A: 0.1% NH4HCO3 in water, Mobile Phase B: acetonitrile) 0-100% of B in A over 0-50 min at Flow rate: 15mL/min. The pure product was eluted at 40-45% of B in A. The appropriate fractions were combined and evaporated in vacuum to afford 2'-chloro-6-ethyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide (60 mg, 0.147 mmol, 61.4 % yield) as white solid.

MS (ESI) calculated for ($C_{17}H_{16}ClN_5O_3S$) $(MH)^+$, 406.07; found, 406.0.

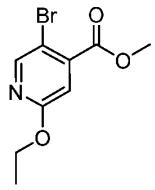
1H-NMR (400 MHz, DMSO-d6): δ 13.00 (s, 1H), 8.58 (s, 1H), 8.14 (s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 4.08 (s, 3H), 3.61 (s, 3H), 2.89 (q, J = 7.60 Hz, 2H), 1.31 (t, J = 7.60 Hz, 3H) .

Example 276

2'-chloro-6-ethoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide



Step-1: Synthesis of methyl 5-bromo-2-ethoxyisonicotinate:



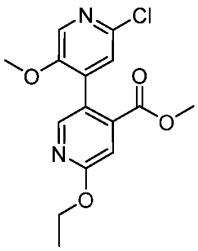
To a stirred solution of methyl 5-bromo-2-hydroxyisonicotinate (700 mg, 3.02 mmol) in Toluene (15 mL) under nitrogen was added silver carbonate (1081 mg, 3.92 mmol) followed by iodoethane (0.364 mL, 4.53 mmol). The reaction mixture was stirred at 100 °C for 1 hour. After completion of the reaction, reaction mixture was cooled to room temperature and passed through celite bed and the celite bed was washed with ethyl acetate (125 mL). The filtrate was washed with with water (100 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude product as yellow liquid.

The pre-absorbed crude product was loaded on the pre-packed column (orochem, 12 g) and eluted at 0-30 % of ethyl acetate in Pet ether for 20 minutes with flow rate 25 ml/min. The pure product was eluated at 5% ethyl acetate in Pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 5-bromo-2-ethoxyisonicotinate (700 mg, 2.61 mmol, 87 % yield) as a white solid

MS (ESI) calculated for ($C_9H_{10}BrNO_3$) $(M+1)^+$, 259.99; found, 260.0

1H-NMR (400 MHz, DMSO-d^6): δ 8.46 (s, 1H), 7.14 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H)

Step-2: Synthesis of methyl 2'-chloro-6-ethoxy-5'-methoxy-[3,4'-bipyridine]-4-carboxylate:

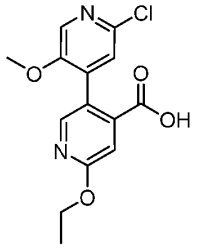


To a stirred solution of methyl 5-bromo-2-ethoxyisonicotinate (700 mg, 2.69 mmol) in 1,4-dioxane (15 mL) and water (2 mL) were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (756 mg, 4.04 mmol) and potassium carbonate (744 mg, 5.38 mmol) at room temperature and the reaction mixture was degassed with nitrogen for 10 minutes. PdCl2(dppf) (98 mg, 0.135 mmol) was added and the reaction mixture was stirred at 100 °C for 2 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad and washed with ethyl acetate (100 mL). The filtrate was washed with water (80 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as brown color liquid.

The pre-absorbed crude product was loaded on the Biotage 24 g snap and eluted at 20 % of ethyl acetate in pet ether for 10 minutes with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2'-chloro-6-ethoxy-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (570 mg, 1.698 mmol, 63.1 % yield) as a white solid

MS (ESI) calculated for ($C_{15}H_{15}ClN_2O_4$) $(M+1)^+$, 323.08; found, 323.0

Step-3: Synthesis of 2'-chloro-6-ethoxy-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid:

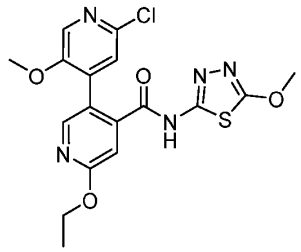


To a stirred solution of methyl 2'-chloro-6-ethoxy-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (670 mg, 2.076 mmol) in mixture of tetrahydrofuran (5.0 mL) and methanol (5.0 mL) was added lithium hydroxide (149 mg, 6.23 mmol) in water (1 mL) dropwise at 0 °C. The

reaction mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was concentrated under vacuum. The resulting residue was diluted with water (50 mL) and washed with DCM (100 mL) to remove impurities, the aqueous layer was acidified with saturated aqueous solution of citric acid upto pH 5-6 and extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2'-chloro-6-ethoxy-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (570 mg, 1.837 mmol, 88 % yield) as white solid.

MS (ESI) calculated for ($C_{14}H_{13}ClN_2O_4$) $(M+1)^+$, 309.06; found, 309.0.

Step-4: Synthesis of 2'-chloro-6-ethoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of 2'-chloro-6-ethoxy-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (100 mg, 0.324 mmol), in acetonitrile (4 mL) and N,N-Dimethylformamide (0.4 mL) were added 1-methyl-1H-imidazole (106 mg, 1.296 mmol), Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (136 mg, 0.486 mmol), and 5-methoxy-1,3,4-thiadiazol-2-amine (42.5 mg, 0.324 mmol) at room temperature. The reaction mixture was stirred at same temperature for 16 h. The reaction mixture was diluted with water, extracted with ethyl acetate (2 X 25 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product as yellow liquid.

The pre-absorbed crude product was loaded on the Orochem 12 g pre-packed column and eluted at 45 % of ethyl acetate in pet ether for 30 minutes with flow rate 25 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford product as a white solid.

The solid was dissolved in 10% methanol in dichloromethane (20 mL) and washed with brine solution (25 mL), the organic layer was dried using sodium sulfate and concentrated under

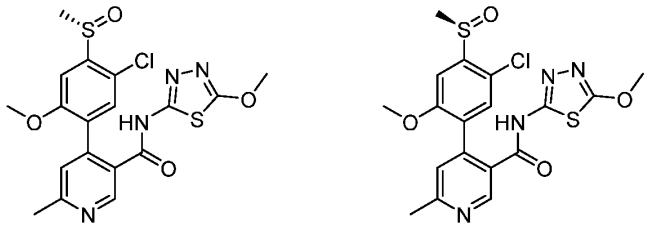
reduced pressure to afford 2'-chloro-6-ethoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide (70 mg, 0.162 mmol, 50% yield).

MS (ESI) calculated for ($C_{17}H_{16}ClN_5O_4S$) $(M+1)^+$, 422.07; found, 422.0

1H-NMR (400 MHz, DMSO-d^6): δ 12.96 (s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 7.54 (s, 1H), 7.16 (s, 1H), 4.42 (q, J = 7.20 Hz, 2H), 4.08 (s, 3H), 3.59 (s, 3H), 1.37 (t, J = 7.20 Hz, 3H).

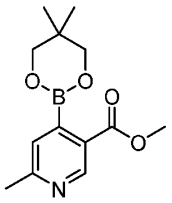
Example 277 and 298

(S)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide and *(R)*-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:



Boronate ester preparation:

Step-1: Synthesis of methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate:



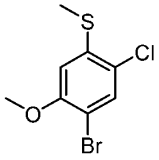
To a stirred solution of methyl 4-chloro-6-methylnicotinate (10 g, 53.9 mmol) in 1,4-Dioxane (100 mL) were added 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (18.26 g, 81 mmol), tert-butyldiphenylphosphane (2.61 g, 10.78 mmol) and potassium acetate (15.86 g, 162 mmol) at room temperature and degassed with nitrogen for 20 minutes. PdOAc2 (1.210 g, 5.39 mmol) was added and the mixture was again degassed with nitrogen for 5 minutes. The reaction mixture was stirred at 100 °C for 3 hours. The reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad and washed with ethyl acetate (500 mL). The filtrate was concentrated under vacuum to afford crude product as brown oil.

The crude product was pre-absorbed on silica (using 20 mL DCM, 50 g of silica (60-120 mesh), loaded on the pre-packed Orochem 120 g column and eluted at 25-40 % of ethyl acetate in PET ether for 45 minutes with flow rate 40 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (14.1 g, 47.7 mmol, 89 % yield) as brown gum.

MS (ESI) calculated for ($C_{13}H_{18}BNO_4$) $(M+1)^+$, 264.14; found, 264.1

Acid preparation:

Step-2: Synthesis of (4-bromo-2-chloro-5-methoxyphenyl)(methyl)sulfane:



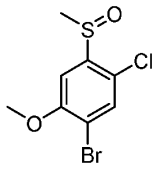
A solution of 4-bromo-2-chloro-5-methoxyaniline (2.5g, 10.57 mmol) in 2N HCl (26.4 mL, 52.9 mmol), was heated to 50 °C for 30 min, then the reaction mixture was cooled to 0 °C, and added sodium nitrite (0.802 g, 11.63 mmol) in water (20 mL) dropwise. The resulting reaction mixture was stirred for 40 min at 0°C, then sodium thiomethoxide (1.482 g, 21.14 mmol) in water (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred again for 18h at room temperature. After completion of the reaction, The reaction mixtures was diluted with 10% NaOH aq. solution (50 mL) and extracted with EtOAc (2 x 200 mL). The separated organic layer was dried over anhydrous Na2SO4 and concentrated under vacuum to afford crude product as light yellow oil.

The crude product was pre-absorbed on silica (using 10 mL DCM, 10 g of silica (60-120 mesh), loaded on the pre-packed Orochem 120 g column and eluted at 0-30 % of ethyl acetate in PET ether for 45 minutes with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford (4-bromo-2-chloro-5-methoxyphenyl)(methyl)sulfane (2.1 g, 6.99 mmol, 66.1 % yield) as yellow solid.

LCMS calculated for ($C_8H_8BrClOS$) $(M)^+$, 267.91; found, (m/z) not ionized

1H-NMR (400 MHz, DMSO-d^6): δ 7.67 (s, 1H), 6.88 (s, 1H), 3.93 (s, 3H), 2.57 (s, 3H).

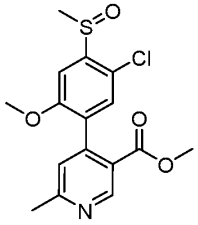
Step-3: Synthesis of 1-bromo-5-chloro-2-methoxy-4-(methylsulfinyl)benzene:



To a stirred solution of (4-bromo-2-chloro-5-methoxyphenyl)(methyl)sulfane (2.1 g, 7.85 mmol) in Dichloromethane (30mL) was added *m*CPBA (1.490 g, 8.63 mmol) portion wise at 0 °C, under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction mixtures was diluted with 10% Na2CO3 aq. solution (100 mL) and extracted with EtOAc (2 x 300 mL), washed with brine. The organic layer was separated and dried over anhydrous Na2SO4, concentrated under vacuum to afford crude product as light yellow oil. The crude product was pre-absorbed on silica (using 15 mL DCM, 9 g of silica (60-120 mesh), loaded on the pre-packed Orochem 50 g column and eluted at 0-100 % of ethyl acetate in PET ether for 60 minutes with flow rate 15 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford 1-bromo-5-chloro-2-methoxy-4-(methylsulfinyl)benzene (1.5 g , 5.27 mmol, 67.2 % yield) as yellow solid.

MS (ESI) calculated for ($C_8H_8BrClO_2S$) $(M+1)^+$, 282.92; found, 283.0

Step-4: Synthesis of methyl 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate:



To a stirred solution of 1-bromo-5-chloro-2-methoxy-4-(methylsulfinyl)benzene (500 mg, 1.763 mmol) in Toluene (30 mL) were added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (1392 mg, 5.29 mmol) and potassium carbonate (731 mg, 5.29 mmol) at room temperature and degassed with nitrogen for 10 minutes. To the resulting reaction mixture was added PdCl2(dppf) (258 mg, 0.353 mmol). The reaction mixture was stirred at 120 °C for 16 hours.

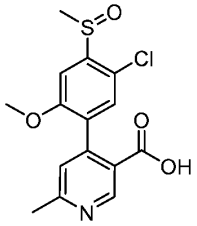
After completion of the reaction, the reaction mixture was cooled to room temperature, The solvent was evaporated then the reaction mixture was dissolved in water (100 mL) and

extracted with EtOAc (100X2 mL), washed with brine water (30 mL)., dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as brown semi solid.

The crude product was mixed with another batch of (500 mg) and combined 2 batched pre-absorbed on silica (using 20 mL DCM, 10 g of silica (60-120 mesh), loaded on the pre-pack orochem 50 g column and eluted at 2-10 % of methanol in DCM for 60 minutes with flow rate 25 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate (1.3 g, 2.83 mmol) as a brown solid.

MS (ESI) calculated for ($C_{16}H_{16}ClNO_4S$) $(M+1)^+$, 354.06; found, 354.0

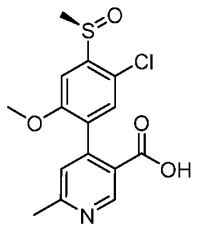
Step-5: Synthesis of *rac*-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid:



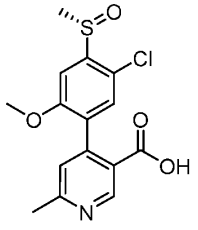
To a stirred solution of methyl methyl 4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate (900 mg, 2.54 mmol) in a mixture of Tetrahydrofuran (1.5 mL), Methanol (1 mL) and Water (0.5 mL) was added lithiumhydroxide (747 mg, 17.81 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum. The resulting residue diluted with water (50 mL) and washed with EtOAc (25 mL). The aqueous layer was acidified with 1.5 N HCl upto pH-6 and extracted with 10% MeOH in DCM (3 X 150 mL). The combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford *rac*-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (750 mg, 2.185 mmol, 86 % yield) as grey solid.

MS (ESI) calculated for ($C_{15}H_{14}ClNO_4S$) $(M+1)^+$, 340.04; found, 340.0

Step-6: Separation of (R)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid and (S)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid



Isomer-1



Isomer-2

Rac-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (650 mg) was purified by Chiral SFC by using the following method:

Column: Chiralpak IG (250*30)mm, 5µm, Mobile Phase : CO2: MeOH (70:30)%, Total Flow : 100 g/min, Back pressure : 100 bar, Wave length : 220 nm ,Cycle time: 5.5 min, 650 mg of sample was dissolved in 8.0 ml of MeOH /THF and injected 700 µl/ injection;

After SFC purification, the two appropriate fractions were collected.

Fraction-1 was concentrated under reduced pressure to afford (R)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid-Isomer-1 (270 mg, 0.763 mmol, 39.9 % yield) as an off-white solid. Chiral SFC purity: 100%; Rt = 2.4 mins;

MS (ESI) calculated for ($C_{15}H_{14}ClNO_4S$) $(M+1)^+$, 340.04; found, 340.0

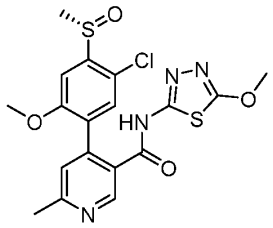
Fraction-2 was concentrated under reduced pressure to afford (S)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (290 mg, 0.819 mmol, 42.8 % yield) as an off-white solid. Chiral SFC purity: 99.74%; Rt = 3.29 mins;

MS (ESI) calculated for ($C_{15}H_{14}ClNO_4S$) $(M+1)^+$, 340.04; found, 340.0

The absolute stereochemistry was not determined.

Acid-Amine coupling:

Step-6: Synthesis of *(S)*-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.



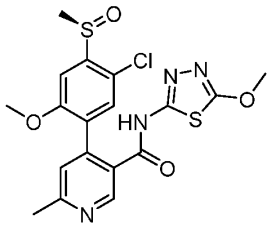
To a stirred solution of (S)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid-Isomer-2 (80 mg, 0.235 mmol), in Acetonitrile (3 mL) and N,N-Dimethylformamide (0.5 mL) were added 1-methyl-1H-imidazole (77 mg, 0.942 mmol), Chloro-N,N,N′,N′-tetramethylformamidiniumhexafluorophosphate (99 mg, 0.353 mmol), and 5-methoxy-1,3,4-thiadiazol-2-amine (37.1 mg, 0.283 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After completion the reaction mixture was quenched with cold water and evaporated all the volatiles. Then diluted with ethyl acetate and extracted by ethyl acetate(150 mL x 3). The combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product as brown solid.

The crude product was purified by prep-HPLC with the following conditions: (Atlantis C18 (19*250 mm)5 MICRON; Mobile Phase A: 10mM ABC in Milli Q Water 70%, Mobile Phase B: Acetonitrile 30%); Flow: 12.00 ml/min; Injection Volume : 200.00 µL; Number of injection : 14; Diluent : THF/ACN; Run time : 19 min; to afford *(S)*-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (40 mg, 0.087 mmol, 37.1 % yield) as a off-white solid. The absolute stereochemistry was not determined.

MS (ESI) calculated for ($C_{18}H_{17}ClN_4O_4S_2$) $(M+1)^+$, 453.05; found, 453.0.

1H-NMR (400 MHz, DMSO-d^6): δ 12.85 (s, 1H), 8.75 (s, 1H), 7.61 (s, 1H), 7.40 (s, 1H), 7.34 (s, 1H), 4.07 (s, 3H), 3.61 (s, 3H), 2.86 (s, 3H), 2.58 (s, 3H).

Step-6: Synthesis of *(R)*-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.



To a stirred solution of (R)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (80 mg, 0.235 mmol), in Acetonitrile (5 mL) and N,N-Dimethylformamide (1 mL) were added 1-methyl-1H-imidazole (77 mg, 0.942 mmol), Chloro-N,N,N′,N′-tetramethylformamidiniumhexafluorophosphate (99 mg, 0.353 mmol), and 5-methoxy-1,3,4-thiadiazol-2-amine (37.1 mg, 0.283 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h. After completion the reaction mixture was quenched with cold water and evaporated all the volatiles. Then diluted with ethyl acetate and extracted by ethyl acetate(50 mL x 3). The combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product as orange solid.

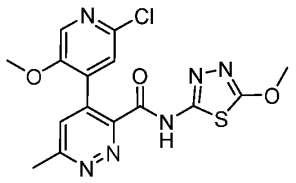
The crude product was purified by prep-HPLC with the following conditions: (X-select (19*250 mm) 5 MICRON; Mobile Phase A: 0.1%FA in MQ water 80%, Mobile Phase B: Acetonitrile 20%); Flow: 12.00 ml/min; Injection Volume : 200 µL; Number of injection : 16; Diluent : THF/ACN; Run time : 18 min; pure product was lyophilized to afford (R)-4-(5-chloro-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (32 mg, 0.07 mmol, 29.6 % yield) as light yellow solid. The absolute stereochemistry was not determined.

MS (ESI) calculated for ($C_{18}H_{17}ClN_4O_4S_2$) $(M+1)^+$, 453.05; found, 453.0.

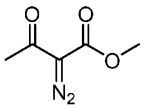
1H-NMR (400 MHz, DMSO-d^6): δ 12.83 (s, 1H), 8.75 (s, 1H), 7.62 (s, 1H), 7.40 (s, 1H), 7.34 (s, 1H), 4.08 (s, 3H), 3.61 (s, 3H), 2.86 (s, 3H), 2.59 (s, 3H).

Example 294

4-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridazine-3-carboxamide



Step-1: Synthesis of methyl 2-diazo-3-oxobutanoate:



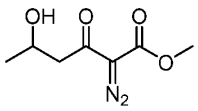
To a stirred solution of methyl 3-oxobutanoate (5 g, 43.1 mmol), in acetonitrile (50 mL) were added successively triethylamine (7.80 mL, 56.0 mmol) and 4-acetamidobenzenesulfonyl azide (10.34 g, 43.1 mmol) at 0 °C .The reaction mixture was stirred at 0 °C for 2 hours. After completion of the reaction, the reaction mixture was allowed to room temperature, diluted with MTBE/hexane (1:1) 100 mL and then filtered. The filterate was concentrated under reduced pressure to afford crude residue as yellow gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Biotage column (50 g) and eluted at 10-20 % of ethyl acetate in Pet ether for 60 minutes with flow rate 30 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2-diazo-3-oxobutanoate (5.1 g, 35.9 mmol, 83 % yield) as yellow oil.

MS (ESI) calculated for ($C_5H_6N_2O_3$) $(M+1)^+$, 143.05; found, poor ionization.

1H-NMR (400 MHz, DMSO-d^6): δ 3.78 (s, 3H), 2.38 (s, 3H)

Step-2: Synthesis of methyl 2-diazo-5-hydroxy-3-oxohexanoate:



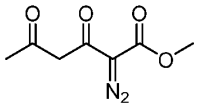
To a stirred solution of methyl 2-diazo-3-oxobutanoate (6 g, 42.2 mmol), in dichloromethane (60 mL) were added successively Titanium tetrachloride (TiCl4) (5.12 mL, 46.4 mmol) and triethylamine (6.47 mL, 46.4 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 1 hour. After 1 hour a solution of acetaldehyde (2.384 mL, 42.2 mmol) in dichloromethane (5 mL) was added at -78 °C and stirred at same temperature for 2 hours. After completion, the reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with

DCM (2 x 100 mL). The combined organic layers were, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as yellow liquid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Biotage column (100 g) and eluted at 20-40 % of ethyl acetate in pet ether for 60 minutes with flow rate 40 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2-diazo-5-hydroxy-3-oxohexanoate (6.1 g, 32.5 mmol, 77 % yield) as yellow oil.

MS (ESI) calculated for ($C_7H_{10}N_2O_4$) $(M+1)^+$, 187.07; found, 187.0

Step-3: Synthesis of methyl 2-diazo-3,5-dioxohexanoate:

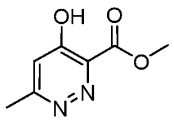


To a stirred solution of methyl 2-diazo-5-hydroxy-3-oxohexanoate (5 g, 26.9 mmol), in acetonitrile (50 mL) was added 2-Iodoxybenzoic acid (IBX) (20.05 g, 32.2 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 2 hours. After completion of the reaction, the reaction mixture was allowed to room temperature, and then filtered. The filterate was concentrated under reduced pressure to afford crude residue as yellow gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Biotage column (50 g) and eluted at 10-20 % of ethyl acetate in pet ether for 60 minutes with flow rate 35 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2-diazo-3,5-dioxohexanoate (5.1 g, 14.49 mmol, 53.9 % yield; LCMS purity: 52.31%) as an off white solid

MS (ESI) calculated for ($C_7H_8N_2O_4$) $(M+1)^+$, 185.06; found, 185.0

Step-4: Synthesis of methyl 4-hydroxy-6-methylpyridazine-3-carboxylate:

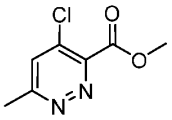


To a stirred solution of methyl 2-diazo-3,5-dioxohexanoate (5.10 g, 14.49 mmol), in t-butylmethyl ether (50 mL) was added tri-n-butylphosphine (3.57 mL, 14.49 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes. After

completion of the reaction, the resulting precipitate was collected and dried under reduced pressure to afford product methyl 4-hydroxy-6-methylpyridazine-3-carboxylate (2.2 g, 12.64 mmol, 87 % yield) as an off white solid.

MS (ESI) calculated for ($C_7H_8N_2O_3$) $(M+1)^+$, 169.06; found, 169.0

Step-5: Synthesis of methyl 4-chloro-6-methylpyridazine-3-carboxylate:



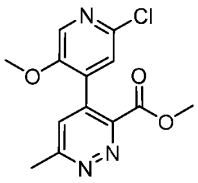
To a solution of methyl 4-hydroxy-6-methylpyridazine-3-carboxylate (2.2 g, 13.08 mmol), in POCl3 (20 mL, 215 mmol) was stirred at 100 °C for 1 hour. After completion of the reaction,

The reaction mixture was cooled to room temperature and excess of POCl3 was distilled out under reduced pressure to afford crude residue. The residue was quenched with saturated sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as yellow gum.

The crude product was pre-absorbed on silica, loaded on the Orochem 40 g snap and eluted at 20-50 % of ethyl acetate in pet ether for 60 minutes with flow rate 30 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford product methyl 4-chloro-6-methylpyridazine-3-carboxylate (1.5 g, 7.99 mmol, 61.1 % yield) as pale yellow solid.

MS (ESI) calculated for ($C_7H_7ClN_2O_2$) $(M+1)^+$, 187.03; found, 187.0

Step-6: Synthesis of methyl 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridazine-3-carboxylate:



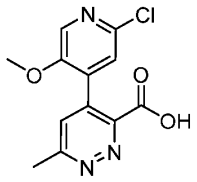
To a stirred solution of methyl 4-chloro-6-methylpyridazine-3-carboxylate (1.5 g, 8.04 mmol) in 1,4-Dioxane (20 mL) were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (2.260 g, 12.06 mmol) and potassium carbonate (3.33 g, 24.12 mmol) at room temperature and the

reaction mixture was degassed with nitrogen for 5 minutes. After degassing, PdCl2(dppf) (0.588 g, 0.804 mmol) was added and the reaction mixture was again degassed with nitrogen for 5 minutes. Then the reaction mixture was stirred at 80 °C for 16 hours. After completion, the reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad and washed with ethyl acetate (100 mL). The filtrate was washed with water (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as brown gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem column (25 g) and eluted at 50-60 % of ethyl acetate in pet ether for 60 minutes with flow rate 30 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridazine-3-carboxylate (1.3 g, 4.37 mmol, 54.3 % yield) as pale yellow solid.

MS (ESI) calculated for ($C_{13}H_{12}ClN_3O_3$) $(M+1)^+$, 294.06; found, 294.0

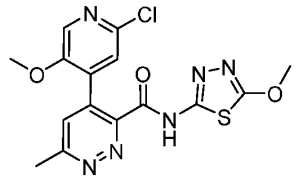
Step-7: Synthesis of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridazine-3-carboxylic acid:



To a stirred solution of methyl 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridazine-3-carboxylate (1.3 g, 4.43 mmol) in tetrahydrofuran (15 mL) was added lithium hydroxide monohydrate (0.929 g, 22.13 mmol) and water (5 mL). Then the reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give crude residue. The resulting residue diluted with water (5 mL), the aqueous layer was acidified with 1.5 N HCl upto pH-6 and precipitated solids were filtered off and dried under reduced pressure to afford the product 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridazine-3-carboxylic acid (700 mg, 2.478 mmol, 56.0 % yield) as an off white solid.

MS (ESI) calculated for ($C_{12}H_{10}ClN_3O_3$) (M+1)+, 280.05; found, 280.0

Step-8: Synthesis of 4-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridazine-3-carboxamide:



To a stirred solution of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridazine-3-carboxylic acid (150 mg, 0.536 mmol), in acetonitrile (4 mL) were added Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (166 mg, 0.590 mmol), 1-methylimidazole (0.128 mL, 1.609 mmol), N,N-Dimethylformamide (DMF) (0.8 mL) and 5-methoxy-1,3,4-thiadiazol-2-amine (70.3 mg, 0.536 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was diluted with water (15 mL) and extracted with 10% MeOH in DCM (2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the product as yellow gum.

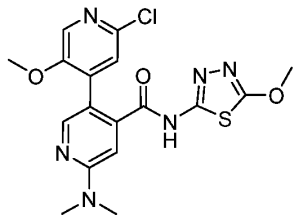
The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem column (12 g) and eluted at 2-3 % MeOH in DCM for 60 minutes with flow rate 25 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to give the product. The product was dissolved in 20% ethanol in acetonitrile (3 mL), concentrated under reduced pressure to afford product to afford 4-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridazine-3-carboxamide (90 mg, 0.227 mmol, 42.4 % yield) as an off white solid.

MS (ESI) calculated for ($C_{15}H_{13}ClN_6O_3S$) $(M+1)^+$, 393.05; found, 393.0.

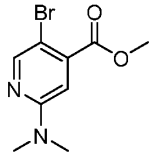
1H-NMR (400 MHz, DMSO-d6): δ 13.21 (s, 1H), 8.24 (s, 1H), 7.89 (s, 1H), 7.68 (s, 1H), 4.10 (s, 3H), 3.67 (s, 3H), 2.78 (s, 3H).

Example 311

2'-chloro-6-(dimethylamino)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide



Step-1: Synthesis of methyl 5-bromo-2-(dimethylamino)isonicotinate:

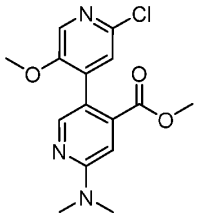


To a stirred suspension of methyl 2-amino-5-bromoisonicotinate (2.5 g, 10.82 mmol) in acetonitrile (75 mL) was added sequentially water (12.50 mL), followed by formaldehyde (24.97 mL, 335 mmol) and acetic acid (6.00 mL, 105 mmol) at 0 °C. The reaction mixture was stirred for 10 mins at same temperature. And then added sodium cyanoborohydride (2.040 g, 32.5 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16h. After completion, the solvent was evaporated and the residue was treated with aqueous sat. sodium bicarbonate solution (15 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated to give crude product as yellow gum.

The crude product was pre-absorbed on silica, loaded on the biotage pre-packed column (110 g) and eluted at 0-100 % of ethyl acetate in Pet ether for 60 minutes with flow rate 40 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 5-bromo-2-(dimethylamino)isonicotinate (1.02 g, 3.93 mmol, 36.3% yield) as yellow solid.

MS (ESI) calculated for ($C_9H_{11}BrN_2O_2$) $(M+1)^+$, 259.01; found, 259.0

Step-2: Synthesis of methyl 2'-chloro-6-(dimethylamino)-5'-methoxy-[3,4'-bipyridine]-4-carboxylate:

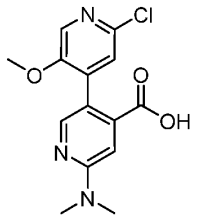


To a stirred solution of methyl methyl 5-bromo-2-(dimethylamino)isonicotinate (860 mg, 3.32 mmol) in 1,4-Dioxane (15 mL) were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (933 mg, 4.98 mmol) and potassium carbonate (1376 mg, 9.96 mmol) at room temperature and degassed with nitrogen for 5 minutes. PdCl2(dppf) (486 mg, 0.664 mmol) was added and the raction mixture was again degassed with nitrogen for 5 minutes. Then the reaction mixture was stirred at 100 °C for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad and washed with ethyl acetate (50 mL). The filtrate was diluted with water (80 mL) and layers were separated. The water layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as brown gum.

The crude product was pre-absorbed on silica, loaded on the biotage pre-packed column (50 g) and eluted at 0-100 % of ethyl acetate in Pet ether for 50 minutes with flow rate 45 ml/min. The pure product was eluated at 30% ethyl acetate in Pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2'-chloro-6-(dimethylamino)-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (590 mg, 1.787 mmol, 53.8 % yield) as yellow solid.

MS (ESI) calculated for ($C_{15}H_{16}ClN_3O_3$) $(M+1)^+$, 322.10; found, 322.0

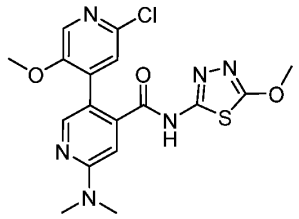
Step-3: Synthesis of 2'-chloro-6-(dimethylamino)-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid:



To a stirred solution of methyl 2'-chloro-6-(dimethylamino)-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (590 mg, 1.834 mmol) in methanol (4 mL), and tetrahydrofuran (4 mL) was added a solution of lithiumhydroxide.monohydrate (115 mg, 2.75 mmol) in water (0.8 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was diluted with water (25 mL), the aqueous was washed with EtOAc (25 mL). The aqueous layer was acidified with sat. aq. solution of citric acid and extracted with ethyl acetate (4 X 25 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2'-chloro-6-(dimethylamino)-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (356 mg, 1.150 mmol, 62.7 % yield) as yellow solid

MS (ESI) calculated for ($C_{14}H_{14}ClN_3O_3$) $(M+1)^+$, 308.08; found, 308.0

Step-4: Synthesis of 2'-chloro-6-(dimethylamino)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of 2'-chloro-6-(dimethylamino)-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (80 mg, 0.260 mmol), in acetonitrile (0.5 mL) and N,N-dimethylformamide (0.10 mL) were added 1-methylimidazole (0.062 mL, 0.780 mmol), Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (146 mg, 0.520 mmol), and 5-methoxy-1,3,4-thiadiazol-2-amine (34.1 mg, 0.260 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hrs. The reaction mixture was quenched with saturated aq. sodium bicarbonate solution (10 mL). and extracted with ethyl acetate (3 x 15 mL). Combined the organic layer was washed with water (15 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product as yellow gum.

The crude product was purified by GRACE revelleris X2 (reverse phase) with the following conditions: (Column: 80 g Grace C18 catriage; Mobile Phase A: 0.1% FA in water, Mobile Phase B: acetonitrile) 0-100% of B in A over 0-50 min. The pure product was eluted at 60%

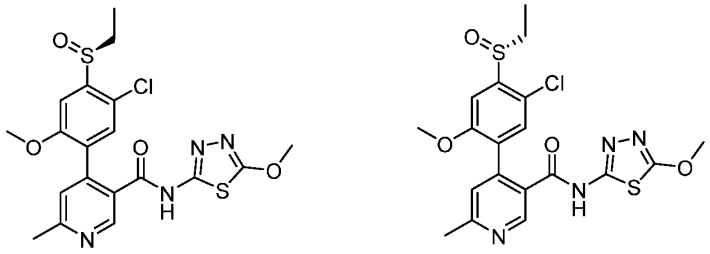
of B in A. The appropriate fractions were combined and evaporated in vacuum to give solid product. The resulted solid freeze was dried to afford 2'-chloro-6-(dimethylamino)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide (86 mg, 0.204 mmol, 78 % yield). The structure was confirmed with X-ray crystallography.

MS (ESI) calculated for ($C_{17}H_{17}ClN_6O_3S$) $(M+1)^+$, 421.09; found, 420.8.

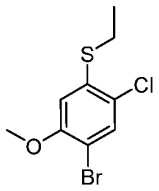
1H-NMR (400 MHz, DMSO-d^6): δ 12.85 (s, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.45 (s, 1H), 6.97 (s, 1H), 4.08 (s, 3H), 3.57 (s, 3H), 3.15 (s, 6H).

Example 312 and 313

(S)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide and (R)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:



Step-1: Synthesis of (4-bromo-2-chloro-5-methoxyphenyl)(ethyl)sulfane:



A solution of 4-bromo-2-chloro-5-methoxyaniline (2.0 g, 8.46 mmol) in 2N HCl (28.2 mL, 42.3 mmol), was heated to 50 °C for 30 min, then the reaction mixture was cooled to 0 °C, and added sodium nitrite (0.642 g, 9.30 mmol) in water (20 mL) dropwise. The resulting reaction mixture was stirred for 40 min at 0°C, then sodium ethanethiolate (1.423 g, 16.91 mmol) in water (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred again for 18h at room temperature. After completion of the reaction. The reaction mixtures was diluted with 10% NaOH aq. solution (50 mL) and extracted with EtOAc (2 x 50 mL). The

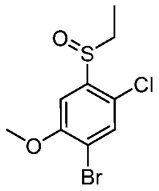
separated organic layer was dried over anhydrous Na2SO4 and concentrated under vacuum to afford crude product as yellow oil.

The crude product was pre-absorbed on silica (using 10 mL DCM, 10 g of silica (60-120 mesh), loaded on the pre-packed Orochem 120 g column and eluted at 0-40 % of ethyl acetate in PET ether with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford (4-bromo-2-chloro-5-methoxyphenyl)(ethyl)sulfane (1.49 g, 3.03 mmol, 35.8 % yield; 57.6% purity by GCMS) as yellow solid.

LCMS calculated for ($C_9H_{10}BrClOS$) $(M)^+$, 279.9; found, (m/z) not ionized

1H-NMR (400 MHz, DMSO-d^6): δ 7.68 (s, 1H), 6.96 (s, 1H), 3.91 (m, 3H), 3.10 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H).

Step-2: Synthesis of 1-bromo-5-chloro-4-(ethylsulfinyl)-2-methoxybenzene:

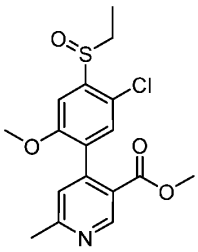


To a stirred solution of (4-bromo-2-chloro-5-methoxyphenyl)(ethyl)sulfane (3.0 g, 10.65 mmol) in Dichloromethane (30 mL) was added *m*CPBA (2.02 g, 11.72 mmol) portion wise at 0 °C, under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 14 h. The reaction mixtures was diluted with 10% sodium bicarbonate aq. solution (20 mL) and extracted with dichloromethane (2 x 50 mL). The organic layer was separated and dried over anhydrous Na2SO4, concentrated under vacuum to afford crude product as brown liquid.

The pre-adsorbed crude product was loaded on the pre-packed Orochem 100 g column and eluted at 0-40 % of ethyl acetate in PET ether with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford 1-bromo-5-chloro-4-(ethylsulfinyl)-2-methoxybenzene (1.3 g , 4.22 mmol, 39.2 % yield) as brown solid.

MS (ESI) calculated for ($C_9H_{10}BrClO_2S$) $(M+1)^+$, 296.93; found, 296.8

Step-3: Synthesis of methyl 4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-6-methylnicotinate:

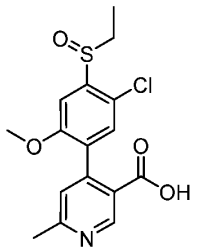


To a stirred solution 1-bromo-5-chloro-4-(ethylsulfinyl)-2-methoxybenzene (1.3 g, 4.37mmol) in dioxane (10 mL) and water (2 mL) were added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (2.069g, 7.86 mmol) and potassium carbonate (1.81g, 13.11 mmol) at room temperature, and the mixture was degassed with nitrogen for 10 minutes. PdCl2(dppf) (0.32g, 0.437 mmol) was then adedd and the reaction mixture was stirred at 90 °C for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, and filtered through celite. The celite bed was washed with ethyl acetate (50 mL). The filtrate was diluted with water (50 mL). The layers were separated. The organic layer washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product as brown liquid.

The pre-adsorbed crude product was loaded on the pre-pack orochem 125 g column and eluted at 5-6 % of methanol in DCM with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-6-methylnicotinate (1.2 g, 3.02 mmol, 69.1%) as a brown gum.

MS (ESI) calculated for ($C_{17}H_{18}ClNO_4S$) $(M+1)^+$, 368.08; found, 367.8.

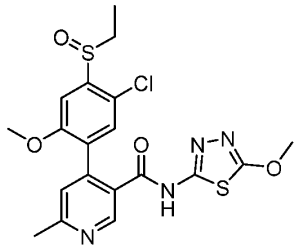
Step-4: Synthesis of 4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-6-methylnicotinic acid:



To a stirred solution of 4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-6-methylnicotinate (1.2g, 3.26 mmol) in a mixture of Tetrahydrofuran (10 mL) and Water (1 mL) was added

lithiumhydroxide monohydrate (0.684g, 16.31 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum. The resulting residue diluted with water (30 mL) and washed with EtOAc (25 mL). The aqueous layer was acidified with 1.5 N HCl upto pH-6 and extracted with 10% MeOH in DCM (2 X 30 mL). The combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-6-methylnicotinic acid (1.1g, 3.10 mmol, 95 % yield) as brown solid. MS (ESI) calculated for ($C_{16}H_{16}ClNO_4S$) $(M+1)^+$, 354.06; found, 354.0.

Step-5: Synthesis of *rac*-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:

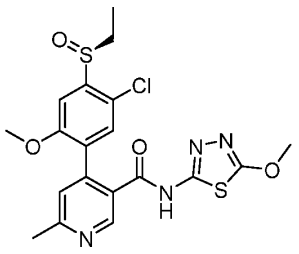


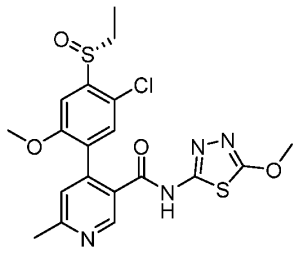
To a stirred 4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-6-methylnicotinic acid (0.6 g, 1.696 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (0.222 g, 1.696 mmol) in Acetonitrile (10 mL) and N, N-Dimethylformamide (DMF) (2.5 mL) were added 1-methylimidazole (0.418g, 5.09mmol), followed by Chloro-N, N,N',N'-tetramethylformamidinium hexafluorophosphate (0.952g, 3.39mmol) at room temperature under nitrogen. The reaction mixture was stirred for 16h. The reaction mixture was quenched with cold water and extracted with 10% methanol in dichloromethane (30 mL X 2). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product as brown liquid.

The pre-adsorbed crude product was loaded on the pre-pack orochem 25 g column and eluted at 6-8 % of methanol in DCM for with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford *rac*-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (0.45g, 0.890 mmol, 52.5%) as an off-white solid.

MS (ESI) calculated for (C19H19ClN4O4S2) $(M+1)^+$, 467.06; found, 467.0.

Step-5: Separation of (S)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide-Isomer-1 and (R)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide-Isomer-2:





rac-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (0.45 g) was purified by Chiral SFC by using the following method: (Column: Lux A1 (250*30)mm, 5µm; Mobile Phase A: CO_2, Mobile Phase B: isopropyl alcohol; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure (bar): 100; Total Flow : 100 g/min; Wave Length: 220 nm; RT1(min): 2.15; RT2(min): 2.92; Sample Solvent: ACN/MeOH-HPLC; Injection Volume: 0.3 mL/Injection; Cycle time: 6.5 min) to afford (S)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (90 mg, 0.192 mmol, 19.96 % yield) as white solid with the first peak on chiral SFC with shorter retention time and (R)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (65 mg, 0.139 mmol, 14.44 % yield) as white solid with the second peak on chiral SFC with longer retention time.

The absolute stereochemistry was not determined.

(S)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

MS (ESI) calculated for ($C_{19}H_{19}ClN_4O_4S_2$) $(M+1)^+$, 467.06; found, 467.0.

1H-NMR (400 MHz, DMSO-d^6): δ 12.82 (brs, 1H), 8.76 (s, 1H), 7.60 (s, 1H), 7.40 (s, 1H), 7.23 (s, 1H), 4.06 (s, 3H), 3.59 (s, 3H), 3.22-3.17 (m, 1H), 2.90-2.85 (m, 1H), 2.58 (s, 3H), 1.12 (t, J = 7.60 Hz, 3H).

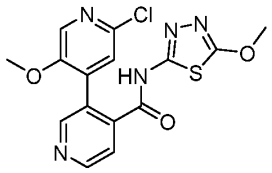
(R)-4-(5-chloro-4-(ethylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

MS (ESI) calculated for ($C_{19}H_{19}ClN_4O_4S_2$) $(M+1)^+$, 467.06; found, 467.0.

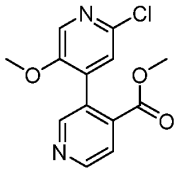
1H-NMR (400 MHz, DMSO-d^6) : δ 12.81 (s, 1H), 8.75 (s, 1H), 7.62 (s, 1H), 7.41 (s, 1H), 7.24 (s, 1H), 4.07 (s, 3H), 3.59 (s, 3H), 3.22-3.16 (m, 1H), 2.92-2.85 (m, 1H), 2.58 (s, 3H), 1.12 (t, J = 7.60 Hz, 3H).

Example 259

2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide.



Step-1: Synthesis of methyl 2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylate:

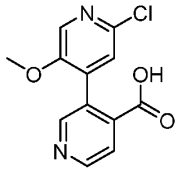


To a stirred solution of methyl 3-bromoisonicotinate (1g, 4.63 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added (2-chloro-5-methoxypyridin-4-yl)boronic acid (1.041 g, 5.55 mmol), potassium carbonate (0.960 g, 6.94 mmol) at room temperature. Then the reaction mixture was degassed by nitrogen gas for 10 minutes. PdCl2(dppf) (3.39 g, 4.63 mmol) was added. The reaction mixture was stirred at 90 °C for 3 hours. After completion, the reaction mixture was cooled to room temperature, filtered through celite bed and washed with ethyl acetate (18 mL). The filtrate was diluted with water (50 ml), layers were separated and aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give crude product as a brown gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (25 g) column and eluted at 0-100 % of ethyl acetate in pet ether with flow rate 25 ml/min. The pure product was eluted at 15-25 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (900 mg, 3.05 mmol, 65.8 % yield) as white solid.

MS (ESI) calculated for ($C_{13}H_{11}ClN_2O_3$) $(M+1)^+$, 279.06; found, 279.0

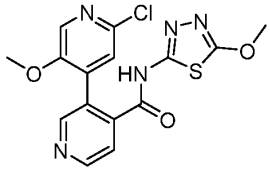
Step-2: Synthesis of 2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid:



To a stirred solution of methyl 2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (900 mg, 3.23 mmol) in a mixture tetrahydrofuran (10 mL), methanol (10 mL) and water (1 mL), was added lithium hydroxide monohydride (155 mg, 6.46 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. After completion, The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (1 mL) and neutralize with 1(N) HCl (8 mL). The precipitate formed was filtered through buchner funnel and washed water (2 mL), dried under vacuum to afford 2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (600 mg, 2.154 mmol, 66.7 % yield) as a white solid.

MS (ESI) calculated for ($C_{12}H_9ClN_2O_3$) $(M+1)^+$, 265.04; found 265.0

Step-3: Synthesis of 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of 2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (150 mg, 0.567 mmol) in acetonitrile (3 mL) and N,N-dimethylformamide (0.6 mL) were added chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (175 mg, 0.623 mmol), 1-methyl-1H-imidazole (140 mg, 1.7 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (74.3 mg, 0.567 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. After completion, The reaction mixture was quenched with ice cold water (10 mL), precipitated solid was filtered through buchner funnel, washed with 1:1 acetonitrile and water (2 mL), dried under vacuum to give crude product as white solid.

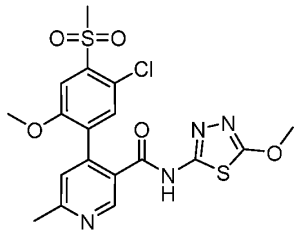
The crude product was purified by GRACE revelleris X2 (reverse phase) with the following conditions: (Column: 100 g Grace C18 catriage; Mobile Phase A: 0.1% formic acid in water, Mobile Phase B: acetonitrile) 0-100% of B in A for 40 minutes with flow rate 18 mL/min. The appropriate fractions were combined and evaporated in vacuum to afford 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide (75 mg, 0.197 mmol, 34.8 % yield) as white solid.

MS (ESI) calculated for ($C_{15}H_{12}ClN_5O_3S$) $(M+1)^+$, 378.05; found, 378.0

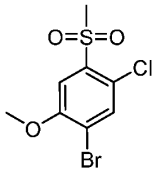
1H-NMR (400 MHz, DMSO-d^6): δ 13.05 (s, 1H), 8.84 (d, J = 4.80 Hz, 1H), 8.72 (s, 1H), 8.16 (s, 1H), 7.76 (d, J = 4.80 Hz, 1H), 7.61 (s, 1H), 4.08 (s, 3H), 3.62 (s, 3H).

Example 272

4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



Step-1: Synthesis of 1-bromo-5-chloro-2-methoxy-4-(methylsulfonyl)benzene:

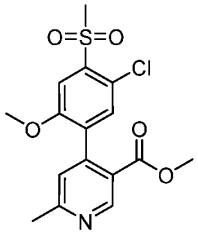


To a stirred solution of (4-bromo-2-chloro-5-methoxyphenyl)(methyl)sulfane (1.1 g, 4.11 mmol) in Dichloromethane (5 mL) was added 3-chloroperbenzoic acid (*m*CPBA) (1.774 g, 10.28 mmol) portion wise at 0 °C, under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction mixtures was diluted with 10% Na2CO3 aq. solution (25 mL) and extracted with ethyl acetate (2 x 25 mL), washed with brine. The organic layer was separated and dried over anhydrous sodium sulfate, concentrated under vacuum to afford 1-bromo-5-chloro-2-methoxy-4-(methylsulfonyl)benzene (1.17 g, 3.91 mmol, 95% yield) as yellow solid.

MS (ESI) calculated for ($C_8H_8BrClO_3S$) $(M+1)^+$, 298.92; found, No ionization

1H-NMR (400 MHz, DMSO-d^6): δ 8.08 (s, 1H), 7.58 (s, 1H), 3.97 (s, 3H), 3.38 (s, 3H).

Step-2: Synthesis of methyl 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-6-methylnicotinate:

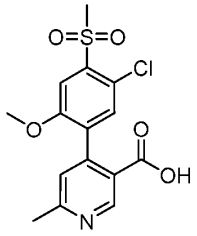


To a stirred solution of 1-bromo-5-chloro-2-methoxy-4-(methylsulfonyl)benzene (500 mg, 1.669 mmol) in 1,4-dioxane (5 mL) and water (1 mL) were added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (527 mg, 2.003 mmol) and potassium carbonate (692 mg, 5.01 mmol) at room temperature and degassed with nitrogen for 10 minutes. To the resulting reaction mixture was added PdCl2(dppf) (122 mg, 0.167 mmol). The reaction mixture was stirred at 90 °C for 16 hours. After completion, the reaction mixture was filtered through celite bed and washed with Ethyl acetate (125 mL). The filtrate was washed with water (100 mL) and brine solution (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product as a brown liquid.

The crude product was pre-absorbed on silica, loaded on the pre-pack orochem 25 g column and eluted at 0-100 % of ethyl acetate in pet ether with flow rate 25 ml/min. The pure product was eluted at 44% of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-6-methylnicotinate (240 mg, 0.6 mmol) as a yellow oil.

MS (ESI) calculated for ($C_{16}H_{16}ClNO_5S$) $(M+1)^+$, 370.05; found, 370.0

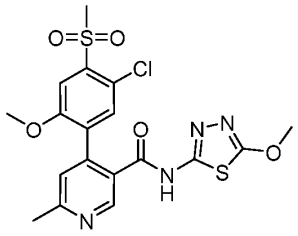
Step-3: Synthesis of 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-6-methylnicotinic acid:



To a stirred solution of methyl 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-6-methylnicotinate (240 mg, 0.649 mmol) in a mixture of Tetrahydrofuran (4 mL), methanol (1.3 mL) and Water (1.3 mL) was added lithium hydroxide (46.6 mg, 1.947 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was concentrated under vacuum. The resulting residue diluted with water (20 mL) and washed with dichloromethane (2 x 30 mL). The aqueous layer was acidified with saturated solution of citric acid up to pH-6 and extracted with ethyl acetate (2 x 40 mL). The combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-6-methylnicotinic acid (126 mg, 0.346 mmol, 53.4% yield) as off-white solid.

MS (ESI) calculated for ($C_{15}H_{14}ClNO_5S$) $(M+1)^+$, 356.04; found, 356.0

Step-4: Synthesis of 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.



To a stirred solution of 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-6-methylnicotinic acid (50 mg, 0.141 mmol), in acetonitrile (2 mL) and N,N-Dimethylformamide (0.4 mL) were added 1-methyl-1H-imidazole (0.045 mL, 0.562 mmol), chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (59.1 mg, 0.211 mmol), and 5-methoxy-1,3,4-thiadiazol-2-amine (18.43 mg, 0.141 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion the reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with

ethyl acetate (2 x 5 mL). The combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product.

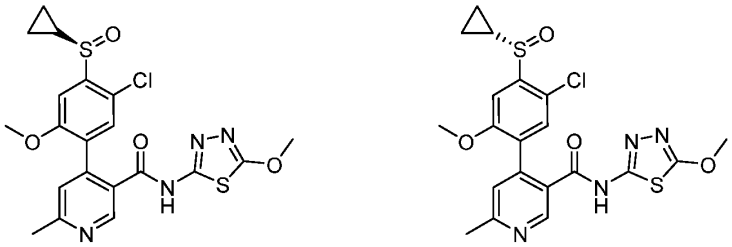
The crude product was pre-absorbed on silica, loaded on the pre-pack orochem 12 g column and eluted at 0-10 % of methanol in dichloromethane with flow rate 20 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford 4-(5-chloro-2-methoxy-4-(methylsulfonyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (25 mg, 0.053 mmol, 37.8 % yield) as off white solid.

MS (ESI) calculated for ($C_{18}H_{17}ClN_4O_5S_2$) $(M+1)^+$, 469.04; found, 469.1

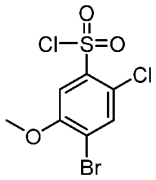
1H-NMR (400 MHz, DMSO-d^6): δ 12.93 (s, 1H), 8.79 (s, 1H), 7.77 (s, 1H), 7.50 (s, 1H), 7.42 (s, 1H), 4.08 (s, 3H), 3.61 (s, 3H), 3.45 (s, 3H), 2.59 (s, 3H).

Example 321 and 318

(R)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide and (S)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.



Step-1: Synthesis of 4-bromo-2-chloro-5-methoxybenzenesulfonyl chloride:



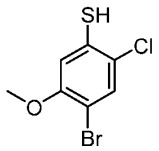
Thionyl chloride (6.17 mL, 85 mmol) was added to Water (30 mL) at -5 °C followed by copper(I) chloride (0.042 g, 0.423 mmol) and resulting reaction mixture was stirred at room temperature for 5 hours. In a separate flask, a 4-bromo-2-chloro-5-methoxyaniline (2.0 g, 8.46 mmol) in acetonitrile (20 mL) was added HCl (12 M) (1.409 mL, 16.91 mmol) dropwise at 0 °C, The mixture was stirred at 0 °C for 10 minutes followed by addition of sodium

nitrite (0.875 g, 12.69 mmol) in Water (15 mL) dropwise 0 °C and stirred for 1 hour at same temperature. After 1 hour, Diazonium salt was added to the thionyl chloride solution at 0 °C and the resulting reaction mixture was stirred at 0 °C for 1 hour. After completion, the reaction mixture was diluted with dichloromethane (100 mL). The layers were separated and aqueous layer was extracted with dichloromethane (100 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 4-bromo-2-chloro-5-methoxybenzenesulfonyl chloride (2.7 g) as a red gum. The crude was forwarded for next step without purification.

MS (ESI) calculated for ($C_7H_5BrCl_2O_3S$) $(M+1)^+$, 318.86; found, No ionization

1H-NMR (400 MHz, DMSO-d^6): δ 7.60 (s, 1H), 7.55 (s, 1H), 3.85 (s, 3H).

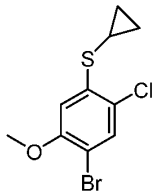
Step-2: Synthesis of 4-bromo-2-chloro-5-methoxybenzenethiol:



To a stirred solution of 4-bromo-2-chloro-5-methoxybenzenesulfonyl chloride (2.70 g, 8.44 mmol) in toluene (30 mL) was added triphenylphosphine (6.64 g, 25.3 mmol). The resulting reaction mixture was stirred at 110 °C for 30 minutes. After 30 minutes, reaction mixture was allowed to cool to 60 °C , and water (6 mL) was added. The resulted mixture was stirred at 60 °C for additional 30 minutes. After completion, The reaction mixture was allowed to cool to room temperature, basified with 20% sodium hydroxide solution (25 mL). The resulted mixture was washed with toluene (100 mL). The aqueous layer was acidified with 1.5 N HCl to pH 2 and extracted with dichloromethane (2 x 50 mL). The combined dichloromethane layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 4-bromo-2-chloro-5-methoxybenzenethiol (1.10 g, 3.28 mmol, 38.8 % yield; LCMS purity: 75.5%) as off-white solid.

MS (ESI) calculated for ($C_7H_6BrClOS$) $(M-1)^-$, 252.89; found, 252.8

Step-3: Synthesis of (4-bromo-2-chloro-5-methoxyphenyl)(cyclopropyl)sulfane:

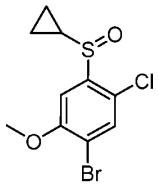


To a stirred solution of 4-bromo-2-chloro-5-methoxybenzenethiol (1.1 g, 3.28 mmol) in 1,2-Dichloroethane (20 mL), was added cyclopropylboronic acid (0.422 g, 4.92 mmol), 2,2'-bipyridine (0.512 g, 3.28 mmol) and copper (II) acetate (0.595 g, 3.28 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 16 hours. After completion, the reaction mixture was cooled to room temperature, quenched with water (30 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give crude product as a black gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (50 g) column and eluted at 0-100 % of ethyl acetate in pet ether over 30 minutes with flow rate 20 ml/min. The pure product was eluted at 10% of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford (4-bromo-2-chloro-5-methoxyphenyl)(cyclopropyl)sulfane (1.6 g, 5.41 mmol, 165 % yield) as off white solid.

MS (ESI) calculated for ($C_{10}H_{10}BrClOS$) $(M)^+$, 293.9; found, GCMS m/z 293.9

Step-4: Synthesis of 1-bromo-5-chloro-4-(cyclopropylsulfinyl)-2-methoxybenzene:



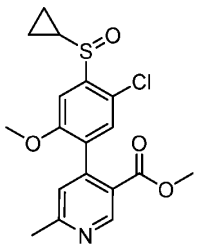
A solution of (4-bromo-2-chloro-5-methoxyphenyl)(cyclopropyl)sulfane (1.17 g, 3.98 mmol) in dichloromethane (20 mL), was cooled to 0 °C then meta-chloroperoxybenzoic acid (*m*-CPBA) (0.688 g, 3.98 mmol) was added portion wise at 0 °C . The reaction mixture was stirred for 1 hours at room temperature. After completion, the reaction mixture was quenched with sat. sodium bicarbonate solution (20 mL) and extracted with dichloromethane (2 x 50

mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under vacuum to afford crude product as colorless gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (50 g) column and eluted at 0-100 % of ethyl acetate in pet ether over 50 minutes with flow rate 20 ml/min. The pure product was eluted at 80 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford 1-bromo-5-chloro-4-(cyclopropylsulfinyl)-2-methoxybenzene (1.2 g, 3.71 mmol, 93 % yield) as off white solid.

MS (ESI) calculated for ($C_{10}H_{10}BrClO_2S$) $(M+1)^+$, 308.94; found, 309.0

Step-5: Synthesis of methyl 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-6-methylnicotinate:

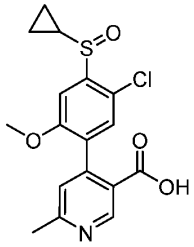


To a stirred solution of 1-bromo-5-chloro-4-(cyclopropylsulfinyl)-2-methoxybenzene (1.0 g, 3.23 mmol) in 1,4-dioxane (10 mL) and water (4 mL) was added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (1.530 g, 5.81 mmol), potassium carbonate (1.339 g, 9.69 mmol) at room temperature. Then the reaction mixture was degassed by nitrogen gas for 10 minutes. PdCl2(dppf) (0.236 g, 0.323 mmol) was added. The reaction mixture was stirred at 90 °C for 16 hours. After completion, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give crude product as a black gum.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (50 g) column and eluted at 0-100 % of ethyl acetate in pet ether over 50 minutes with flow rate 30 ml/min. The pure product was eluted at 80 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford product methyl 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-6-methylnicotinate (0.8 g, 2.027 mmol, 62.8 % yield) as off-white solid.

MS (ESI) calculated for ($C_{18}H_{18}ClNO_4S$) $(M+1)^+$, 380.08; found, 380.0

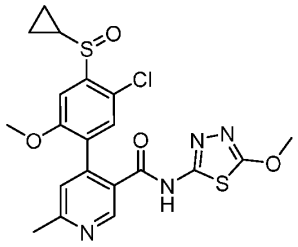
Step-6: Synthesis of 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-6-methylnicotinic acid:



To a stirred solution of methyl 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-6-methylnicotinate (0.8 g, 2.106 mmol) in a mixture methanol (15 mL), and water (5 mL), was added lithium hydroxide monohydrate (0.252 g, 10.53 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and neutralized with 1.5(N) HCl. The aqueous layer was purified by GRACE revelleris X2 (reverse phase) with the following conditions: (Column: 50 g Grace C18 catriage; Mobile Phase A: 0.1% formic acid in water, Mobile Phase B: acetonitrile) 0-100% of B in A for 30 minutes with flow rate 20 mL/min, the pure product was eluted at 55% of B in A. The appropriate fractions were combined and evaporated in vacuum to afford 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-6-methylnicotinic acid (0.7 g, 1.907 mmol, 91 % yield) as off-white solid.

MS (ESI) calculated for ($C_{17}H_{16}ClNO_4S$) $(M+1)^+$, 366.05; found 366.0

Step-7: Synthesis of 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:

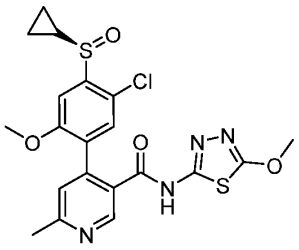


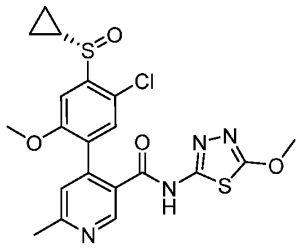
To a stirred solution of 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-6-methylnicotinic acid (150 mg, 0.410 mmol) in acetonitrile (5 mL) and N,N-dimethylformamide (1 mL) were added, 1-methyl-1H-imidazole (0.131 mL, 1.640 mmol), chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (173 mg, 0.615 mmol) and 5-methoxy-1,3,4-thiadiazol-2-amine (64.5 mg, 0.492 mmol) at room temperature. stirred at room temperature for 16 hours. After completion The reaction mixture was quenched with water (2 mL) and purified by GRACE revelleris X2 (reverse phase) with the following conditions: (Column: 50 g Grace C18 catriage; Mobile Phase A: 0.1% formic acid in water, Mobile Phase B: acetonitrile) 0-100% of B in A with flow rate 25 mL/min, the pure product was eluted at 40% of B in A. The appropriate fractions were combined and evaporated in vacuum to afford 4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (125 mg, 0.258 mmol, 62.9 % yield) as off-white solid .

MS (ESI) calculated for ($C_{20}H_{19}ClN_4O_4S_2$) $(M+1)^+$, 479.06; found, 479.0

1H-NMR (400 MHz, DMSO-d^6): δ 12.83 (s, 1H), 8.74 (s, 1H), 7.63 (s, 1H), 7.43 (s, 1H), 7.20 (s, 1H), 4.07 (s, 3H), 3.59 (s, 3H), 2.74-2.67 (m, 1H), 2.58 (s, 3H), 1.08-0.95 (m, 3H), 0.80-0.72 (m, 1H).

Step 8: Chiral separation of (R)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide and (S)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:





4-(5-Chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (160 mg) was separated by prep-chiral SFC with the following conditions: (Column: Lux Amylose-1 (250*30)mm, 5µm; Mobile Phase A: CO_2, Mobile Phase B: Methanol; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.16; RT2(min): 3.52; (Sample

Solvent: 3 mL MeOH-HPLC; Injection Volume: 0.4 mL/Injection; Cycle time: 9 min) to afford (R)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (70 mg, 0.146 mmol, 43.7 % yield) as off-white solid with the first peak on chiral SFC with shorter retention time and (S)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (65 mg, 0.134 mmol, 40.1 % yield) as off-white solid with the second peak on chiral SFC with longer retention time.

The absolute stereochemistry was not determined.

(R)-4-(5-chloro-4-(cyclopropylsulfinyl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

MS (ESI) calculated for ($C_{20}H_{19}ClN_4O_4S_2$) $(M+1)^+$, 479.06; found, 478.8

1H-NMR (400 MHz, DMSO-d^6): δ 12.84 (s, 1H), 8.76 (s, 1H), 7.61 (s, 1H), 7.41 (s, 1H), 7.20 (s, 1H), 4.06 (s, 3H), 3.59 (s, 3H), 2.74-2.67 (m, 1H), 2.58 (s, 3H), 1.08-0.95 (m, 3H), 0.80-0.72 (m, 1H).

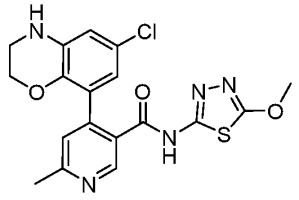
(S)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

MS (ESI) calculated for ($C_{20}H_{19}ClN_4O_4S_2$) $(M-1)^-$, 477.04; found, 477.0

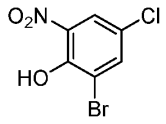
1H-NMR (400 MHz, DMSO-d^6): δ 12.83 (s, 1H), 8.75 (s, 1H), 7.63 (s, 1H), 7.43 (s, 1H), 7.20 (s, 1H), 4.07 (s, 3H), 3.59 (s, 3H), 2.74-2.67 (m, 1H), 2.58 (s, 3H), 1.08-0.94 (m, 3H), 0.80-0.71 (m, 1H).

Example 320

4-(6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.



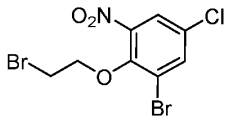
Step-1: Synthesis of 2-bromo-4-chloro-6-nitrophenol:



A solution of 4-chloro-2-nitrophenol (10 g, 57.6 mmol) in Acetic Acid (80 mL) was cooled to 5-10 °C and bromine (3.56 mL, 69.1 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes at 10 °C and then for 16 hour at room temperature. After completion, The reaction mixture was quenched with ice cold water (220 mL) and extracted with dichloromethane (2 X 30 mL). The combined organic phase was washed with 10% sodium bicarbonate solution (100 mL), water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-bromo-4-chloro-6-nitrophenol (14 g, 49.1 mmol, 85 % yield) as yellow solid.

MS (ESI) calculated for ($C_6H_3BrClNO_3$) $(M-1)^-$, 249.89; found, 249.8

Step-2: Synthesis of 1-bromo-2-(2-bromoethoxy)-5-chloro-3-nitrobenzene:

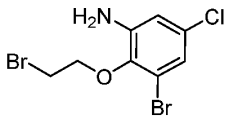


To a stirred solution of 2-bromo-4-chloro-6-nitrophenol (14 g, 49.1 mmol) in N,N-dimethylformamide (100 mL) was added portion wise potassium carbonate (20.35 g, 147 mmol), followed by 1,2-dibromoethane (21.15 mL, 245 mmol). The reaction mixture was stirred at 80 °C for 5 hours. After completion, the reaction mixture was quenched with ice cold water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude product as brown solid.

The crude product was pre-absorbed on silica, loaded on pre-packed Orochem (125 g) column and eluted at 0-10 % of ethyl acetate in pet ether with flow rate 20 ml/min. The pure product was eluted at 4-6 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford 1-bromo-2-(2-bromoethoxy)-5-chloro-3-nitrobenzene (14.2 g, 36.7 mmol, 74.8 % yield) as yellow solid.

MS (ESI) calculated for ($C_8H_6Br_2ClNO_3$) $(M+1)^+$, 329.6; found, 329.8

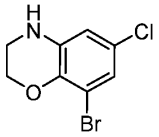
Step-3: Synthesis of 3-bromo-2-(2-bromoethoxy)-5-chloroaniline:



To a stirred solution of 1-bromo-2-(2-bromoethoxy)-5-chloro-3-nitrobenzene (14 g, 39.0 mmol)) in acetic acid (100 mL) was added iron (8.70 g, 156 mmol) portion wise at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, The reaction mixture was diluted with ethyl acetate (400 mL) and filtered through celite. The celite bed was washed with ethyl acetate (100 mL). The filtrate was diluted with water (200 mL) and layers were separated. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 3-bromo-2-(2-bromoethoxy)-5-chloroaniline (12.1 g, 29.7 mmol, 76 % yield; LCMS purity: 80.8%) as brown Liquid.

MS (ESI) calculated for ($C_8H_8Br_2ClNO$) $(M)^+$, 329.42; found, 329.8

Step-4: Synthesis of 8-bromo-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine:

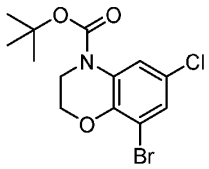


To a mixture of 3-bromo-2-(2-bromoethoxy)-5-chloroaniline (12 g, 29.4 mmol) in N,N-Dimethylformamide (120 mL) was added potassium carbonate (18.31 g, 132 mmol) portion wise at room temperature. The reaction was stirred at 80 °C for 3 hours. After completion, the reaction mixture was quenched with ice cold water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude product as brown liquid.

The crude product was pre-absorbed on silica, loaded on pre-packed Orochem (125 g) column and eluted at 0-10 % of ethyl acetate in pet ether with flow rate 20 ml/min. The pure product was eluted at 15-18% of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford 8-bromo-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine (7.1 g, 28.3 mmol, 96 % yield) as brown gum.

MS (ESI) calculated for ($C_8H_7BrClNO$) $(M+2)^+$, 250.52; found, 250.0

Step-5: Synthesis of tert-butyl 8-bromo-6-chloro-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate:



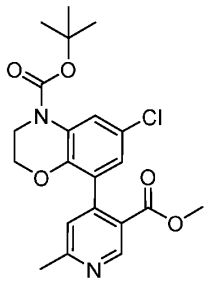
To a stirred solution of 8-bromo-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine (3 g, 12.07 mmol) in tetrahydrofuran (45 mL) were added DMAP (0.737 g, 6.04 mmol) and Boc-anhydride (3.36 mL, 14.49 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was quenched with ice cold water (50 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product as brown liquid.

The crude product was pre-absorbed on silica, loaded on pre-packed Orochem (125 g) column and eluted at 0-50 % of ethyl acetate in pet ether with flow rate 20 ml/min. The pure product was eluted at 8-10% of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford tert-butyl 8-bromo-6-chloro-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (3.1 g, 8.87 mmol, 73.5 % yield) as off-white solid.

MS (ESI) calculated for ($C_{13}H_{15}BrClNO_3$) $(M-100)^-$, 248; found, 247.8

1H-NMR (400 MHz, DMSO-d^6): δ 7.90 (brs, 1H), 7.41 (d, J = 2.4 Hz, 1H), 4.33 (t, J = 4.4 Hz 2H), 3.83 (t, J = 4.4 Hz 2H), 1.50 (s, 9H).

Step-6: Synthesis of *tert*-butyl 6-chloro-8-(5-(methoxycarbonyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate:

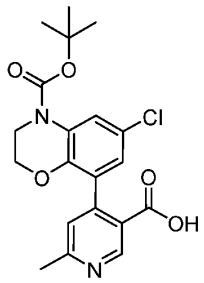


To a stirred solution of tert-butyl 8-bromo-6-chloro-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (1.5 g, 4.30 mmol) in 1,4-dioxane (10 mL) and water (0.5 mL), were added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (1.698 g, 6.45 mmol), potassium carbonate (1.784 g, 12.91 mmol) at room temperature. Then the reaction mixture was degassed by nitrogen gas for 5 minutes. PdCl2(dppf) (0.315 g, 0.430 mmol) was added. The reaction mixture was stirred at 90 °C for 16 hours. After completion, the reaction mixture was cooled to room temperature, filtered through celite bed and washed with ethyl acetate (50 mL). The filtrate was diluted with water (50 ml), layers were separated and aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give crude product as a brown liquid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (125 g) column and eluted at 0-100 % of ethyl acetate in pet ether with flow rate 20 ml/min. The pure product was eluted at 42% of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford *tert*-butyl 6-chloro-8-(5-(methoxycarbonyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (1.7 g, 3.99 mmol, 93 % yield) as yellow gum.

MS (ESI) calculated for ($C_{21}H_{23}ClN_2O_5$) $(M+1)^+$, 419.14; found, 419.0

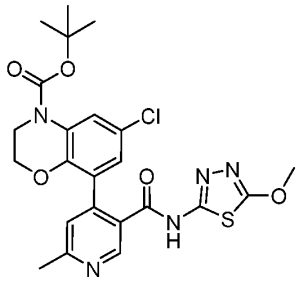
Step-7: Synthesis of 4-(4-(tert-butoxycarbonyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinic acid:



To a stirred solution of tert-butyl 6-chloro-8-(5-(methoxycarbonyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (1.7 g, 4.06 mmol) in a mixture tetrahydrofuran (20 mL), and water (6.67 mL), was added lithium hydroxide monohydrate (0.852 g, 20.29 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL) and neutralized with 1.5(N) HCl (15 mL) and extracted with 10% methanol in dichloromethane (2 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford 4-(4-(tert-butoxycarbonyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinic acid (1.2 g, 2.87 mmol, 70.7 % yield) as a yellow solid.

MS (ESI) calculated for ($C_{20}H_{21}ClN_2O_5$) $(M+1)^+$, 405.12; found 405.0

Step-8: Synthesis of tert-butyl 6-chloro-8-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate:



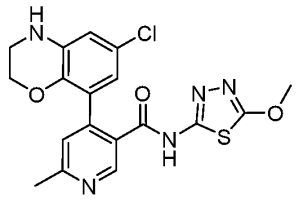
To a stirred solution of 4-(4-(tert-butoxycarbonyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinic acid (300 mg, 0.741 mmol) in acetonitrile (3 mL) and N,N-dimethylformamide (075 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (97 mg, 0.741 mmol), 1-methyl-1H-imidazole (0.177 mL, 2.223 mmol) and chloro-

N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (312 mg, 1.112 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was quenched with ice cold water (50 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with water (40 mL), brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product as brown liquid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (25 g) column and eluted at 0-10 % of methanol in dichloromethane with flow rate 30 ml/min. The pure product was eluted at 6-8% of methanol in dichloromethane. The appropriate fractions were collected and concentrated under reduced pressure to afford tert-butyl 6-chloro-8-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (110 mg, 0.202 mmol, 27.3 % yield) as off-white solid

MS (ESI) calculated for ($C_{23}H_{24}ClN_5O_5S$) $(M+1)^+$, 518.13; found, 518.0

Step-9: 4-(6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:



To a stirred solution of tert-butyl 6-chloro-8-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (110 mg, 0.212 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.082 mL, 1.062 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 13 hours. After completion, The reaction mixture was quenched with ice cold water (20 mL) at room temperature and extracted with 10% methanol in dihloromethane (2 x 20 mL). The combined organic layer was washed with water (20 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product as brown solid.

The crude product was purified by Isolera biotage (reverse phase) with the following conditions: (Column: 30 g Grace C18 Redisep Gold; Mobile Phase A: water, Mobile Phase

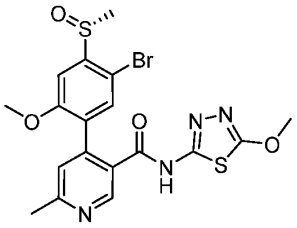
B: acetonitrile; neutral method) 0-100% of B in A for 30 minutes with flow rate 25 mL/min. The appropriate fractions were combined and evaporated in vacuum to afford 4-(6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (51 mg, 0.118 mmol, 55.6 % yield) as white solid .

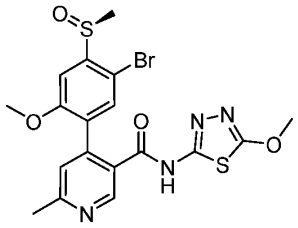
MS (ESI) calculated for ($C_{18}H_{16}ClN_5O_3S$) $(M+1)^+$, 418.08; found, 418.0

1H-NMR (400 MHz, DMSO-d^6): δ 12.75 (s, 1H), 8.66 (s, 1H), 7.33 (s, 1H), 6.62 (d, J = 2.4 Hz 1H), 6.56 (d, J = 2.4 Hz 1H), 6.19 (brs, 1H), 4.08 (s, 3H), 3.76 (brs, 2H), 3.14 (t, J = 4.00 Hz, 2H), 2.56 (s, 3H).

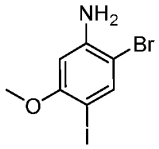
Example 319 and 322

(R)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide and (S)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide.





Step-1: Synthesis of 2-bromo-4-iodo-5-methoxyaniline:



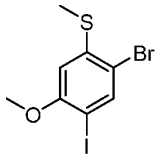
To a mixture of 2-bromo-5-methoxyaniline (2.5 g, 12.37 mmol) and Calcium carbonate (1.610 g, 16.09 mmol) in dichloromethane (50 mL) and methanol (25 mL) was added tetramethylammonium dichloroiodate(I) (3.70 g, 13.61 mmol) in one portion at room temperature. The reaction was stirred for 1 hour at room temperature. After completion, the reaction mixture was mixed with another batch (0.5 g) and diluted with dichloromethane (500 mL) washed with water (2 x 200 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product as black solid.

The crude product was pre-absorbed on silica, loaded on pre-packed Orochem (120 g) column and eluted at 0-10 % of ethyl acetate in pet ether with flow rate 50 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford product 2-bromo-4-iodo-5-methoxyaniline (4g, 11.71 mmol, 95% yield) as brown solid.

MS (ESI) calculated for (C_7H_7BrINO) $(M+2)^+$, 329.89; found, 329.8

1H-NMR (400 MHz, DMSO-d^6): δ 7.56 (s, 1H), 6.49 (s, 1H), 5.51 (brs, 2H), 3.72 (s, 3H).

Step-2: Synthesis of (2-bromo-4-iodo-5-methoxyphenyl)(methyl)sulfane:

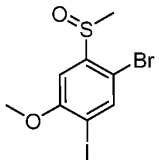


To a stirred solution of 2-bromo-4-iodo-5-methoxyaniline (4g, 12.20 mmol) in 2N HCl hydrogen chloride (48.8 mL, 98 mmol), the reaction mixture was heated to 50 °C for 30 minutes, then the reaction mixture was cooled to 0 °C, was added sodium nitrite (0.926 g, 13.42 mmol) in water (40 mL) drop wise and stirred for 40 minutes at 0 °C, then sodium thiomethoxide (1.710 g, 24.39 mmol) in water (40 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 18 hours. After completion, the reaction mixture was diluted in ethyl acetate (200 mL) and layers were separated. The organic layer dried over anhydrous sodium sulfate and concentrated under vacuum to afford crude product as dark brown oil.

The crude product was pre-absorbed on silica, loaded on pre-packed Orochem (120 g) column and eluted at 0-100 % of ethyl acetate in pet ether with flow rate 50 ml/min. The pure product was eluted at 15-20 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford product (2-bromo-4-iodo-5-methoxyphenyl)(methyl)sulfane (3g, 7.37 mmol, 60.4 % yield) as brown solid.

MS (ESI) calculated for (C_8H_8BrIOS) $(M)^+$, 357.85; found, GCMS m/z 357.8

Step-3: Synthesis of 1-bromo-5-iodo-4-methoxy-2-(methylsulfinyl)benzene:

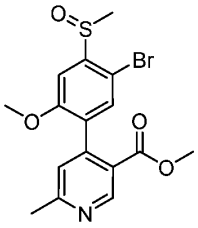


A solution of (2-bromo-4-iodo-5-methoxyphenyl)(methyl)sulfane (3g, 8.36 mmol) in dichloromethane (30 mL), was cooled to 0 °C then meta-chloroperoxybenzoic acid (*m*-CPBA) (1.442 g, 8.36 mmol) was added portion wise at 0 °C . The reaction mixture was stirred for 16 hours at room temperature. After completion, the reaction mixture was quenched with sat. sodium bicarbonate solution (50 mL) and extracted with dichloromethane (2 x 100 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under vacuum to afford crude product as orange solid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (40 g) column and eluted at 0-100 % of ethyl acetate in pet ether with flow rate 20 ml/min. The pure product was eluted at 45-50 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford product 1-bromo-5-iodo-4-methoxy-2-(methylsulfinyl)benzene (1.25g, 3.12 mmol, 37.3 % yield) as orange solid and starting material was recovered (0.4 g)

MS (ESI) calculated for ($C_8H_8BrIO_2S$) $(M+1)^+$, 374.86; found, 374.8

Step-4: Synthesis of methyl 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate:



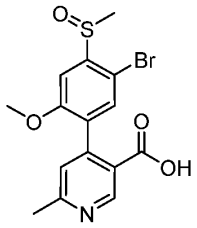
To a stirred solution of 1-bromo-5-iodo-4-methoxy-2-(methylsulfinyl)benzene (600 mg, 1.498 mmol) in 1,4-dioxane (25 mL), was added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylnicotinate (621 mg, 2.246 mmol), potassium carbonate (621 mg, 4.49 mmol) at room temperature. Then the reaction mixture was degassed by nitrogen gas for 10 minutes. PdCl2(dppf) (219 mg, 0.300 mmol) was added. The reaction mixture was stirred at 90 °C for 16 hours. After completion, the reaction mixture was cooled to room temperature, filtered

through celite bed and washed with ethyl acetate (40 mL). The filtrate was diluted with water (40 ml), layers were separated and aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give crude product as a brown liquid.

The crude product was pre-absorbed on silica, loaded on the pre-packed Orochem (50 g) column and eluted at 0-100 % of ethyl acetate in pet ether with flow rate 15 ml/min. The pure product was eluted at 75-80 % of ethyl acetate in pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford product methyl 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate (330 mg, 0.813 mmol, 54.3 % yield) as brown solid.

MS (ESI) calculated for ($C_{16}H_{16}BrNO_4S$) $(M+1)^+$, 398.0; found, 397.8

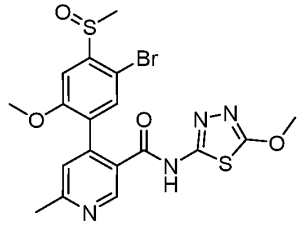
Step-5: Synthesis of 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid:



To a stirred solution of methyl 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinate (330 mg, 0.829 mmol) in a mixture tetrahydrofuran (10 mL), and water (2 mL), was added lithium hydroxide monohydrate (174 mg, 4.14 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10mL) and washed with ethyl acetate (2 x 15 mL). The aqueous layer was neutralized with 1.5(N) HCl (5 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (300 mg, 0.773 mmol, 93 % yield) as a brown solid.

MS (ESI) calculated for ($C_{15}H_{14}BrNO_4S$) $(M+1)^+$, 383.99; found 383.8

Step-6: Synthesis of 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:



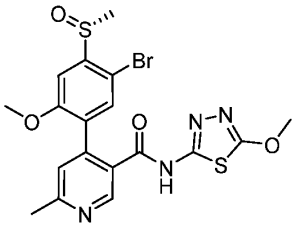
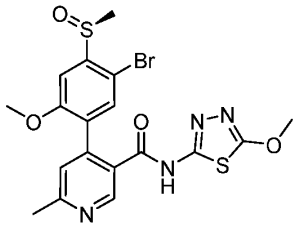
To a stirred solution of 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-6-methylnicotinic acid (70 mg, 0.180 mmol) in acetonitrile (5 mL) and N,N-dimethylformamide (0.5 mL) were added 5-methoxy-1,3,4-thiadiazol-2-amine (28.4 mg, 0.216 mmol), 1-methyl-1H-imidazole (0.043 mL, 0.541 mmol) and chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (76 mg, 0.271 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours. After completion, The reaction mixture was concentrated under reduced pressure. The residue was diluted water (10 ml) and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude product as a brown solid.

The crude product was purified by GRACE revelleris X2 (reverse phase) with the following conditions: (Column: 40 g Grace C18 catriage; Mobile Phase A: 0.1% ammonium bicarbonate in water, Mobile Phase B: acetonitrile) 0-100% of B in A for 30 minutes with flow rate 25 mL/min, the pure product was eluted at 40% of B in A. The appropriate fractions were combined and evaporated in vacuum to afford 4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (70 mg, 0.134 mmol, 74.4 % yield) as white solid .

MS (ESI) calculated for ($C_{18}H_{17}BrN_4O_4S_2$) $(M+2)^+$, 499.0; found, 499.0

1H-NMR (400 MHz, DMSO-d^6): δ 12.84 (s, 1H), 8.75 (s, 1H), 7.73 (s, 1H), 7.41 (s, 1H), 7.34 (s, 1H), 4.07 (s, 3H), 3.60 (s, 3H), 2.85 (s, 3H), 2.58 (s, 3H).

Step 7: Chiral separation of (R)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide and (S)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide:

4-(5-Bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (69 mg) was separated by prep-chiral SFC with the following conditions: (Column: YMC Cellulose SZ (250*30)mm, 5μm; Mobile Phase A: CO_2, Mobile Phase B: Methanol; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.54; RT2(min): 5.52; (Sample Solvent: 2 mL THF/MeOH-HPLC; Injection Volume: 0.5 mL/Injection; Cycle time: 7.5 min) to afford (R)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (30 mg, 0.059 mmol, 44.6 % yield) as white solid with the first peak on chiral SFC with shorter retention time and (S)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (22 mg, 0.043 mmol, 32.6 % yield) as white solid with the second peak on chiral SFC with longer retention time.

The absolute stereochemistry was not determined.

(R)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

MS (ESI) calculated for ($C_{18}H_{17}BrN_4O_4S_2$) $(M+2)^+$, 499.0; found, 499.0

1H-NMR (400 MHz, DMSO-d^6): δ 12.82 (s, 1H), 8.75 (s, 1H), 7.62 (s, 1H), 7.34 (s, 1H), 7.28 (s, 1H), 4.01 (s, 3H), 3.60 (s, 3H), 2.85 (s, 3H), 2.55 (s, 3H).

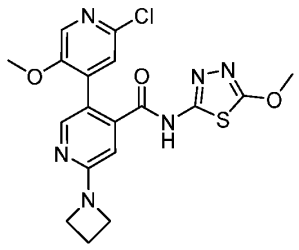
(S)-4-(5-bromo-2-methoxy-4-(methylsulfinyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

MS (ESI) calculated for ($C_{18}H_{17}BrN_4O_4S_2$) $(M+2)^+$, 499.0; found, 499.0

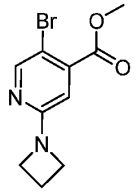
1H-NMR (400 MHz, DMSO-d^6): δ 12.85 (s, 1H), 8.80 (s, 1H), 7.66 (s, 1H), 7.34 (s, 1H), 7.30 (s, 1H), 4.03 (s, 3H), 3.60 (s, 3H), 2.85 (s, 3H), 2.56 (s, 3H).

Example 323

6-(azetidin-1-yl)-2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide



Step-1: Synthesis of methyl 2-(azetidin-1-yl)-5-bromoisonicotinate:

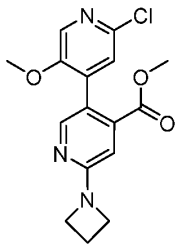


To a stirred solution of methyl 5-bromo-2-chloroisonicotinate (1.5 g, 5.99 mmol) in N,N-dimethylformamide (30 mL) was added sequentially diisopropylethylamine (3.13 mL, 17.97 mmol), followed by azetidine (0.444 mL, 6.59 mmol) at room temperature. The resulting reaction mixture was stirred at 90 °C for 6h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate (2 x 200 mL). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated to give crude product as brown solid.

The crude product was pre-absorbed on silica, loaded on the biotage pre-packed column (40 g) and eluted at 0-100 % of ethyl acetate in Pet ether for 60 minutes with flow rate 25 ml/min. The pure product was eluted at 10-20 % of ethyl acetate in Pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 2-(azetidin-1-yl)-5-bromoisonicotinate (700 mg, 2.350 mmol, 39.2 % yield) as yellow solid.

MS (ESI) calculated for ($C_{10}H_{11}BrN_2O_2$) $(M+1)^+$, 271.01; found, 271.0

Step-2: Synthesis of methyl 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylate:

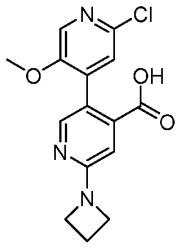


To a stirred solution of methyl 2-(azetidin-1-yl)-5-bromoisonicotinate (100 mg, 0.369 mmol) in 1,4-dioxane (5 mL) and water (1 mL) were added (2-chloro-5-methoxypyridin-4-yl)boronic acid (83 mg, 0.443 mmol) and potassium carbonate (102 mg, 0.738 mmol) at room temperature and degassed with nitrogen for 15 minutes. After 15 minutes to this was added PdCl2(dppf) (27.0 mg, 0.037 mmol). Then the reaction mixture was stirred at 80 °C for 16 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, inorganic solids were filtered through celite pad. The filtrate was concentrated under reduced pressure to afford crude product as brown gum.

The crude product was pre-absorbed on silica, loaded on the biotage pre-packed column (12 g) and eluted at 0-100 % of ethyl acetate in Pet ether for 50 minutes with flow rate 25 ml/min. The pure product was eluated at 5-15% ethyl acetate in Pet ether. The appropriate fractions were collected and concentrated under reduced pressure to afford methyl 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (110 mg, 0.319 mmol, 86 % yield) as off-white solid.

MS (ESI) calculated for ($C_{16}H_{16}ClN_3O_3$) $(M+1)^+$, 334.10; found, 334.0

Step-3: Synthesis of 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid:

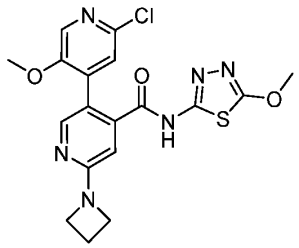


To a stirred solution of methyl 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylate (110 mg, 0.330 mmol) in tetrahydrofuran (5 mL), methanol (1 mL) and water (1

mL) was added lithiumhydroxide monohydrate (55.3 mg, 1.318 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL), the aqueous was washed with ethyl acetate (25 mL). The aqueous layer was acidified with 1.5N HCl and extracted with 10% methanol in dichloromethane (3 X 50 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (45 mg, 0.134 mmol, 40.6 % yield) as off-white solid

MS (ESI) calculated for ($C_{15}H_{14}ClN_3O_3$) $(M+1)^+$, 320.08; found, 320.0

Step-4: Synthesis of 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide:



To a stirred solution of 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-[3,4'-bipyridine]-4-carboxylic acid (45 mg, 0.141 mmol), in acetonitrile (3 mL) and N,N-dimethylformamide (1 mL) were added 1-methyl-1H-imidazole (46.2 mg, 0.563 mmol), 5-methoxy-1,3,4-thiadiazol-2-amine (22.15 mg, 0.169 mmol) and chloro-N,N,N′,N′-tetramethylformamidiniumhexafluorophosphate (59.2 mg, 0.211 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with cold water and concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). Combined organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford crude product as orange solid.

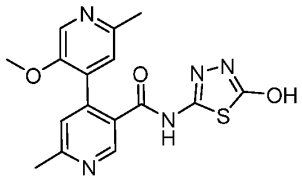
The crude product was pre-absorbed on silica, loaded on the biotage pre-packed column (10 g) and eluted at 0-10 % of methanol in dichloromethane for 50 minutes with flow rate 25 ml/min. The appropriate fractions were collected and concentrated under reduced pressure to afford 6-(azetidin-1-yl)-2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide (20.22 mg, 0.046 mmol, 32.8 % yield) as off-white solid.

MS (ESI) calculated for ($C_{18}H_{17}ClN_6O_3S$) $(M+1)^+$, 433.09; found, 433.0

1H-NMR (400 MHz, DMSO-d^6): δ 12.87 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.42 (s, 1H), 6.70 (s, 1H), 4.13-4.03 (m, 7H), 3.57 (s, 3H), 2.44-2.36 (m, 2H).

Example 325

N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide

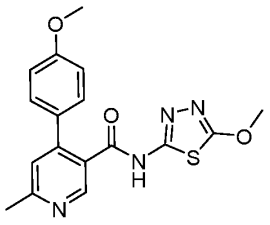


N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (5 g, 10.35 mmol, Example 8) was dissolved in 6N HCl (20.71 ml, 124 mmol) and stirred at room temperature for 20 minutes, after which time LCMS (Waters CSH C18 column (30mm x 2.1mm, 1.7 micron), 0.1% TFA in CH_3CN/H_2O, 2 minutes) indicated that the reaction had only partially progressed. After two hours, LCMS showed further progression of the reaction, but the rate was slow, so 2 mL of concentrated HCl was added and the mixture was stirred overnight, after which time the reaction had progressed further but was not complete. An additional aliquot of concentrated HCl (20.71 ml, 248 mmol) and 12g of sodium chloride were added and stirred for 30 minutes, after which time cleavage of the benzyl ether was complete. The benzyl chloride by-product, 5-chloro-2-(chloromethyl)pyridine, that formed during the reaction was converted in-situ to the benzylamine, (5-chloropyridin-2-yl)methanamine, because this benzylamine compound is easier to separate from the product than the benzyl chloride. To do this, ammonia, 28-30% (35.0 ml, 518 mmol) was added and stirred for two hours, after which time LCMS indicated that all of the benzyl chloride had been converted to the benzylamine. The pH was adjusted to between 6 and 7, first with concentrated HCl and then with citric acid, which caused the product to precipitate out of solution. The suspension was stirred vigorously and occasionally sonicated until all of the chunks broke up, so that the suspension was a fine white powder in a light yellow liquid. The solid was filtered off and air dried for one hour, then placed under high vacuum overnight to provide N-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide (2.55 g, 7.06 mmol, 68% yield). MS

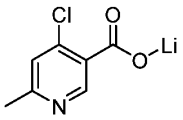
(ESI) calc'd for ($C_{16}H_{15}N_5O_3S$) $(M+1)^+$, 358.1; found 358.1. ^1H NMR (400 MHz, DMSO-d_6) δ 12.4 (s, 1H), 8.75 (s, 1H), 8.25 (s, 1H), 7.42 (s, 1H), 7.25 (s, 1H), 3.70 (s, 3H), 2.62 (s, 3H), 2.48 (s, 3H).

Example 377

N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(4-methoxyphenyl)-6-methylpyridine-3-carboxamide

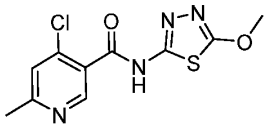


Step 1: lithium 4-chloro-6-methylnicotinate



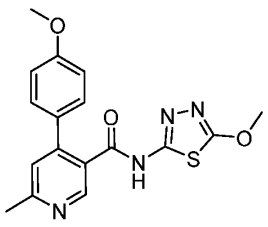
Methyl 4-chloro-6-methylnicotinate (10 g, 53.9 mmol) was suspended in water (20 mL) and 1,4-dioxane (100.0 mL) with rapid stirring and treated with lithium hydroxide (2.261 g, 53.9 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 minutes, after which time LCMS (Waters CSH C18 column (30mm x 2.1mm, 1.7 micron), 0.1% TFA in CH_3CN/H_2O, 2 minutes) indicated that the reaction was only partially complete. The reaction mixture was stirred at room temperature for 72 hours, after which time the reaction was complete. The solvent was removed by rotary evaporation, and the crude residue was re-suspended in 200 mL of dioxane and the solvent was again removed by rotary evaporation to azeotrope out any remaining water. This process was repeated twice more, and then the resulting light orange solid was placed under high vacuum for 48 hours to provide lithium 4-chloro-6-methylnicotinate (9.76 g, 53.9 mmol, 100 % yield) which was used in the next step as a synthetic intermediate. MS (ESI) calc'd for ($C_7H_5ClLiNO_2$) (M+H-Li, free acid form from acid/base exchange on LCMS)$^+$, 172; found 172.0. ^1H NMR (400 MHz, D_2O) δ 8.45 (s, 1H), 7.38 (s, 1H), 2.50 (s, 3H).

Step 2: 4-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide



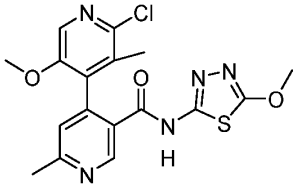
Lithium 4-chloro-6-methylnicotinate (19.57 g, 110 mmol) was suspended in acetonitrile (100 mL) and treated with 5-methoxy-1,3,4-thiadiazol-2-amine (17.35 g, 132 mmol), 1-methylimidazole (30.8 mL, 386 mmol), and N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (46.4 g, 165 mmol) in that order at room temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred at room temperature for 18 hours, after which time LCMS (Waters CSH C18 column (30mm x 2.1mm, 1.7 micron), 0.1% TFA in CH_3CN/H_2O, 2 minutes) indicated that the reaction was complete. The solvent was removed by rotary evaporation and the resulting residue was poured into a solution of KOH (40 g, 713 mmol) in 2L of water and stirred vigorously for five minutes in order to hydrolyze the uronium species by-product that was observed by LCMS at a retention time slightly less than that of the desired product. At high pH (~14), the mixture was a homogeneous solution. A solution of citric acid (128 g, 666 mmol) dissolved in 300 mL of water was then added all at once, causing the product to precipitate. The amount of base to acid in this mixture was calculated to produce a potassium/1-methylimidazolium citrate buffer at a pH of 4. This mixture with a measured pH of 4 was stirred vigorously for 20 minutes. The precipitate was filtered off and washed with water (3 x 2L), a 50/50 mixture of acetonitrile/water (1 x 2L), acetonitrile (1 x 500 ml), and diethyl ether (2 x 1L). The solid was air dried for one hour and then placed under high vacuum overnight to provide 4-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (25.6 g, 89 mmol, 81 % yield) as a pale tan solid which was used in the next step as a synthetic intermediate. MS (ESI) calc'd for ($C_{10}H_9ClN_4O_2S$) $(M+H)^+$, 285.0; found 285.0. ^1H NMR (400 MHz, DMSO-d_6) δ 13.2 (s, 1H), 8.71 (s, 1H), 7.59 (s, 1H), 4.31 (s, 3H), 2.50 (s, 3H).

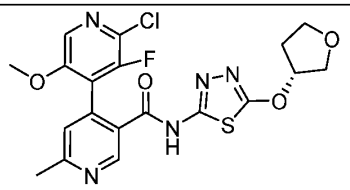
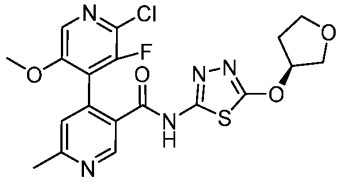
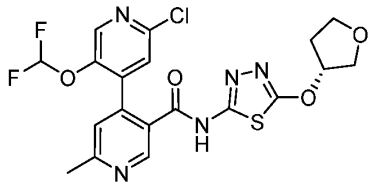
Step 3: N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(4-methoxyphenyl)-6-methylnicotinamide

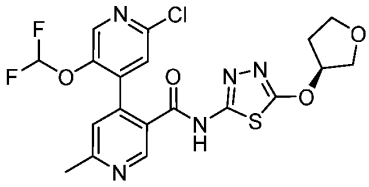
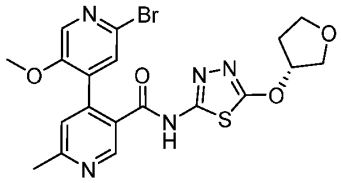
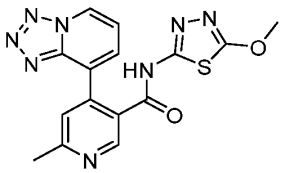


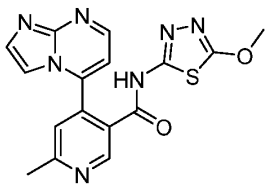
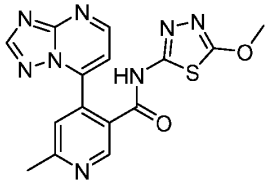
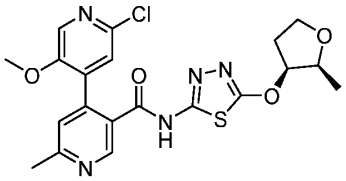
4-Chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (0.030 g, 0.105 mmol) was dissolved in dimethyl sulfoxide (DMSO) (2 mL) and treated with (4-methoxyphenyl)boronic acid (0.019 g, 0.126 mmol), potassium carbonate, 2M solution in nitrogen degassed water (0.158 mL, 0.316 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (8.60 mg, 10.54 μmol) under an atmosphere of dry argon. The reaction mixture was heated to 75 °C and stirred overnight, after which time LCMS (Waters CSH C18 column (30mm x 2.1mm, 1.7 micron), 0.1% TFA in CH_3CN/H_2O, 2 minutes) indicated that the reaction was complete. The reaction mixture was allowed to cool to room temperature and was then filtered through a 0.2 um PTFE filter disk and purified by reverse phase preparative chromatography (XBridge C18 column (75 mm x 30mm i.d. 5μm packing diameter) at ambient temperature, Solvent A = 10 mM Ammonium Bicarbonate in H_2O adjusted to pH 10 with Ammonia. Solvent B = Acetonitrile. Gradient elution from 95%A/5%B to 0%A/100%B over 12.5 minutes, flow rate = 43 mL/min) to provide N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(4-methoxyphenyl)-6-methylnicotinamide. MS (ESI) calc'd for $(C_{17}H_{16}N_4O_3S)$ $(M+H)^+$, 357.1; found 357.1.

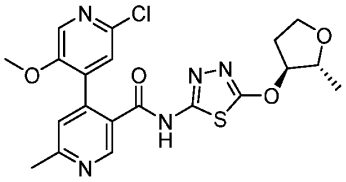
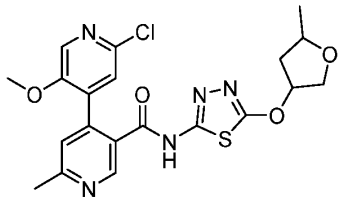
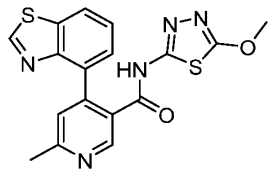
Following general chemistry described above and knowledge known in the art, the following examples were synthesized. Unless otherwise indicated, the stereochemistry of the compounds listed below is not determined and is arbitrarily assigned.

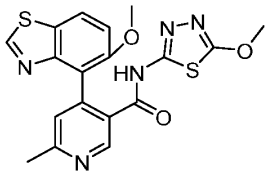
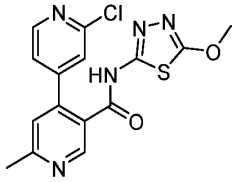
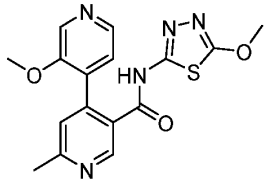
Example	Structure / Name	^{1}H NMR	LCMS
Example 79	 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-3',6-dimethyl-(4,4'-bipyridine)-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.96 (s, 1H), 8.08 (s, 1H), 7.26 (s, 1H), 4.06 (s, 3H), 3.67 (s, 3H), 2.58 (s, 3H), 2.04 (s, 3H).	MS (ESI) calc'd for $(C_{17}H_{16}ClN_5O_3S)$ $(M+1)^+$, 406.1, found 406.1.

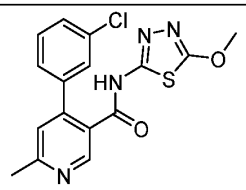
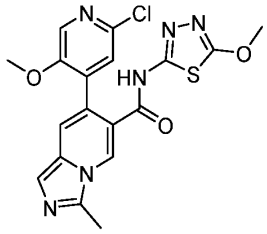
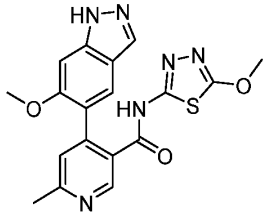
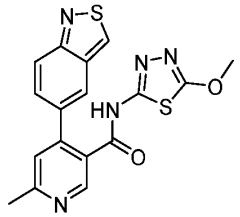
Example 80	 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((R)-tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.97 (s, 1H), 8.19 (s, 1H), 7.48 (s, 1H), 5.54 – 5.47 (m, 1H), 3.93 – 3.81 (m, 3H), 3.81 –3.74 (m, 4H), 2.60 (s, 3H), 2.34 – 2.21 (m, 1H), 2.11– 2.01 (m, 1H).	MS (ESI) calc'd for ($C_{19}H_{17}ClFN_5O_4S$) $(M+1)^+$, 466.1, found, 466.2
Example 81	 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((S)-tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1} H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.42 (s, 1H), 5.49 – 5.47 (m, 1H), 3.95 – 3.75 (m, 3H), 3.76 – 3.72 (m, 4H), 2.59 (s, 3H), 2.31 – 2.21 (m, 1H), 2.14 – 2.06 (m, 1H).	MS (ESI) calc'd for ($C_{19}H_{17}ClFN_5O_4S$) $(M+1)^+$, 466.1, found 466.2.
Example 82	 (R)-2'-chloro-5'-(difluoromethoxy)-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), δ 9.08 (s, 1H), 8.27 (s, 1H), 7.52 (s, 1H), 7.20 – 7.11 (m, 2H), 5.40 – 5.36 (m, 1H), 3.88 – 3.78 (m, 3H), 3.78 – 3.68 (m, 1H), 2.55 (s, 3H), 2.28 – 2.15 (m, 1H), 2.10 – 2.00 (m, 1H).	MS (ESI) calc'd for ($C_{19}H_{16}ClF_2N_5O_4S$) $(M+1)^+$, 484.1. found: 484.2

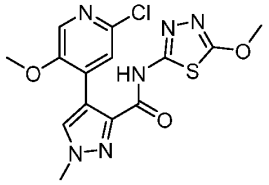
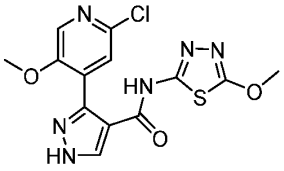
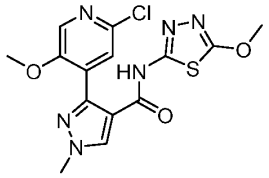
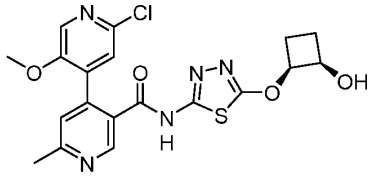
Example 83	 (S)-2'-chloro-5'-(difluoromethoxy)-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.98 (s, 1H), 8.32 (s, 1H), 7.69 (s, 1H), 7.43 (s, 1H), 7.32 – 6.98 (m, 1H), 5.40 – 5.36 (m, 1H), 3.95 – 3.80 (m, 3H), 3.79 – 3.75 (m, 1H), 2.60 (s, 3H), 2.33 – 2.20 (m, 1H), 2.16 – 2.07 (m, 1H).	MS (ESI) calc'd for ($C_{19}H_{16}ClF_2N_5O_4S$) (M+1)+, 484.1; found 484.2.
Example 84	 (R)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridine-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.93 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.65 (s, 1H), 7.47 (s, 1H), 5.55 – 5.48 (m, 1H), 3.96 – 3.82 (m, 3H), 3.81 – 3.71 (m, 1H), 3.63 (s, 3H), 2.60 (s, 3H), 2.34 – 2.22 (m, 1H), 2.18 – 2.08 (m, 1H).	MS (ESI) calc'd for ($C_{19}H_{18}BrN_5O_4S$) $(M+1)^+$, 492.0; found 492.1.
Example 85	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(tetrazolo(1,5-a)pyridin-8-yl)nicotinamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.17 (s, 1H), 9.42 – 9.36 (m, 1H), 8.97 (s, 1H), 8.00 – 7.93 (m, 1H), 7.66 (s, 1H), 7.63 – 7.55 (m, 1H), 4.05 (s, 3H), 2.66 (s, 3H).	MS (ESI) calc'd for ($C_{15}H_{12}N_8O_2S$) $(M+1)^+$, 369.1; found, 369.1

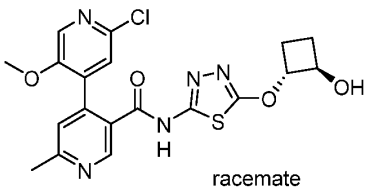
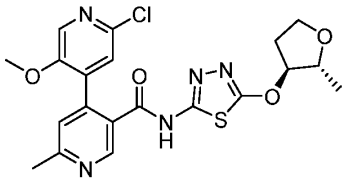
Example 88	 4-(imidazo(1,2-a)pyrimidin-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 9.19 (s, 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.41 (s, 1H), 7.09 (d, J = 4.4 Hz, 1H), 4.04 (s, 3H), 2.66 (s, 3H).	MS (ESI) calc'd for ($C_{16}H_{13}N_7O_2S$) $(M+1)^+$, 368.1, found 368.1.
Example 91	 4-((1,2,4)triazolo(1,5-a)pyrimidin-7-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.28 (s, 1H), 9.17 (s, 1H), 9.01 (d, J = 4.4 Hz, 1H), 8.53 (s, 1H), 7.64 (s, 1H), 7.53 (d, J = 4.4 Hz, 1H), 4.00 (s, 3H), 2.66 (s, 3H).	MS (ESI) calc'd for ($C_{15}H_{12}N_8O_2S$) $(M+1)^+$, 369.0, found 369.1
Example 92	 rac-2'-Chloro-5'-methoxy-6-methyl-N-(5-(((2R,3R)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 5.40 (s, 1H), 3.98 – 3.87 (m, 2H), 3.70 – 3.34 (m, 4H), 2.58 (s, 3H), 2.47 – 2.34 (m, 1H), 2.15 – 2.04 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1.

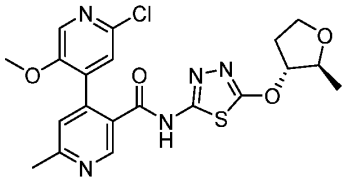
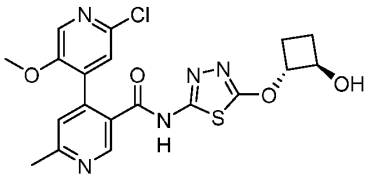
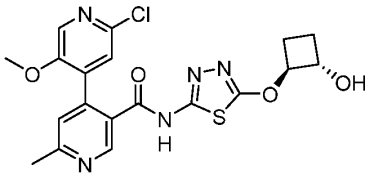
Example 93	 rac-2'-Chloro-5'-methoxy-6-methyl-N-(5-(((2R,3S)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 5.14 – 5.07 (m, 1H), 4.17 – 4.07 (m, 1H), 3.99 – 3.89 (m, 1H), 3.84 – 3.74 (m, 1H), 3.64 (s, 3H), 2.60 (s, 3H), 2.39 – 2.25 (m, 1H), 2.15 – 2.05 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1.
Example 94	 2'-chloro-5'-methoxy-6-methyl-N-(5-((5-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide	1H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 5.54 – 5.42 (m, 1H), 4.22 – 4.00 (m, 1H), 3.99 – 3.86 (m, 1H), 3.84 – 3.73 (m, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.63 – 2.51 (m, 1H), 1.69 – 1.59 (m, 1H), 1.28 – 1.17 (m, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0, found 462.1.
Example 98		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.07 (d, J = 7.6 Hz, 1H), 8.33 (s, 1H), 8.18 (d, J = 8.0 Hz,	MS (ESI) calculated for ($C_{17}H_{13}N_5O_2S_2$) $(M+1)^+$, 384.1,

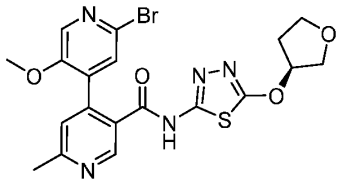
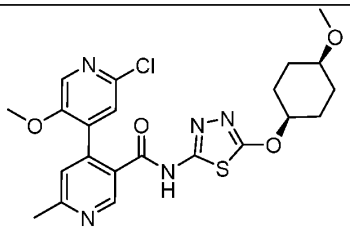
	4-(benzo(d)thiazol-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 3.99 (s, 3H), 2.71 (s, 3H).	
Example 99	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(5-methoxybenzo(d)thiazol-4-yl)-6-methylnicotinamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.84 (s, 1H), 8.84 (s, 1H), 8.16 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 4.08 (s, 3H), 3.63 (s, 3H), 3.43 – 3.33 (m, 1H), 2.12 – 2.00 (s, 2H), 1.87 – 1.75 (m, 4H), 1.70 – 1.65 (m, 2H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_3S$) $(M+1)^+$, 446.1; found, 446.1.
Example 100	 2'-chloro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 13.03 (br, 1H), 8.85 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.51 (s, 1H), 7.36 (dd, *J* = 5.2, 1.6 Hz, 1H), 4.08 (s, 3H), 2.61 (s, 3H).	MS (ESI) calc'd for ($C_{15}H_{12}ClN_5O_2S$) $(M+1)^+$, 362.0; found, 362.1.
Example 101	 3'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.85 (b, 1H), 8.80 (s, 1H), 8.38 – 8.29 (m, 2H), 7.37 – 7.29 (m, 2H), 4.05 (s, 3H), 3.64 (s, 3H), 2.58 (s, 3H).	(ESI) calc'd for ($C_{16}H_{15}N_5O_3S$) (M+1)+, 358.1; found 358.1.

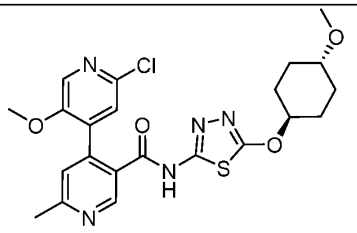
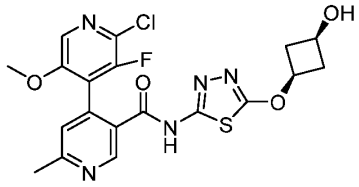
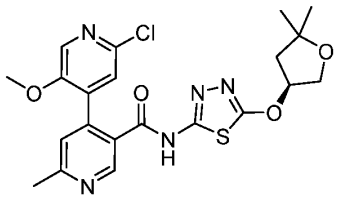
Example 102	 4-(3-chlorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.87 (s, 1H), 8.73 (s, 1H), 7.54 – 7.42 (m, 4H), 7.30 (d, *J* = 8.4 Hz, 1H), 4.08 (s, 3H), 2.59 (s, 3H).	MS (ESI) calc'd for ($C_{16}H_{13}ClN_4O_2S$) $(M+1)^+$, 361.0, 363.0; found, 361.1, 363.1.
Example 103	 7-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-3-methylimidazo(1,5-a)pyridine-6-carboxamide	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.79 (s, 1H), 8.70 (s, 1H), 8.07 (s, 1H), 7.68 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 4.09 (s, 3H), 3.61 (s, 3H), 2.71 (s, 3H).	MS (ESI) calc'd for ($C_{18}H_{15}ClN_6O_3S$) $(M+1)^+$,431.0; found, 431.1.
Example 104	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(6-methoxy-1H-indazol-5-yl)-6-methylnicotinamide	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.93 (s, 1H), 12.65 (s, 1H), 8.67 (s, 1H), 8.04 (s, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 6.90 (s, 1H), 4.05 (s, 3H), 3.55 (s, 3H), 2.50 (s, 3H).	MS (ESI) calculated for ($C_{18}H_{16}N_6O_3S$). $(M+1)^+$, 397.1; found, 397.1.
Example 105	 4-(benzo(c)isothiazol-5-yl)-N-(5-	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.92 (s, 1H), 9.88 (d, *J* = 1.2 Hz, 1H), 8.75 (s, 1H), 7.99 (s, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 7.52	MS (ESI) calc'd for ($C_{17}H_{13}N_5O_2S_2$) $(M+1)^+$, 384.1; found, 384.0.

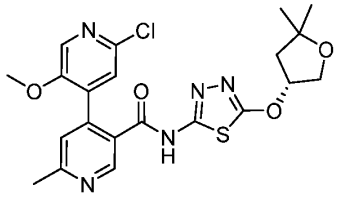
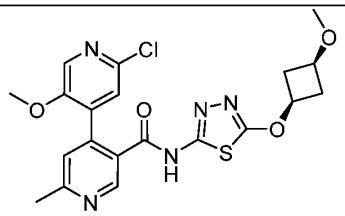
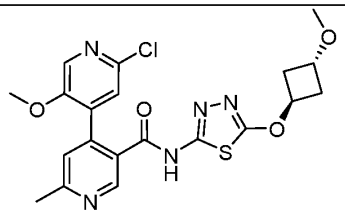
	methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	(s, 1H), 7.47 – 7.37 (m, 1H), 4.05 (s, 3H), 2.61 (s, 3H).	
Example 107	 4-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1-methyl-1H-pyrazole-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 8.21 – 8.19 (m, 2H), 7.46 (s, 1H), 4.07 (s, 3H), 3.98 (s, 3H), 3.75 (s, 3H).	MS (ESI) calculated for ($C_{14}H_{13}ClN_6O_3S$) $(M+1)^+$, 381.0, 383.0; found, 381.1, 383.1.
Example 109	 3-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1H-pyrazole-4-carboxamide	1H-NMR (400 MHz, CD3OD): δ 8.34 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 4.14 (s, 3H), 3.81 (s, 3H).	MS (ESI) calculated for ($C_{13}H_{11}ClN_6O_3S$) $(M+1)^+$; 367.04; found, 367.0
Example 110	 3-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1-methyl-1H-pyrazole-4-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 8.49 (s, 1H), 8.23 (s, 1H), 7.40 (s, 1H), 4.06 (s, 3H), 3.96 (s, 3H), 3.71 (s, 3H).	MS (ESI) calc'd for ($C_{14}H_{13}ClN_6O_3S$) $(M+1)^+$, 381.0; found, 381.0.
Example 112		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.81 (s, 1H), 8.18 (s, 1H), 7.53 (s,	MS (ESI) calculated for ($C_{19}H_{18}ClN_5O_4S$)

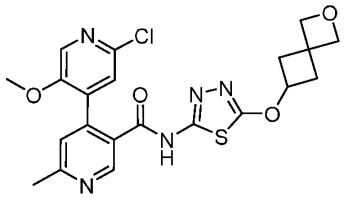
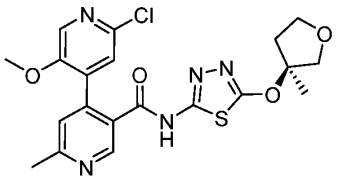
	rac-2'-chloro-N-(5-((1R,2S)-2-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	1H), 7.42 (s, 1H), 5.30 – 5.29 (m, 1H), 5.12 – 5.11 (m, 1H), 4.40 – 4.34 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.18 – 2.07 (m, 3H), 2.07 – 1.95 (m, 1H)	$(M+1)^+$, 448.0; found, 448.1.
Example 114	 racemate rac-2'-chloro-N-(5-((1R,2R)-2-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.60 (d, J = 4.0 Hz, 1H), 4.82 – 4.79 (m, 1H), 4.18 – 4.06 (m, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.19 – 2.16 (m, 1H), 2.06 – 2.04 (m, 1H), 1.54 – 1.32 (m, 2H)	MS (ESI) calculated for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.0; found, 448.1.
Example 115	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2R,3S)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 5.14 – 5.07 (m, 1H), 4.17 – 4.07 (m, 1H), 3.99 – 3.89 (m, 1H), 3.84 – 3.74 (m, 1H), 3.64 (s, 3H), 2.60 (s, 3H), 2.39 – 2.25 (m, 1H), 2.15 – 2.05 (m,	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0; found, 462.1.

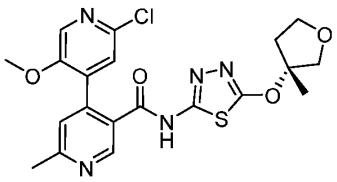
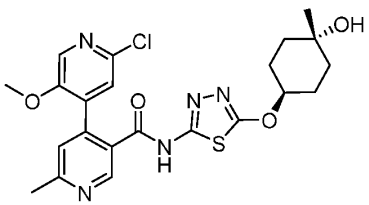
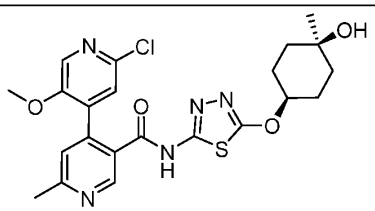
		1H), 1.21 (d, J = 6.4 Hz, 3H).	
Example 116	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((2S,3R)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.89 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.13 – 5.06 (m, 1H), 4.16 – 4.07 (m, 1H), 3.98 – 3.89 (m, 1H), 3.84 – 3.73 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.39 – 2.25 (m, 1H), 2.15 – 2.04 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H)	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0; found, 462.1.
Example 118	 2'-chloro-N-(5-((1R,2R)-2-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.60 (d, J = 6.8 Hz, 1H), 4.85 – 4.75 (m, 1H), 4.17 – 4.05 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.25 – 2.14 (m, 1H), 2.12 – 2.00 (m, 1H), 1.54 – 1.32 (m, 2H).	MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$) $(M+1)^+$, 448.1; found, 448.0.
Example 119		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.82 (s, 1H), 8.16 (s, 1H), 7.51 (s,	MS (ESI) calc'd for ($C_{19}H_{18}ClN_5O_4S$)

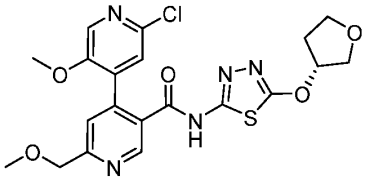
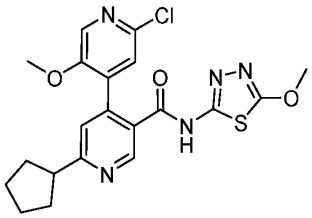
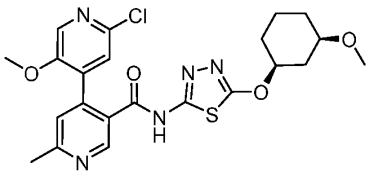
	2'-chloro-N-(5-((1S,2S)-2-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	1H), 7.40 (s, 1H), 5.59 (d, J = 6.4 Hz, 1H), 4.84 – 4.74 (m, 1H), 4.14 – 4.08 (m, 1H), 3.63 (s, 3H), 2.58 (s, 3H), 2.24 – 2.13 (m, 1H), 2.11 – 2.00 (m, 1H), 1.54 – 1.32 (m, 2H).	$(M+1)^+$, 448.1; found, 448.0.
Example 122	 (S)-2'-bromo-5'-methoxy-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.62 (s, 1H), 7.40 (s, 1H), 5.51 – 5.48 (m, 1H), 3.94 – 3.83 (m, 3H), 3.79 – 3.73 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.32 – 2.23 (m, 1H), 2.15 – 2.09 (m, 1H).	MS (ESI) calculated for ($C_{19}H_{18}BrN_5O_4S$) $(M+1)^+$, 492.0; found, 492.0.
Example 124	 2'-chloro-5'-methoxy-N-(5-(((1s,4s)-4-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 4.97 – 4.89 (m, 1H), 3.64 (s, 3H), 3.29 – 3.28 (m, 1H), 3.24 (s, 3H), 2.59 (s, 3H), 1.93 – 1.75 (m, 4H), 1.75 – 1.61 (m, 4H).	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.2.

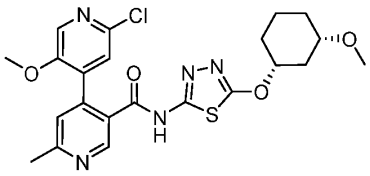
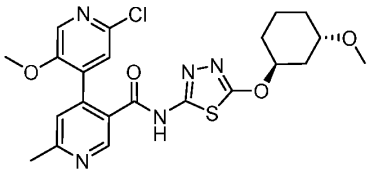
Example 125	 2'-chloro-5'-methoxy-N-(5-(((1r,4r)-4-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.84 (s, 1H), 8.16 (s, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 4.92 – 4.83 (m, 1H), 3.63 (s, 3H), 3.24 (s, 4H), 2.58 (s, 3H), 2.15 – 2.05 (m, 2H), 1.98 – 1.89 (m, 2H), 1.64 – 1.51 (m, 2H), 1.44 – 1.31 (m, 2H).	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.2.
Example 129	 2'-chloro-3'-fluoro-N-(5-((1s,3s)-3-hydroxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 5.26 – 5.21 (m, 1H), 4.77 – 4.66 (m, 1H), 3.87 –3.74 (m, 1H), 3.63 (s, 3H), 2.86 – 2.76 (m, 2H), 2.60 (s, 3H), 2.06 – 1.95 (m, 2H).	MS (ESI) calc'd for ($C_{19}H_{17}ClFN_5O_4S$) $(M+1)^+$, 466.1; found, 466.1.
Example 130	 (S)-2'-chloro-N-(5-((5,5-dimethyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.53 – 5.45 (m, 1H), 3.11 – 4.03 (m, 1H), 3.99 – 3.92 (m, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.05 – 1.97 (m,	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1; found, 476.2

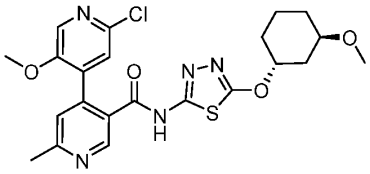
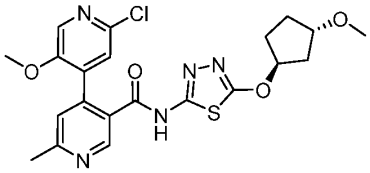
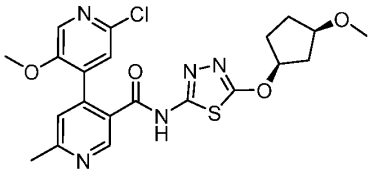
	stereochemistry was not determined.	1H), 2.25 – 2.15 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H).	
Example 131	 (R)-2'-chloro-N-(5-((5,5-dimethyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.53 – 5.45 (m, 1H), 3.11 – 4.03 (m, 1H), 3.99 – 3.92 (m, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.05 – 1.97 (m, 1H), 2.25 – 2.15 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1; found, 476.2.
Example 132	 2'-chloro-5'-methoxy-N-(5-((1s,3s)-3-methoxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.90 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 5.29 – 5.19 (m, 1H), 4.14 – 4.04 (m, 1H), 3.63 (s, 3H), 3.17 (s, 3H), 2.58 (s, 3H), 2.42 – 2.38 (m, 4H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1.
Example 133	 2'-chloro-5'-methoxy-N-(5-	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.91 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.88 – 4.78 (m, 1H),	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.1; found, 462.1.

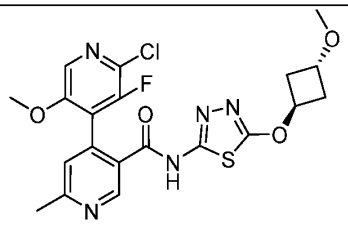
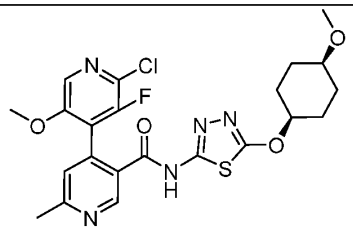
	((1r,3r)-3-methoxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	3.63 (s, 4H), 3.16 (s, 3H), 2.91 – 2.81 (m, 2H), 2.59 (s, 3H), 2.07 – 1.98 (m, 2H).	
Example 135	 N-(5-((2-oxaspiro (3.3) heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 5.06 – 4.96 (m, 1H), 4.63 (s, 2H), 4.55 (s, 2H), 3.63 (s, 3H), 2.82 – 2.72 (m, 2H), 2.59 (s, 3H), 2.45 – 2.31 (m, 2H).	MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_4S$) (M+1) $^+$, 474.1; found, 474.1.
Example 138	 (S)-2'-chloro-5'-methoxy-6-methyl-N-(5-((3-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The absolute stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.90 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 4.18 (d, J = 9.6 Hz, 1H), 3.92 – 3.78 (m, 2H), 3.65 – 3.60 (m, 4H), 2.60 (s, 3H), 2.59 – 2.52 (m, 1H), 2.15 – 2.03 (m, 1H), 1.72 (s, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) (M+1)$^+$, 462.0; found, 462.1.

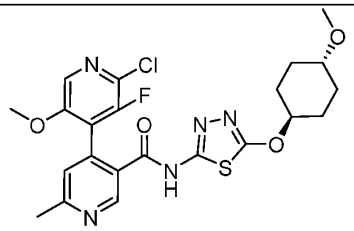
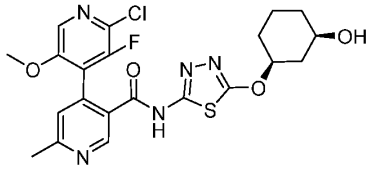
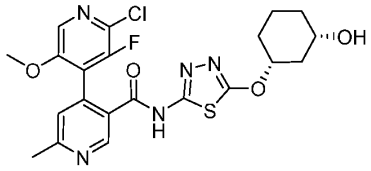
Example 139	 (R)-2'-chloro-5'-methoxy-6-methyl-N-(5-((3-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The absolute stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.19 (d, J = 9.6 Hz, 1H), 3.92 – 3.78 (m, 2H), 3.69 – 3.62(m, 4H), 2.60 (s, 3H), 2.59 – 2.50 (m, 1H), 2.14 – 2.02 (m, 1H), 1.72 (s, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0; found, 462.1.
Example 140	 2'-chloro-N-(5-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.05 – 4.98 (m, 1H), 4.22 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.03 – 1.91 (m, 2H), 1.84 – 1.72 (m, 2H), 1.62 – 1.50 (m, 2H), 1.48 – 1.38 (m, 2H), 1.15 (s, 3H).	MS (ESI) calculated for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.1.
Example 141	 2'-chloro-N-(5-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.80 (s, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 4.88 – 4.76 (m, 1H), 4.21 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H),	MS (ESI) calculated for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.1.

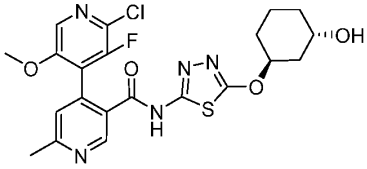
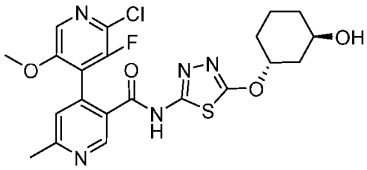
	thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	1.95 – 1.77 (m, 4H), 1.68 – 1.57 (m, 2H), 1.52 – 1.36 (m, 2H), 1.12 (s, 3H).	
Example 142	 (R)-2'-chloro-5'-methoxy-6-(methoxymethyl)-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.89 (s, 1H), 8.19 (s, 1H), 7.54 (s, 1H), 7.52 (s, 1H), 5.59 – 5.46 (m, 1H), 4.62 (s, 2H), 4.02 – 3.81 (m, 3H), 3.81 – 3.72 (m, 1H), 3.65 (s, 3H), 3.42 (s, 3H), 2.36 – 2.22 (m, 1H), 2.19 – 2.05 (m, 1H).	MS (ESI) calculated for ($C_{20}H_{20}ClN_5O_5S$) $(M+1)^+$, 478.1; found, 478.0
Example 143	 2'-chloro-6-cyclopentyl-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.84 (s, 1H), 8.16 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 4.08 (s, 3H), 3.63 (s, 3H), 3.43 – 3.33 (m, 1H), 2.12 – 2.00 (s, 2H), 1.87 – 1.75 (m, 4H), 1.70 – 1.65 (m, 2H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_3S$) $(M+1)^+$, 446.1; found, 446.1.
Example 145	 2'-chloro-5'-methoxy-N-(5-	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.16 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.86 – 4.79 (m, 1H), 3.62 (s, 3H),	MS (ESI) calculated for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.0; found, 490.0.

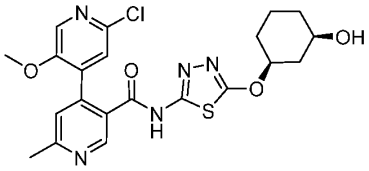
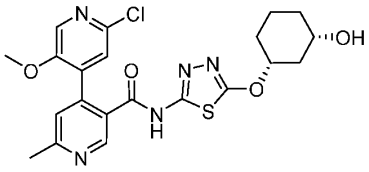
	(((1S,3R)-3-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	3.23 (s, 3H), 3.24 – 3.22 (m, 1H), 2.58 (s, 3H), 2.56 – 2.55 (m, 1H), 2.14 – 2.11 (m, 1H), 1.97 – 1.94 (m, 1H), 1.79 – 1.74 (m, 1H), 1.38 – 1.22 (m, 3H), 1.10 – 1.01 (m, 1H).	
Example 146	 2'-chloro-5'-methoxy-N-(5-(((1R,3S)-3-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.88 – 4.78 (m, 1H), 3.63 (s, 3H), 3.24 – 3.23 (m, 4H), 2.58 (s, 3H), 2.56 – 2.55 (m, 1H), 2.15 – 2.13 (m, 1H), 2.01 – 1.92 (m, 1H), 1.82 – 1.72 (m, 1H), 1.35 – 1.250 (m, 3H), 1.11 – 1.01 (m, 1H).	MS (ESI) calculated for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.0; found, 490.0.
Example 147	 2'-chloro-5'-methoxy-N-(5-(((1S,3S)-3-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 5.16 – 5.06 (m, 1H), 3.63 (s, 3H), 3.56 – 3.53 (m, 1H), 3.24 (s, 3H), 2.58 (s, 3H), 2.00 – 1.98 (m, 1H), 1.92 – 1.82 (m,	MS (ESI) calculated for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.0; found, 490.0.

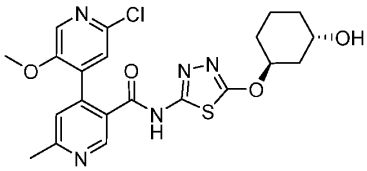
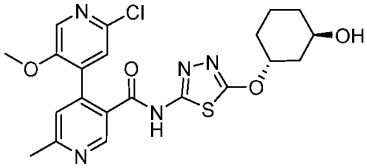
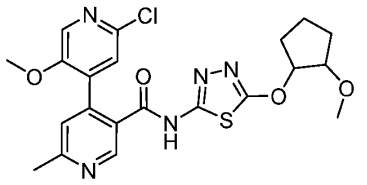
	stereochemistry was not determined.	2H), 1.69 – 1.49 (m, 5H).	
Example 148	 2'-chloro-5'-methoxy-N-(5-(((1R,3R)-3-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.16 – 5.06 (m, 1H), 3.63 (s, 3H), 3.56 – 3.55 (m, 1H), 3.24 (s, 3H), 2.58 (s, 3H), 2.00 – 1.98 (m, 1H), 1.93 – 1.83 (m, 2H), 1.70 – 1.50 (m, 5H).	MS (ESI) calculated for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.0;found, 490.0.
Example 149	 rac-2'-chloro-5'-methoxy-N-(5-(((1R,3R)-3-methoxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}1H NMR (400 MHz, DMSO-d_6) δ 12.85 (b, 1H), 8.82 (s, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 7.40 (s, 1H), 5.38 – 5.28 (m, 1H), 3.99 – 3.89 (m, 1H), 3.63 (s, 3H), 3.19 (s, 3H), 2.58 (s, 3H), 2.13 – 2.03 (m, 3H), 1.93 – 1.75 (m, 2H), 1.75 – 1.65 (m, 1H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$,476.1; found, 476.1.
Example 150	 rac-2'-chloro-5'-methoxy-N-(5-(((1R,3S)-3-	^{1}1H NMR (400 MHz, DMSO-d_6) δ 12.85 (b, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.30 – 5.20 (m, 1H), 3.87 – 3.77 (m, 1H),	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$,476.1; found, 476.1.

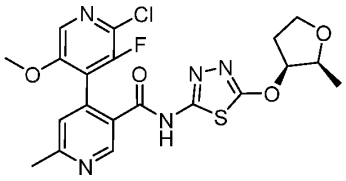
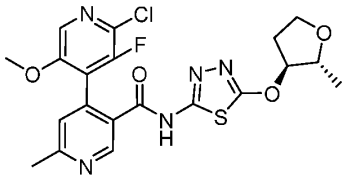
	methoxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	3.64 (s, 3H), 3.19 (s, 3H), 2.59 (s, 3H), 2.37 – 2.27 (m, 1H), 2.08 – 1.98 (m, 1H), 1.97 – 1.71 (m, 4H).	
Example 151	 2'-chloro-3'-fluoro-5'-methoxy-N-(5-((1r,3r)-3-methoxycyclobutoxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 4.88 – 4.78 (m, 1H), 3.74 (s, 3H), 3.67 – 3.57 (m, 1H), 3.18 (s, 3H), 2.92 – 2.80 (m, 2H), 2.60 (s, 3H), 2.09 – 1.97 (m, 2H).	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $(M+1)^+$, 480.1; found, 480.1
Example 152	 2'-chloro-3'-fluoro-5'-methoxy-N-(5-(((1s,4s)-4-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-*d*6) δ 13.05 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 4.96 – 4.86 (m, 1H), 3.74 (s, 3H), 3.30 – 3.24 (m, 4H), 2.60 (s, 3H), 2.14 – 2.02 (m, 2H), 1.94 – 1.82 (m, 2H), 1.65 – 1.52 (m, 2H), 1.45 – 1.31 (m, 2H).	MS (ESI) calc'd for ($C_{22}H_{23}ClFN_5O_4S$) $(M+1)^+$, 508.1; found, 508.1.

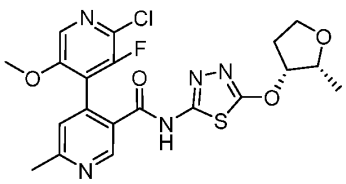
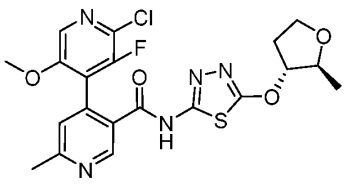
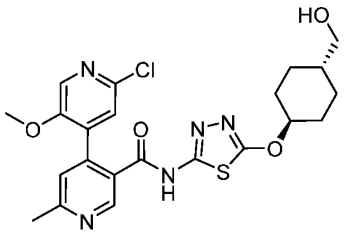
Example 153	 2'-chloro-3'-fluoro-5'-methoxy-N-(5-(((1r,4r)-4-methoxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-*d*6) δ 13.03 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.48 (s, 1H), 4.98 – 4.91 (m, 1H), 3.74 (s, 3H), 3.30 – 3.16 (m, 4H), 2.60 (s, 3H), 1.88 – 1.71 (m, 4H), 1.71 – 1.61 (m, 4H).	MS (ESI) calc'd for ($C_{22}H_{23}ClFN_5O_4S$) $(M+1)^+$, 508.1; found, 508.1.
Example 154	 2'-chloro-3'-fluoro-N-(5-(((1S,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 5.18 (s, 1H), 4.62 (d, J = 4.0 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.74 (s, 3H), 2.60 (s, 3H), 1.96 – 1.85 (m, 1H), 1.80 – 1.77 (m, 2H), 1.70 – 1.59 (m, 3H), 1.43 – 1.39 (m, 1H), 1.38 – 1.35 (m, 1H).	MS (ESI) calc'd for ($C_{21}H_{21}ClFN_5O_4S$) $(M+1)^+$, 494.1, found 494.1.
Example 155	 2'-chloro-3'-fluoro-N-(5-(((1R,3S)-3-	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 9.00 (s, 1H), 8.17 (s, 1H), 7.42 (s, 1H), 5.16 (s, 1H), 4.61 (d, J = 4.0 Hz,	MS (ESI) calc'd for ($C_{21}H_{21}ClFN_5O_4S$) $(M+1)^+$, 494.1, found 494.1.

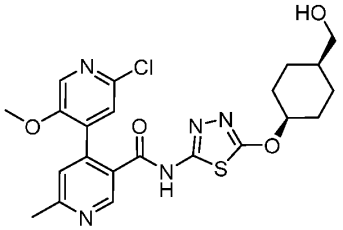
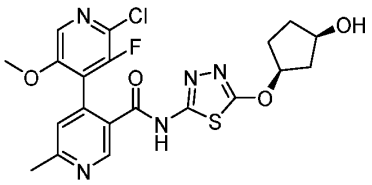
	hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	1H), 3.91 – 3.83 (m, 1H), 3.74 (s, 3H), 2.59 (s, 3H), 1.95 – 1.86 (m, 1H), 1.80 – 1.77 (m, 2H), 1.67 – 1.59 (m, 3H), 1.43 – 1.39 (m, 1H), 1.38 – 1.31 (m, 1H).	
Example 156	 2'-chloro-3'-fluoro-N-(5-(((1S,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 4.85 – 4.75 (m, 2H), 3.74 (s, 3H), 3.56 – 3.45 (m, 1H), 2.60 – 2.57 (s, 3H), 2.40 – 2.37 (m, 1H), 2.12 – 2.10 (m, 1H), 1.81 – 1.78 (m, 1H), 1.72 – 1.70 (m, 1H), 1.37 – 1.19 (m, 4H).	MS (ESI) calc'd for ($C_{21}H_{21}ClFN_5O_4S$) $(M+1)^+$, 494.1, found 494.1.
Example 157	 2'-chloro-3'-fluoro-N-(5-(((1R,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.46 (s, 1H), 4.86 – 4.74 (m, 2H), 3.74 (s, 3H), 3.54 – 3.46 (m, 1H), 2.60 (s, 3H), 2.41 – 2.38 (m, 1H), 2.11 – 2.08 (m, 1H), 1.80 –	MS (ESI) calc'd for ($C_{21}H_{21}ClFN_5O_4S$) $(M+1)^+$, 494.1, found 494.1.

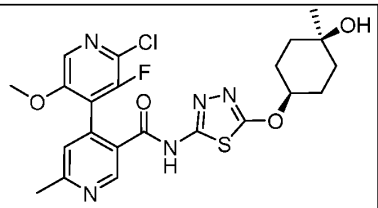
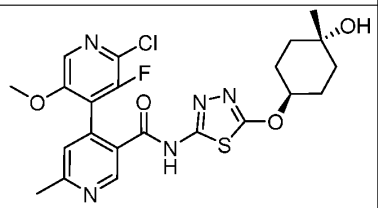
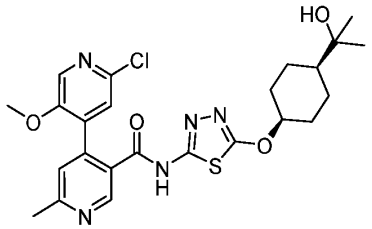
	carboxamide. The stereochemistry was not determined.	1.77 (m, 1H), 1.74 – 1.70 (m, 1H), 1.37 – 1.19 (m, 3H), 1.16 – 1.02 (m, 1H).	
Example 159	 2'-chloro-N-(5-(((1S,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.85 (s, 1H), 8.16 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 5.15 – 5.13 (m, 1H), 4.63 – 4.58 (m, 1H), 3.87 – 3.86 (m, 1H), 3.64 (s, 3H), 2.57 (s, 3H), 1.90 – 1.88 (m, 1H), 1.80 – 1.78 (m, 2H), 1.64 – 1.58 (m, 3H), 1.54 – 1.52 (m, 1H), 1.41 – 1.34 (m, 1H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1, found 476.1.
Example 160	 2'-chloro-N-(5-(((1R,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.28 (s, 1H), 8.16 (s, 1H), 7.42 – 7.36 (m, 1H), 7.29 – 7.21 (m, 1H), 5.10 – 5.08 (m, 1H), 4.58 – 4.56 (m, 1H), 3.64 (s, 3H), 2.55 (s, 3H), 1.88 – 1.84 (m, 1H), 1.77 – 1.32 (m, 6H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1, found 476.1.

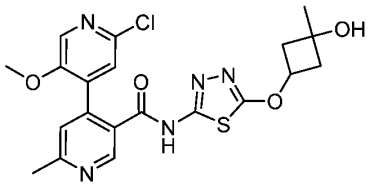
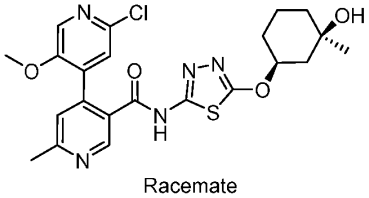
Example 161	 2'-chloro-N-(5-(((1R,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 4.81 – 4.75 (m, 2H), 3.64 (s, 3H), 3.54 – 3.46 (m, 1H), 2.58 (s, 3H), 2.44 – 2.37 (m, 1H), 2.11 – 2.09 (m, 1H), 1.84 – 1.76 (m, 1H), 1.37 – 1.22 (m, 1H), 1.28 – 1.23 (m, 3H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1, found 476.1.
Example 162	 2'-chloro-N-(5-(((1S,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.15 (s, 1H), 7.47 (s, 1H), 7.35 (s, 1H), 4.76 – 4.70 (m, 2H), 3.64 (s, 3H), 3.38 – 3.36 (m, 1H), 2.58 (s, 3H), 2.43 – 2.36 (m, 1H), 2.11 – 2.10 (m, 1H), 1.84 – 1.76 (m, 1H), 1.74 – 1.70 (m, 1H), 1.35 – 1.22 (m, 3H), 1.12 – 1.04 (m, 1H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1, found 476.1.
Example 163		1H NMR (400 MHz, DMSO-d6) δ 12.90 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H),	MS (ESI) calculated for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1; found, 476.2.

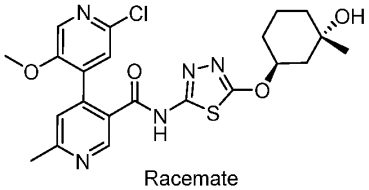
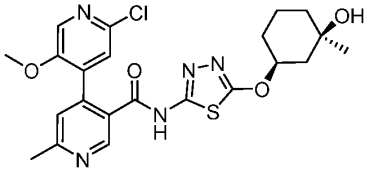
	2'-chloro-5'-methoxy-N-(5-((2-methoxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide	5.22 – 5.10 (m, 1H), 3.98 – 3.79 (m, 1H), 3.64 (s, 3H), 3.31 (s, 3H), 2.59 (s, 3H), 2.16 – 2.06 (m, 1H), 1.99 – 1.89 (m, 1H), 1.81 – 1.56 (m, 4H).	
Example 164	 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((2S,3S)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.97 (s, 1H), 8.19 (s, 1H), 7.48 (s, 1H), 5.39 – 5.38 (m, 1H), 3.96 – 3.88 (m, 2H), 3.75 (s, 3H), 3.66 – 3.62 (m, 1H), 2.62 (s, 3H), 2.44 – 2.37 (m, 1H), 2.17 – 2.09 (m, 1H), 1.24 – 1.20 (m, 3H).	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $[M+1]^+$, 480.0, found 480.1.
Exaple 165	 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((2R,3S)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.97 (s, 1H), 8.19 (s, 1H), 7.49 (s, 1H), 5.10 – 5.07 (m, 1H), 4.14 – 4.09 (m, 1H), 3.96 – 3.91 (m, 1H), 3.21 – 3.77 (m, 1H), 3.74 (s, 3H), 2.60 (s, 3H), 2.36 – 2.26 (m, 1H), 2.10 – 2.06 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H).	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $[M+1]^+$, 480.0, found 480.1.

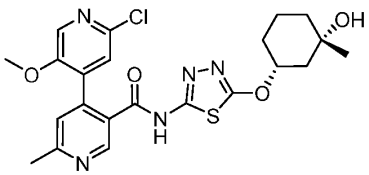
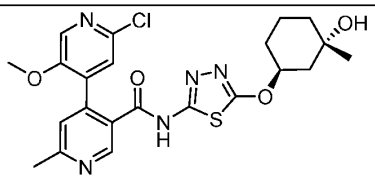
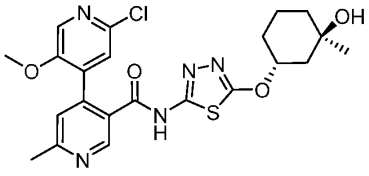
Example 166	 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((2R,3R)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.06 (s, 1H), 8.97 (s, 1H), 8.19 (s, 1H), 7.48 (s, 1H), 5.39 – 5.38 (m, 1H), 3.49 – 3.85 (m, 2H), 3.74 (s, 3H), 3.66 – 3.62 (m, 1H), 2.63 (s, 3H), 2.47 – 2.34 (m, 1H), 2.17 – 2.09 (m, 1H), 1.24 – 1.20 (m, 3H).	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $[M+1]^+$, 480.0, found 480.1.
Example 167	 2'-chloro-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((2S,3R)-2-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.06 (s, 1H), 8.97 (s, 1H), 8.15 (s, 1H), 7.47 (s, 1H), 5.10 – 5.07 (m, 1H), 4.14 – 4.08 (m, 1H), 3.96 – 3.91 (m, 1H), 3.81 – 3.77 (m, 1H), 3.74 (s, 3H), 2.60 (s, 3H), 2.36 – 2.26 (m, 1H), 2.10 – 2.05 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H).	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $[M+1]^+$, 480.0, found 480.1.
Example 168	 2'-chloro-N-(5-(((1r,4r)-4-(hydroxymethyl)cyclohexyl)oxy)-	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.85 (s, 1H), 8.82 (s, 1H), 8.17 (s, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 4.83 – 4.71 (m, 1H), 4.48 – 4.40 (m, 1H), 3.63 (s, 3H), 3.27 –	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.1.

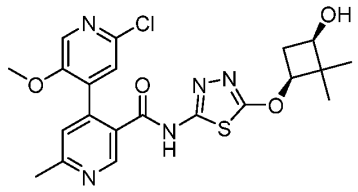
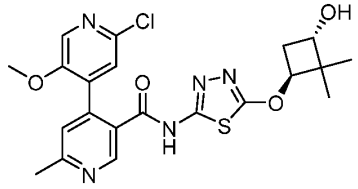
	1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was determined.	3.20 (m, 2H), 2.58 (s, 3H), 2.25 – 2.16 (m, 2H), 1.86 – 1.77 (m, 2H), 1.50 – 1.34 (m, 3H), 1.12 – 0.97 (m, 2H).	
Examplse 169	 2'-chloro-N-(5-(((1s,4s)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.09 (s, 1H), 4.41 (t, J = 5.2 Hz, 1H), 3.64 (s, 3H), 3.31 – 3.23 (m, 2H), 2.59 (s, 3H), 2.08 – 1.98 (m, 2H), 1.69 – 1.52 (m, 5H), 1.34 – 1.20 (m, 2H).	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1, found 490.1.
Example 170	 rac-2'-chloro-3'-fluoro-N-(5-(((1R,3S)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.01 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.48 (s, 1H), 5.21 – 5.19 (m, 1H), 4.68 – 4.65 (m, 1H), 4.13 – 4.08 (m, 1H), 3.74 (s, 3H), 2.60 (s, 3H), 2.32 – 2.29 (m, 1H), 2.06 – 1.88 (m, 2H), 1.81 – 1.59 (m, 3H).	MS (ESI) calculated for ($C_{20}H_{19}ClFN_5O_4S$) $(M+1)^+$, 480.1; found, 480.2.

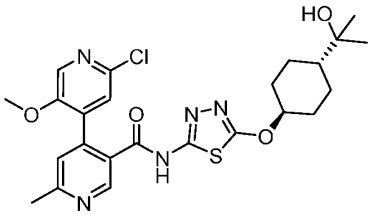
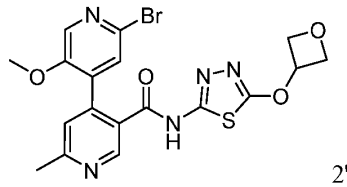
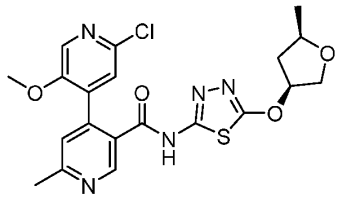
Example 171	 2'-chloro-3'-fluoro-N-(5-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.45 (s, 1H), 4.85 – 4.76 (m, 1H), 4.20 (s, 1H), 3.74 (s, 3H), 2.59 (s, 3H), 1.90 – 1.76 (m, 4H), 1.61 – 1.48 (m, 2H), 1.47 – 1.36 (m, 2H), 1.12 (s, 3H).	MS (ESI) calc'd for ($C_{22}H_{23}ClFN_5O_4S$) $(M+1)^+$, 508.1; found, 508.1.
Example 172	 2'-chloro-3'-fluoro-N-(5-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 5.00 (s, 1H), 4.21 (s, 1H), 3.74 (s, 3H), 2.60 (s, 3H), 2.02 – 1.91 (m, 2H), 1.82 – 1.72 (m, 2H), 1.61 – 1.50 (m, 2H), 1.48 – 1.37 (m, 2H), 1.15 (s, 3H).	MS (ESI) calc'd for ($C_{22}H_{23}ClFN_5O_4S$) $(M+1)^+$, 508.1; found, 508.1.
Example 175	 2'-chloro-N-(5-(((1s,4s)-4-(2-hydroxypropan-2-	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.84 (s, 1H), 8.16 (s, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 5.08 – 5.02 (m, 1H), 4.05 (s, 1H), 3.64 (s,	MS (ESI) calc'd for ($C_{24}H_{28}ClN_5O_4S$) $(M+1)^+$, 518.2, found 518.2.

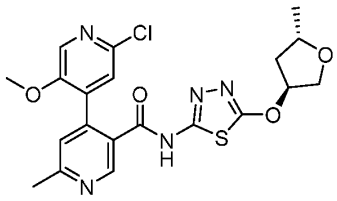
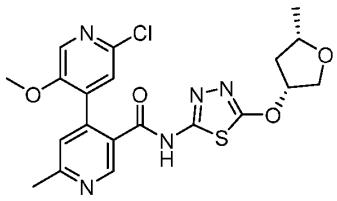
	yl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was determined.	3H), 2.58 (s, 3H), 2.17 – 2.09 (m, 2H), 1.67 – 1.59 (m, 2H), 1.59 – 1.49 (m, 2H), 1.28 (s, 3H), 1.04 (s, 6H).	
Example 176	 2'-chloro-N-(5-(3-hydroxy-3-methylcyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide	Product is a mixture of diastereomers that were not further separated (ratio = 4:1). ^{1}H NMR (major isomer) (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.22 (s, 1H), 4.90 – 4.78 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.58 – 2.51 (m, 2H), 2.26 – 2.15 (m, 2H), 1.25 (s, 3H). The activity data for this Example is the potency for the mixture.	MS (major isomer) (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0, found, 462.1.
Example 177	 Racemate rac-2'-chloro-N-(5-(((1R,3S)-3-	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.92 – 4.82 (m, 1H),	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1, found 490.1.

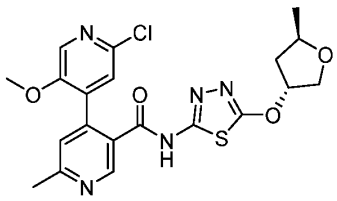
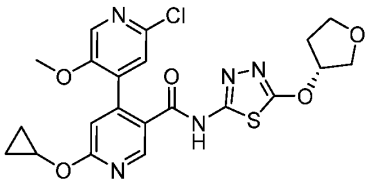
	hydroxy-3-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	4.55 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.15 – 2.04 (m, 2H), 1.72 – 1.48 (m, 4H), 1.44 – 1. 32 (m, 2H), 1.14 (s, 3H).	
Example 178	 Racemate rac-2'-chloro-N-(5-(((1R,3R)-3-hydroxy-3-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.10 – 5.07 (m, 1H), 4.32 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.15 – 2.04 (m, 2H), 1.66 – 1.20 (m, 6H), 1.14 (s, 3H).	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1, found 490.1.
Example 179	 2'-chloro-N-(5-(((1S,3R)-3-hydroxy-3-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.92 – 4.82 (m, 1H), 4.55 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.15 – 2.04 (m, 2H), 1.75 – 1.71 (m, 1H), 1.60 – 1.48 (m, 2H),	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.1.

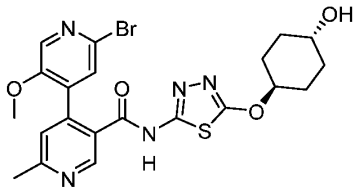
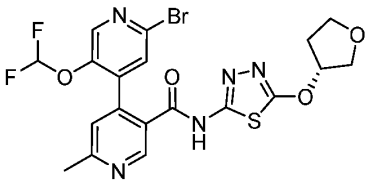
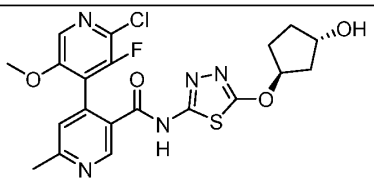
		1.44 – 1.32 (m, 3H), 1.14 (s, 3H).	
Example 180	 2'-chloro-N-(5-(((1R,3S)-3-hydroxy-3-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.92 – 4.82 (m, 1H), 4.55 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.15 – 2.04 (m, 2H), 1.75 – 1.71 (m, 1H), 1.60 – 1.48 (m, 2H), 1.44 – 1.32 (m, 3H), 1.14 (s, 3H).	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.1.
Example 181	 2'-chloro-N-(5-(((1S,3S)-3-hydroxy-3-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 5.14 – 5.02 (m, 1H), 4.32 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.20 – 2.05 (m, 2H), 1.77 – 1.20 (m, 6H), 1.16 (s, 3H).	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$,490.1; found, 490.1.
Example 182	 2'-chloro-N-(5-(((1R,3R)-3-	^{1}H NMR (400 MHz, DMSO-d_6) δ12.84 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H),	MS (ESI) calc'd for ($C_{22}H_{24}ClN_5O_4S$) $(M+1)^+$, 490.1; found, 490.1.

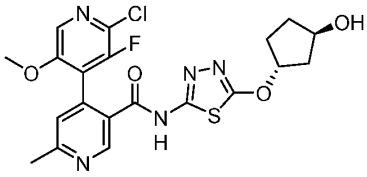
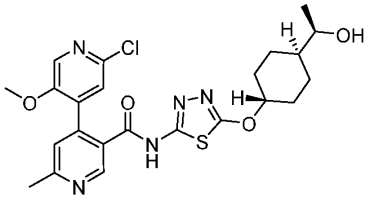
	hydroxy-3-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	5.14 – 5.02 (m, 1H), 4.32 (s, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.20 – 2.05 (m, 2H), 1.77 – 1.20 (m, 6H), 1.16 (s, 3H).	
Example 183	 2'-chloro-N-(5-((1r,3s)-3-hydroxy-2,2-dimethylcyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.03 (d, J = 6.0 Hz, 1H), 4.55 (t, J = 7.6 Hz, 1H), 3.63 (s, 3H), 3.56 – 3.48 (m, 1H), 2.75 – 2.63 (m, 1H), 2.59 (s, 3H), 2.02 – 1.90 (m, 1H), 1.18 (s, 3H), 0.95 (s, 3H).	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1; found, 476.2.
Example 184	 2'-chloro-N-(5-((1r,3r)-3-hydroxy-2,2-dimethylcyclobutoxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.04 (d, J = 5.6 Hz, 1H), 4.55 (t, J = 7.6 Hz, 1H), 3.63 (s, 3H), 3.55 – 3.49 (m, 1H), 2.75 – 2.63 (m, 1H), 2.59 (s, 3H), 2.02 –	MS (ESI) calc'd for ($C_{21}H_{22}ClN_5O_4S$) $(M+1)^+$, 476.1; found, 476.2.

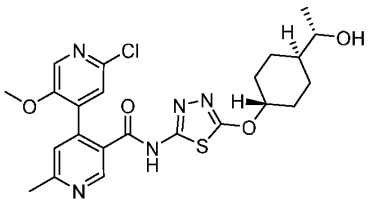
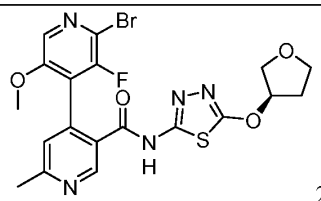
		1.90 (m, 1H), 1.18 (s, 3H), 0.95 (s, 3H	
Example 187	 2'-chloro-N-(5-(((1r,4r)-4-(2-hydroxypropan-2-yl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 4.82 – 4.71 (m, 1H), 4.10 (s, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.23 – 2.21 (m, 2H), 1.87 – 1.85 (m, 2H), 1.47 – 1.34 (m, 2H), 1.27 – 1.08 (m, 3H), 1.05 (s, 6H).	MS (ESI) calc'd for ($C_{24}H_{28}ClN_5O_4S$) $(M+1)^+$, 518.1; found, 518.2
Example 188	 2'-bromo-5'-methoxy-6-methyl-N-(5-(oxetan-3-yloxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 5.72 – 5.62 (m, 1H), 4.94 – 4.86 (m, 2H), 4.71 – 4.61 (m, 2H), 3.62 (s, 3H), 2.59 (s, 3H).	MS (ESI) calc'd for ($C_{18}H_{16}BrN_5O_4S$) $(M+1)^+$, 478.0; found, 478.0.
Example 189	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((3S,5R)-5-	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.50 – 5.42 (m, 1H), 4.03 (d, J = 12.0 Hz,	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0, found 462.1.

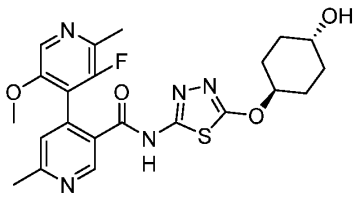
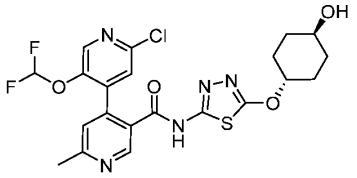
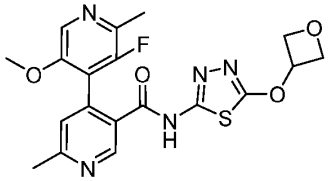
	methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	1H), 3.99 – 3.86 (m, 1H), 3.81 – 3.73 (m, 1H), 3.63 (s, 3H), 2.61 – 2.57 (m, 3H), 2.62 – 2.53 (m, 1H), 1.69 – 1.58 (m, 1H), 1.25 (d, J = 6.0 Hz, 3H).	
Example 190	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((3S,5S)-5-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.53 – 5.46 (m, 1H), 4.22 – 4.05 (m, 2H), 3.84 – 3.76 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.33 – 2.23 (m, 1H), 1.83 – 1.71 (m, 1H), 1.20 (d, J = 6.0 Hz, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0, found 462.1
Example 191	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((3R,5S)-5-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.50 – 5.42 (m, 1H), 4.04 (d, J = 12.0 Hz, 1H), 3.99 – 3.86 (m, 1H), 3.81 – 3.73 (m, 1H), 3.64 (s, 3H), 2.59 (s, 3H), 2.63 – 2.51 (m, 1H), 1.69 –	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0, found 462.1.

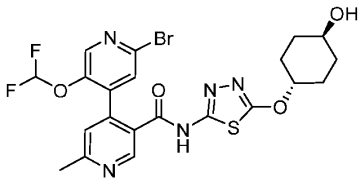
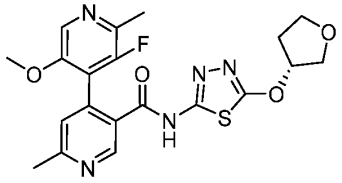
		1.59 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H).	
Example 192	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((3R,5R)-5-methyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.88 (br, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 5.54 – 5.47 (m, 1H), 4.22 – 4.14 (m, 1H), 4.17 – 4.06 (m, 1H), 3.84 – 3.77 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.33 – 2.24 (m, 1H), 1.83 – 1.71 (m, 1H), 1.20 (d, J = 6.0 Hz, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_4S$) $(M+1)^+$, 462.0, found 462.1.
Example 193	 (R)-2'-chloro-6-cyclopropoxy-5'-methoxy-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide (Stereochemistry determined)	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.61 (s, 1H), 8.16 (s, 1H), 7.54 (s, 1H), 6.99 (s, 1H), 5.54 – 5.47 (m, 1H), 4.40 – 4.31 (m, 1H), 3.96 – 3.81 (m, 3H), 3.81 – 3.71 (m, 1H), 3.64 (s, 3H), 2.33 – 2.21 (m, 1H), 2.17 – 2.06 (m, 1H), 0.89 – 0.72 (m, 4H)	MS (ESI) calc'd for ($C_{20}H_{20}ClN_5O_5S$) $(M+1)^+$ 490.1; found 490.1

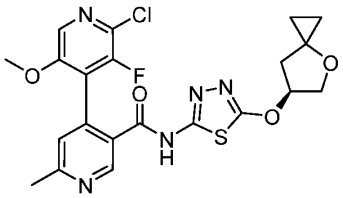
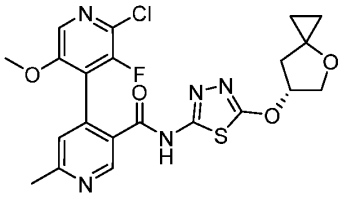
Example 194	 2'-bromo-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.63 (s, 1H), 7.42 (s, 1H), 4.91 – 4.80 (m, 1H), 4.61 (d, J = 4.0 Hz, 1H), 3.65 – 3.60 (m, 3H), 3.59 – 3.50 (m, 1H), 2.59 (s, 3H), 2.18 – 2.05 (m, 2H), 1.88 – 1.79 (m, 2H), 1.62 – 1.48 (m, 2H), 1.40 – 1.27 (m, 2H).	MS (ESI) calc'd for ($C_{21}H_{22}BrN_5O_4S$) $(M+1)^+$, 520.1, found 520.1.
Example 195	 (R)-2'-bromo-5'-(difluoromethoxy)-6-methyl-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The absolute stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.95 (s, 1H), 8.32 (s, 1H), 7.83 (s, 1H), 7.45 (s, 1H), 7.31 – 6.95 (m, 1H), 5.53– 5.48 (m, 1H), 3.96 – 3.81 (m, 3H), 3.81 – 3.74 (m, 1H), 2.61 (s, 3H), 2.33 – 2.21 (m, 1H), 2.16 – 2.11 (m, 1H).	MS (ESI) calculated for ($C_{19}H_{16}BrF_2N_5O_4S$) $(M+1)^+$, 528.0; found, 528.0.
Example 197	 2'-chloro-3'-fluoro-N-(5-(((1S,3S)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 5.36 (s, 1H), 4.66 (d, J = 3.6 Hz, 1H), 4.28 – 4.26 (m,	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $(M+1)^+$, 480.1; found,480.1.

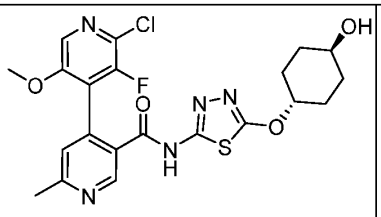
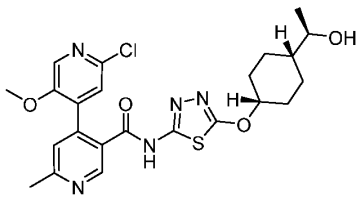
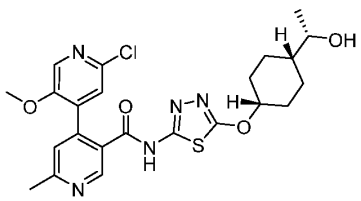
	methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry is not determined.	1H), 3.74 (s, 3H), 2.59 (s, 3H), 2.23 – 2.13 (m, 1H), 1.99 (s, 2H), 1.94 – 1.82 (m, 1H), 1.80 – 1.77 (m, 1H), 1.59 – 1.49 (m, 1H).	
Example 198	 2'-chloro-3'-fluoro-N-(5-(((1R,3R)-3-hydroxycyclopentyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry is not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.01 (s, 1H), 8.97 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 5.36 (s, 1H), 4.66 (d, J = 3.6 Hz, 1H), 4.28 – 4.26 (m, 1H), 3.74 (s, 3H), 2.59 (s, 3H), 2.24 – 2.14 (m, 1H), 1.99 (s, 2H), 1.93 – 1.71 (m, 2H), 1.59 – 1.49 (m, 1H).	MS (ESI) calc'd for ($C_{20}H_{19}ClFN_5O_4S$) $(M+1)^+$, 480.1; found,480.1.
Example 199	 2'-chloro-N-(5-(((1R,4r)-4-((R)-1-hydroxyethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry is not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.88 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.82 – 4.70 (m, 1H), 4.36 (d, J = 4.8 Hz, 1H), 3.63 (s, 3H), 3.41 – 3.36 (m, 1H), 2.59 (s, 3H), 2.26 – 2.17 (m, 2H), 1.97 – 1.87 (m, 1H), 1.71 – 1.69 (m, 1H), 1.50 –	MS (ESI) calc'd for ($C_{23}H_{26}ClN_5O_4S$) $(M+1)^+$,504.1; found, 504.1.

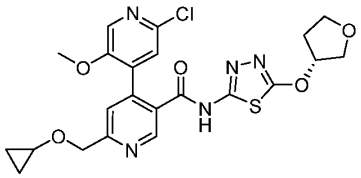
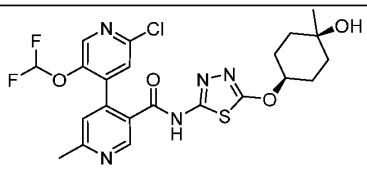
		1.33 (m, 2H), 1.31 – 1.05 (m, 3H), 1.04 (d, J = 6.4 Hz, 3H).	
Example 200	 2'-chloro-N-(5-(((1S,4r)-4-((S)-1-hydroxyethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry is not determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.88 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 4.82 – 4.70 (m, 1H), 4.36 (d, J = 4.8 Hz, 1H), 3.63 (s, 3H), 3.41 – 3.36 (m, 1H), 2.59 (s, 3H), 2.26 – 2.17 (m, 2H), 1.97 – 1.87 (m, 1H), 1.71 – 1.69 (m, 1H), 1.50 – 1.33 (m, 2H), 1.31 – 1.05 (m, 3H), 1.04 (d, J = 6.4 Hz, 3H).	MS (ESI) calc'd for ($C_{23}H_{26}ClN_5O_4S$) $(M+1)^+$, 504.1; found, 504.1.
Example 201	 2'-bromo-3'-fluoro-5'-methoxy-6-methyl-N-(5-(((R)-tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The absolute stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.97 (s, 1H), 8.20 (s, 1H), 7.47 (s, 1H), 5.51 – 5.49 (m, 1H), 3.90 – 3.84 (m, 3H), 3.84 – 3.73 (m, 4H), 2.60 (s, 3H), 2.34 – 2.20 (m, 1H), 2.16 – 2.08 (m, 1H).	MS (ESI) calc'd for ($C_{19}H_{17}BrFN_5O_4S$) $(M+1)^+$, 510.0; found, 510.1.

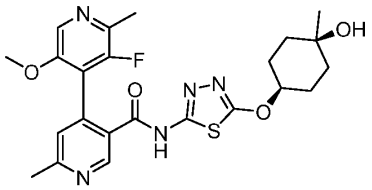
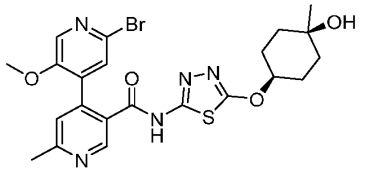
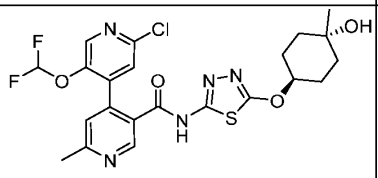
Example 202	 3'-fluoro-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.94 (s, 1H), 8.16 (s, 1H), 7.33 (s, 1H), 4.87 – 4.77 (m, 1H), 4.60 (br, 1H), 3.68 (s, 3H), 3.58 – 3.48 (m, 1H), 2.57 (s, 3H), 2.42 (s, 3H), 2.15 – 2.04 (m, 2H), 1.83 – 1.80 (m, 2H), 1.58 – 1.48 (m, 2H), 1.39 – 1.23 (m, 2H).	MS (ESI) calc'd for ($C_{22}H_{24}FN_5O_4S$) $(M+1)^+$,474.2; found, 474.3.
Example 203	 2'-chloro-5'-(difluoromethoxy)-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.96 (s, 1H), 8.33 (s, 1H), 7.72 (s, 1H), 7.45 (s, 1H), 7.14 – 6.95 (m, 1H), 4.85 – 4.82 (m, 1H), 4.61 (d, J = 4.0 Hz, 1H), 3.55 – 3.54 (m, 1H), 2.61 (s, 3H), 2.16 – 2.06 (m, 2H), 1.83 – 1.80 (m, 2H), 1.55 – 1.50 (m, 2H), 1.40 – 1.27 (m, 2H).	MS (ESI) calculated for ($C_{21}H_{20}ClF_2N_5O_4S$) $(M+1)^+$, 512.1; found, 512.1.
Example 204	 (2'-bromo-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 8.91 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 5.71 – 5.61 (m, 1H), 4.93 – 4.85 (m,	(ESI) calc'd for ($C_{19}H_{18}FN_5O_4S$) $(M+1)^+$, 432.1; found, 432.1.

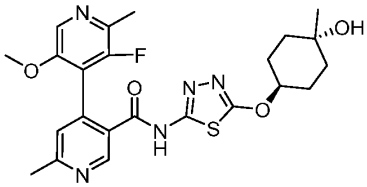
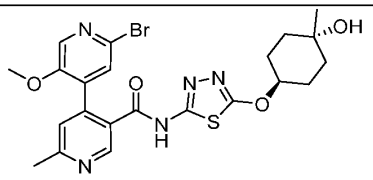
	thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide	2H), 4.68 – 4.59 (m, 2H), 3.68 (s, 3H), 2.59 (s, 3H), 2.43 (s, 3H).	
Example 205	 2'-bromo-5'-(difluoromethoxy)-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 8.95 (s, 1H), 8.32 (s, 1H), 7.82 (s, 1H), 7.44 (s, 1H), 7.32 – 6.85 (m, 1H), 4.93 – 4.82 (s, 1H), 4.61 (d, J = 4.4 Hz, 1H), 3.59 – 3.52 (m, 1H), 2.61 (s, 3H), 2.13 – 2.09 (m, 2H), 1.85 – 1.81 (m, 2H), 1.62 – 1.48 (m, 2H), 1.40 – 1.26 (m, 2H).	MS (ESI) calculated for ($C_{21}H_{20}BrF_2N_5O_4S$) $(M+1)^+$, 556.0, 558.0; found, 556.0, 558.0.
Example 206	 (R)-6-(2,4-difluorophenyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-2-oxo-1,2-dihydropyridine-3-carboxamide. The absolute stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.91 (s, 1H), 8.18 (s, 1H), 7.41 (s, 1H), 5.54 – 5.47 (m, 1H), 3.95 – 3.82 (m, 3H), 3.81 – 3.71 (m, 1H), 3.69 (s, 3H), 2.59 (s, 3H), 2.43 (s, 3H), 2.33 – 2.21 (m, 1H), 2.17 – 2.07 (m, 1H).	MS (ESI) calc'd for ($C_{20}H_{20}FN_5O_4S$) $(M+1)^+$, 446.1; found,446.1

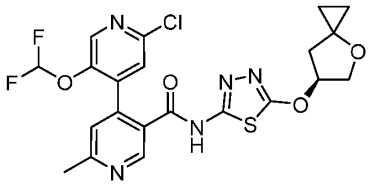
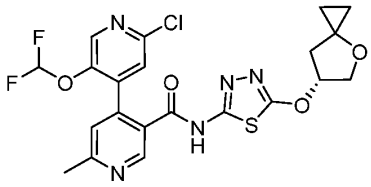
Example 209	 N-(5-(((S)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.97 (s, 1H), 8.19 (s, 1H), 7.49 (s, 1H), 5.64 – 5.56 (m, 1H), 4.09 – 3.94 (m, 2H), 3.74 (s, 3H), 2.60 (s, 3H), 2.51 – 2.43 (m, 1H), 2.19 – 2.11 (m, 1H), 0.88 – 0.77 (m, 1H), 0.77 – 0.68 (m, 1H), 0.66 – 0.56 (m, 1H), 0.55 – 0.46 (m, 1H).	MS (ESI) calc'd for ($C_{21}H_{19}ClFN_5O_4S$) $(M+1)^+$, 492.1, found 492.1.
Example 210	 N-(5-(((R)-4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-3'-fluoro-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 5.63 – 5.55 (m, 1H), 4.10 – 3.94 (m, 2H), 3.74 (s, 3H), 2.60 (s, 3H), 2.50 – 2.42 (m, 1H), 2.18 – 2.10 (m, 1H), 0.87 – 0.77 (m, 1H), 0.77 – 0.68 (m, 1H), 0.66 – 0.56 (m, 1H), 0.55 – 0.45 (m, 1H).	MS (ESI) calc'd for ($C_{21}H_{19}ClFN_5O_4S$) $(M+1)^+$, 492.1, found 492.1.

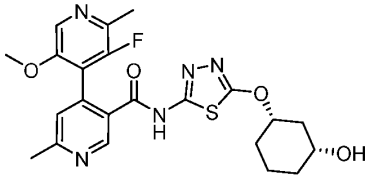
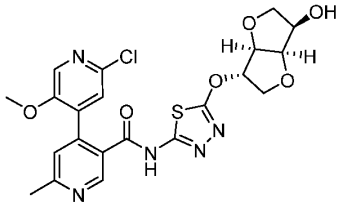
Example 211	 2'-chloro-3'-fluoro-N-(5-(((1r,4r)-4-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.01 (s, 1H), 8.96 (s, 1H), 8.19 (s, 1H), 7.48 (s, 1H), 4.91 – 4.80 (m, 1H), 3.74 (s, 3H), 3.60 – 3.49 (m, 1H), 2.60 (s, 3H), 2.17 – 2.06 (m, 2H), 1.91 – 1.76 (m, 2H), 1.62 – 1.48 (m, 2H), 1.40 – 1.22 (m, 2H).	MS (ESI) calculated for ($C_{21}H_{21}ClFN_5O_4S$) $(M+1)^+$, 494.1; found, 494.1.
Example 212	 2'-chloro-N-(5-(((1S,4s)-4-((R)-1-hydroxyethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.08 (s, 1H), 4.32 (d, J = 4.8 Hz, 1H), 3.64 (s, 3H), 3.45 – 3.37 (m, 1H), 2.59 (s, 3H), 2.09 – 2.07 (m, 2H), 1.69 – 1.55 (m, 3H), 1.51 – 1.43 (m, 1H), 1.40 – 1.21 (m, 3H), 1.04 (d, J = 6.4 Hz, 3H).	MS (ESI) calc'd for ($C_{23}H_{26}ClN_5O_4S$) $(M+1)^+$, 504.1; found, 504.1.
Example 213	 2'-chloro-N-(5-(((1R,4s)-4-((S)-1-	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.42 (s, 1H), 5.08 (s, 1H), 4.32 (d,	MS (ESI) calc'd for ($C_{23}H_{26}ClN_5O_4S$) $(M+1)^+$, 504.1; found, 504.1.

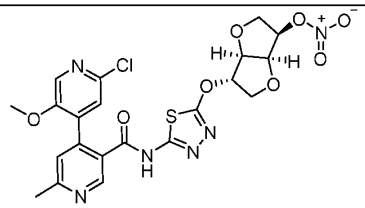
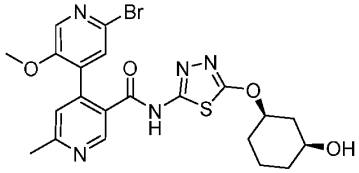
	hydroxyethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The stereochemistry was not determined.	*J* = 4.8 Hz, 1H), 3.64 (s, 3H), 3.45 – 3.37 (m, 1H), 2.59 (s, 3H), 2.09 – 2.07 (m, 2H), 1.70 – 1.52 (m, 3H), 1.51 – 1.43 (m, 1H), 1.41 – 1.19 (m, 3H), 1.04 (d, *J* = 6.4 Hz, 3H).	
Example 214	 (R)-2'-chloro-6-(cyclopropoxymethyl)-5'-methoxy-N-(5-((tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-(4,4'-bipyridine)-3-carboxamide. The absolute stereochemistry is determined.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.89 (s, 1H), 8.19 (s, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 5.56 – 5.50 (m, 1H), 4.70 (s, 2H), 3.93 – 3.81 (m, 3H), 3.77 – 3.75 (m, 1H), 3.64 (s, 3H), 3.53 – 3.51 (m, 1H), 2.33 – 2.21 (m, 1H), 2.15 – 2.11 (m, 1H), 0.61 – 0.59 (m, 2H), 0.52 – 0.49 (m, 2H).	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_5S$) $(M+1)^+$, 504.1; found, 504.1.
Example 220	 2'-chloro-5'-(difluoromethoxy)-N-(5-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The	1H-NMR (400 MHz, DMSO-d^6): δ 13.02 (s, 1H), 8.95 (s, 1H), 8.33 (s, 1H), 7.73 (s, 1H), 7.45 (s, 1H), 7.14 (t, J = 72.0 Hz, 1H), 4.89-4.77 (m, 1H), 4.23 (s, 1H), 2.61 (s, 3H), 1.95-	MS (ESI) calculated for ($C_{22}H_{22}ClF_2N_5O_4S$) $(M+1)^+$, 526.11; found, 526.1.

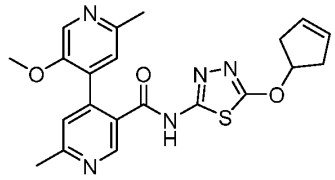
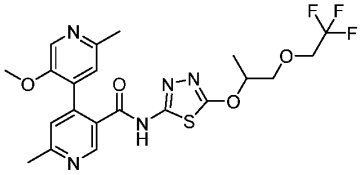
	relative stereochemistry was not determined.	1.76 (m, 4H), 1.67-1.55 (m, 2H), 1.50	
Example 221	 3'-fluoro-N-(5-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.97 (s, 1H), 8.92 (s, 1H), 8.17 (s, 1H), 7.37 (s, 1H), 4.85-4.75 (m, 1H), 4.22 (s, 1H), 3.69 (s, 3H), 2.58 (s, 3H), 2.42 (d, J = 3.2 Hz, 3H), 1.91-1.76 (m, 4H), 1.66-1.57 (m, 2H), 1.47-1.37 (m, 2H), 1.12 (s, 3H).	MS (ESI) calculated for ($C_{23}H_{26}FN_5O_4S$) $(M+1)^+$, 488.18; found, 488.2.
Example 222	 2'-bromo-N-(5-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.87 (s, 1H), 8.83 (s, 1H), 8.16 (s, 1H), 7.59 (s, 1H), 7.37 (s, 1H), 4.84-4.74 (m, 1H), 4.22 (s, 1H), 3.62 (s, 3H), 2.58 (s, 3H), 1.92-1.77 (m, 4H), 1.65-1.57 (m, 2H), 1.47-1.37 (m, 2H), 1.12 (s, 3H).	MS (ESI) calculated for ($C_{22}H_{24}BrN_5O_4S$) $(M+1)^+$, 534.08; found, 534.0.
Example 223		1H-NMR (400 MHz, DMSO-d6): δ 13.03 (s, 1H), 8.95 (s, 1H), 8.33 (s, 1H), 7.72 (s,	MS (ESI) calculated for ($C_{22}H_{22}ClF_2N_5O_4S$) $(M+1)^+$,

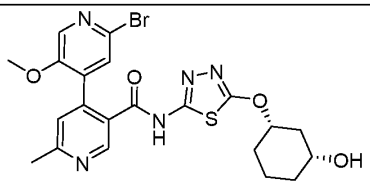
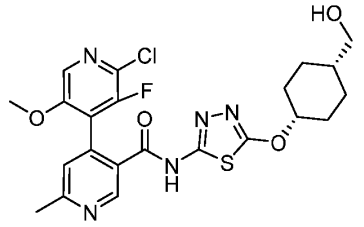
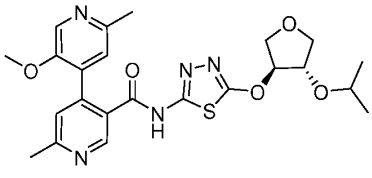
	2'-chloro-5'-(difluoromethoxy)-N-(5-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	1H), 7.45 (s, 1H), 7.14 (t, J = 71.4 Hz, 1H), 5.05-4.97 (m, 1H), 4.23 (s, 1H), 2.61 (s, 3H), 2.02-1.90 (m, 2H), 1.84-1.72 (m, 2H), 1.62-1.50 (m, 2H), 1.49-1.38 (m, 2H), 1.15 (s, 3H).	526.11; found, 526.0
Example 224	 3'-fluoro-N-(5-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-(4,4'-bipyridine)-3-carboxamide. The relative stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.94 (s, 1H), 8.91 (s, 1H), 8.18 (s, 1H), 7.38 (s, 1H), 5.02-4.95 (m, 1H), 4.22 (s, 1H), 3.69 (s, 3H), 2.58 (s, 3H), 2.42 (d, J = 3.20 Hz, 3H), 2.02-1.90 (m, 2H), 1.81-1.70 (m, 2H), 1.60-1.50 (m, 2H), 1.48-1.39 (m, 2H), 1.14 (s, 3H).	MS (ESI) calculated for ($C_{23}H_{26}FN_5O_4S$) $(M-1)^-$, 486.16; found, 486.1.
Example 225	 2'-bromo-N-(5-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-(4,4'-bipyridine)-3-	1H-NMR (400 MHz, DMSO-d^6): δ 12.87 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.63 (s, 1H), 7.42 (s, 1H), 5.06-4.97 (m, 1H), 4.23 (s, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 2.03-1.90 (m, 2H),	MS (ESI) calculated for ($C_{22}H_{24}BrN_5O_4S$) $(M+1)^+$, 534.08; found, 534.0.

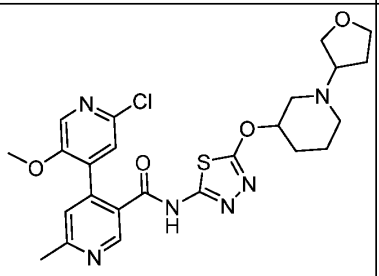
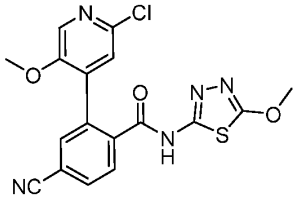
	carboxamide. The relative stereochemistry was not determined.	1.85-1.73 (m, 2H), 1.62-1.50 (m, 2H), 1.49-1.38 (m, 2H), 0.58 (s, 3H).	
Example 232	 (S)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-carboxamide. The absolute stereochemistry is not determined.	^{1}H-NMR (400 MHz, DMSO-d^6): δ 13.14 (s, 1H), 8.98 (s, 1H), 8.32 (s, 1H), 7.70 (s, 1H), 7.42 (s, 1H), 7.14 (t, J = 72.8 Hz, 1H), 5.61-5.55 (m, 1H), 4.02 (dd, J = 4.4 Hz, 10.4 Hz, 1H), 3.97 (d, J = 10.0 Hz, 1H), 2.60 (s, 3H), 2.50-2.40 (m, 1H), 2.13 (d, J = 13.6 Hz, 1H), 0.85-0.78 (m, 1H), 0.77-0.69 (m, 1H), 0.65-0.57 (m, 1H), 0.54-0.46 (m, 1H).	MS (ESI) calculated for ($C_{21}H_{18}ClF_2N_5O_4S$) $(M+1)^+$, 510.08; found, 510.0.
Example 233	 (R)-N-(5-((4-oxaspiro(2.4)heptan-6-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-(difluoromethoxy)-6-methyl-(4,4'-bipyridine)-3-	^{1}H-NMR (400 MHz, DMSO-d^6): δ 13.14 (s, 1H), 8.97 (s, 1H), 8.33 (s, 1H), 7.72 (s, 1H), 7.44 (s, 1H), 7.15 (t, J = 72.4 Hz, 1H), 5.62-5.55 (m, 1H), 4.02 (dd, J = 4.8 Hz, 10.8 Hz, 1H),	MS (ESI) calculated for ($C_{21}H_{18}ClF_2N_5O_4S$) $(M+1)^+$, 510.08; found, 510.0.

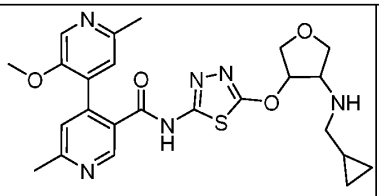
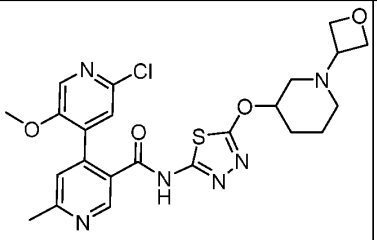
	carboxamide. The absolute stereochemistry is not determined.	3.97 (d, J = 10.0 Hz, 1H), 2.60 (s, 3H), 2.50-2.40 (m, 1H), 2.13 (d, J = 14.0 Hz, 1H), 0.86-0.78 (m, 1H), 0.77-0.69 (m, 1H), 0.65-0.56 (m, 1H), 0.53-0.46 (m, 1H).	
Example 236	 3'-fluoro-N-(5-(((1S,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not determined and the relative stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d^6): δ 12.96 (s, 1H), 8.90 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 4.86-4.75 (m, 2H), 3.69 (s, 3H), 3.55-3.46 (m, 1H), 2.59 (s, 3H), 2.43 (d, J = 3.2 Hz, 3H) 2.43-2.38 (m, 1H), 2.15-2.08 (m, 1H), 1.83-1.68 (m, 2H), 1.35-1.20 (m, 3H), 1.15-1.03 (m, 1H).	MS (ESI) calculated for ($C_{22}H_{24}FN_5O_4S$) $(M+1)^+$, 474.16; found, 474.1.
Example 237	 2'-chloro-N-(5-(((3S,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 – 12.84 (m, 1H), 8.81 (s, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 7.47 – 7.33 (m, 1H), 5.29 (d, J = 3.4 Hz, 1H), 4.98 (d, J = 6.4 Hz, 1H),	MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_6S$) $(M+1)^+$, 506.0, found 506.1

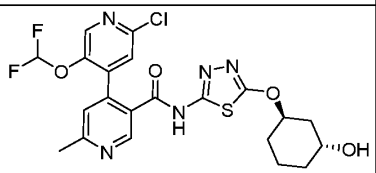
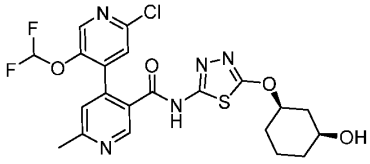
	b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	4.63 (d, J = 4.4 Hz, 1H), 4.51 (t, J = 4.9 Hz, 1H), 4.20 – 4.12 (m, 1H), 4.12 – 4.06 (m, 1H), 4.05 – 3.98 (m, 1H), 3.77 (dd, J = 8.8, 6.4 Hz, 1H), 3.62 (s, 3H), 3.40 (dd, J = 8.6, 7.6 Hz, 1H), 2.58 (s, 3H)	
Example 238	 (3R,3aS,6S,6aR)-6-((5-(2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamido)-1,3,4-thiadiazol-2-yl)oxy)hexahydrofuro[3,2-b]furan-3-yl nitrate	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 12.74 (br s, 1H), 8.99 (s, 1H), 8.04 (s, 1H), 7.30 (s, 1H), 7.21 (s, 1H), 5.45 – 5.39 (m, 2H), 5.09 (t, J = 5.4 Hz, 1H), 4.70 (d, J = 4.9 Hz, 1H), 4.25 (d, J = 11.7 Hz, 1H), 4.13 – 4.03 (m, 2H), 4.00 – 3.94 (m, 1H), 3.73 (s, 3H), 2.72 (s, 3H).	MS (ESI) calc'd for ($C_{21}H_{19}ClN_6O_8S$) $(M+1)^+$, 551.0, found 551.1.
Example 239	 2'-bromo-N-(5-(((1R,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not	1H-NMR (400 MHz, DMSO-d^6): δ 12.90 (s, 1H), 8.84 (s, 1H), 8.16 (s, 1H), 7.59 (s, 1H), 7.37 (s, 1H), 4.78 (d, J = 4.80 Hz, 2H), 3.63 (s, 3H), 3.55-3.42 (m, 1H), 2.57 (s, 3H), 2.43-2.34 (m, 1H), 2.15-2.06 (m,	MS (ESI) calculated for ($C_{21}H_{22}BrN_5O_4S$) $(M+1)^+$, 520.0; found, 519.8 .

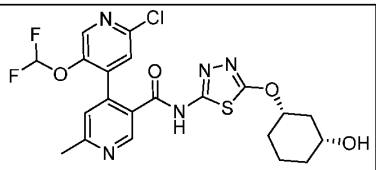
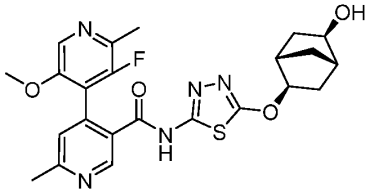
	determined and the relative stereochemistry was determined by X-ray crystallography.	1H), 1.83-1.67 (m, 2H), 1.35-1.20 (m, 3H), 1.18-1.00 (m, 1H).	
Example 240	 N-(5-(cyclopent-3-en-1-yloxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide.	^{1}H NMR (700 MHz, DMSO-d_6) δ ppm 12.85 (br s, 1 H), 8.75 (s, 1 H), 8.18 (s, 1 H), 7.36 (s, 1 H), 7.25 (s, 1 H), 5.78 (s, 2 H), 5.54 (t, *J*=6.00 Hz, 1 H), 3.58 (s, 3 H), 2.83 (dd, *J*=17.20, 6.50 Hz, 2 H), 2.58 (s, 3 H), 2.53 (d, *J*=17.60 Hz, 2 H), 2.47 (s, 3 H).	MS (ESI) calc'd for ($C_{21}H_{21}N_5O_3S$) $(M+1)^+$, 424.49, found 424.3
Example 241	 5'-methoxy-2',6-dimethyl-N-(5-((1-(2,2,2-trifluoroethoxy)propan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide.	^{1}H NMR (700 MHz, DMSO-d_6) δ ppm 12.86 (br s, 1 H), 8.75 (br s, 1 H), 8.19 (s, 1 H), 7.37 (s, 1 H), 7.26 (s, 1 H), 5.18 - 5.23 (m, 1 H), 4.13 (qd, *J*=9.39, 2.37 Hz, 2 H), 3.85 (dd, *J*=11.00, 3.50 Hz, 1 H), 3.81 (dd, *J*=11.00, 6.50 Hz, 1 H), 3.59 (s, 3 H), 2.58 (s, 3 H), 2.47 (s, 3 H), 1.35 (d, *J*=6.45 Hz, 3 H).	MS (ESI) calc'd for ($C_{21}H_{22}F_3N_5O_4S$) $(M+1)^+$, 498.49, found 498.2.

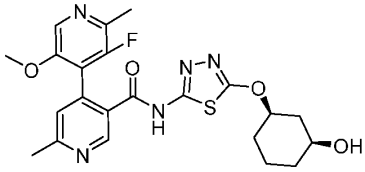
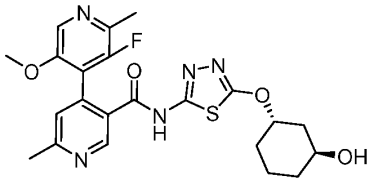
Example 244	 2'-bromo-N-(5-(((1S,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not determined and the relative stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d6): δ 12.88 (s, 1H), 8.79 (s, 1H), 8.18 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 4.90-4.77 (m, 2H), 3.63 (s, 3H), 3.57-3.45 (m, 1H), 2.59 (s, 3H), 2.45-2.37 (m, 1H), 2.18-2.06 (m, 1H), 1.86-1.77 (m, 1H), 1.77-1.68 (m, 1H), 1.38-1.22 (m, 3H), 1.17-1.03 (m, 1H),	MS (ESI) calculated for ($C_{21}H_{22}BrN_5O_4S$) $(M+1)^+$, 520.07; found, 520.0.
Example 245	 2'-chloro-3'-fluoro-N-(5-(((1s,4s)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 13.00 (brs, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.46 (s, 1H), 5.11-5.03 (m, 1H), 4.43 (t, J = 5.2 Hz, 1H), 3.75 (s, 3H), 3.25-3.15 (m, 2H), 2.59 (s, 3H), 2.08-1.97 (m, 2H), 1.70-1.50 (m, 5H), 1.35-1.20 (m, 2H)	MS (ESI) calculated for ($C_{22}H_{23}ClFN_5O_4S$) $(M+1)^+$, 508.12; found, 508.0
Example 246		^{1}H NMR (700 MHz, DMSO-d_6) δ ppm 12.90 (br s, 1 H), 8.75 (s, 1 H), 8.19 (s, 1 H), 7.37 (s, 1 H), 7.26 (s, 1 H) 5.28 (d, *J*=3.44	MS (ESI) calculated for ($C_{23}H_{27}N_5O_4S$) $(M+1)^+$, 486.56; found, 486.3.

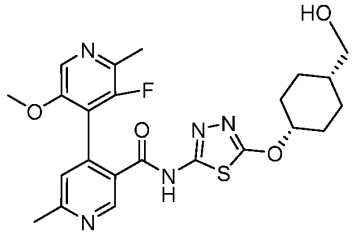
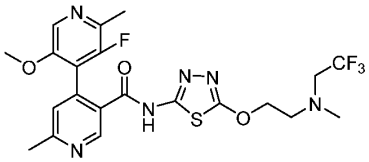
	N-(5-(((3R,4S)-4-isopropyltetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3- carboxamide. The relative stereochemistry was determined as synthesis used starting material with known relative sterochemistry.The absolute stereochemistry was not determined.	Hz, 1 H), 4.29 - 4.31, (m, 1 H), 3.96 - 4.01 (m, 2 H), 3.92 (d, *J*=11.19 Hz, 1 H), 3.87 (quin, *J*=6.00 Hz, 1 H), 3.60 (d, *J*=2.58 Hz, 1 H), 3.59 (s, 3 H), 2.59 (s, 3 H), 2.47 (s, 3 H), 1.14 (d, *J*=6.02 Hz, 3 H), 1.11 (d, *J*=6.02 Hz, 3 H).	
Example 247	 2'-chloro-5'-methoxy-6-methyl-N-(5-((1-(tetrahydrofuran-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide		MS (ESI) calc'd for ($C_{24}H_{27}ClN_6O_4S$) $(M+1)^+$, 531.0, found 531.2
Example 248.	 2-(2-chloro-5-methoxypyridin-4-yl)-4-cyano-N-(5-methoxy-1,3,4-thiadiazol-2-yl)benzamide	^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.97 (br s, 1H), 8.14 (s, 1H), 8.09 (dd, 1H, *J*=1.5, 8.3 Hz), 8.03 (d, 1H, *J*=1.0 Hz), 7.94 (d, 1H, *J*=8.3 Hz), 7.58 (s, 1H), 4.07 (s, 3H), 3.61 (s, 3H)	MS (ESI) calc'd for ($C_{17}H_{12}ClN_5O_3S$) $(M+1)^+$, 402.0, found 402.0.

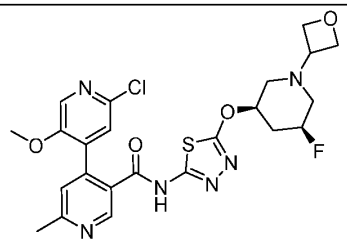
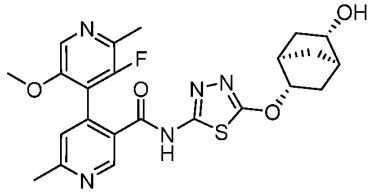
Example 249	 N-(5-((4-((cyclopropylmethyl)amino)tetrahydrofuran-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide.	^{1}H NMR (700 MHz, DMSO-d_6) δ ppm 12.32 (br s, 1 H), 8.75 (s, 1 H), 8.17 - 8.20 (m, 1 H), 7.36 (s, 1 H), 7.25 (s, 1 H), 5.20 - 5.25 (m, 1 H), 4.04 (dd, *J*=8.82, 5.81 Hz, 1 H), 4.00 (dd, *J*=10.76, 4.30 Hz, 1 H), 3.91 (d, *J*=10.76 Hz, 1 H), 3.67 (s, 1 H), 3.58 (s, 3 H), 3.43 - 3.52 (m, 2 H), 2.58 (s, 3 H), 2.47 (s, 3 H), 2.08 (s, 2 H), 0.84 - 0.93 (m, 1 H), 0.37 - 0.43 (m, 2 H), 0.10 - 0.15 (m, 2 H).	MS (ESI) calculated for ($C_{24}H_{28}N_6O_4S$) $(M+1)^+$, 497.19; found, 497.3.
Example 250	 2'-chloro-5'-methoxy-6-methyl-N-(5-((1-(oxetan-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.98 (s, 1H), 8.04 (s, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 5.16 – 5.02 (m, 1H), 4.71 – 4.58 (m, 4H), 3.75 (s, 3H), 3.69 – 3.54 (m, 1H), 2.92 – 2.81 (m, 1H), 2.73 (s, 3H), 2.55 – 2.40 (m, 2H), 2.32 – 2.21 (m, 1H), 2.13 – 2.04 (m, 1H),	MS (ESI) calc'd for ($C_{23}H_{25}ClN_6O_4S$) $(M+1)^+$, 517.0, found 517.2

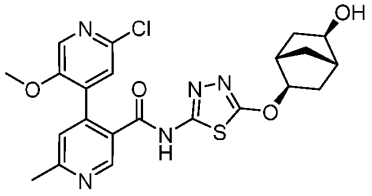
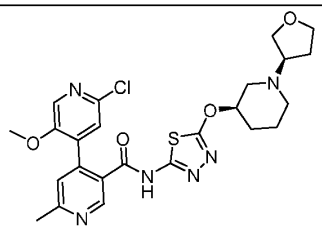
		1.97 – 1.87 (m, 1H), 1.78 – 1.65 (m, 2H)	
Example 251	 2'-chloro-5'-(difluoromethoxy)-N-(5-(((1R,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not determined and the relative stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d^6): δ 13.01 (s, 1H), 8.96 (s, 1H), 8.33 (s, 1H), 7.72 (s, 1H), 7.45 (s, 1H), 7.14 (t, J = 72.4 Hz, 1H), 5.22-5.15 (m, 1H), 4.63 (d, J = 4.0 Hz, 1H), 3.91-3.82 (m, 1H), 2.61 (s, 3H), 1.96-1.88 (m, 1H), 1.87-1.75 (m, 2H), 1.74-1.50 (m, 4H), 1.45-1.34 (m, 1H).	MS (ESI) calculated for ($C_{21}H_{20}ClF_2N_5O_4S$) $(M+1)^+$, 512.10; found, 512.0
Example 252	 2'-chloro-5'-(difluoromethoxy)-N-(5-(((1R,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 9.03 (s, 1H), 8.30 (s, 1H), 7.61 (s, 1H), 7.31 (s, 1H), 7.12 (t, J = 73.2 Hz, 1H), 4.81-4.69 (m, 2H), 3.55-3.45 (m, 1H), 2.59 (s, 3H), 2.41-2.35 (m, 1H), 2.12-2.05 (m, 1H), 1.82-1.65 (m, 2H), 1.32-1.20 (m, 3H), 1.13-1.00 (m, 1H).	MS (ESI) calculated for ($C_{21}H_{20}ClF_2N_5O_4S$) $(M+1)^+$, 512.0; found, 512.0

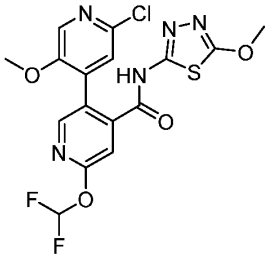
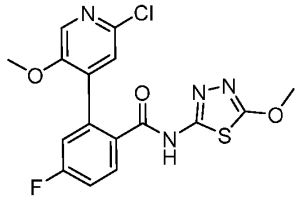
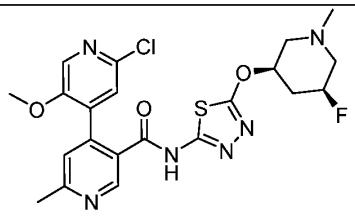
Example 253	 2'-chloro-5'-(difluoromethoxy)-N-(5-(((1S,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methyl-[4,4'-bipyridine]-3-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 9.02 (s, 1H), 8.30 (s, 1H), 7.62 (s, 1H), 7.32 (s, 1H), 7.12 (t, J = 72.8 Hz, 1H), 4.81-4.69 (m, 2H), 3.55-3.45 (m, 1H), 2.59 (s, 3H), 2.41-2.35 (m, 1H), 2.12-2.05 (m, 1H), 1.82-1.66 (m, 2H), 1.32-1.20 (m, 3H), 1.13-1.00 (m, 1H).	MS (ESI) calculated for ($C_{21}H_{20}ClF_2N_5O_4S$) $(M+1)^+$, 512.0; found, 512.0,
Example 254	 3'-fluoro-N-(5-(((1S,2R,4S,5R)-5-hydroxybicyclo[2.2.1]heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d_6): δ 12.97 (brs, 1H), 8.91 (s, 1H), 8.17 (s, 1H), 7.38 (s, 1H), 4.67-4.50 (m, 2H), 3.68 (d, J = 1.20 Hz, 3H), 3.58-3.53 (m, 1H), 2.56 (s, 3H), 2.46-2.42 (m, 1H), 2.42 (d, J = 2.8 Hz, 3H), 2.10 (d, J = 4.4 Hz, 1H), 1.67-1.59 (m, 2H), 1.57-1.49 (m, 1H), 1.48-1.40 (m, 2H), 1.24-1.19 (m, 1H).	MS (ESI) calculated for ($C_{23}H_{24}FN_5O_4S$) $(M+1)^+$ 486.16; found, 486.2

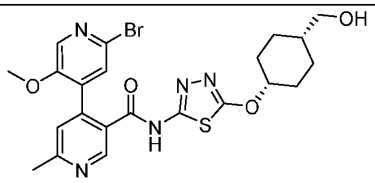
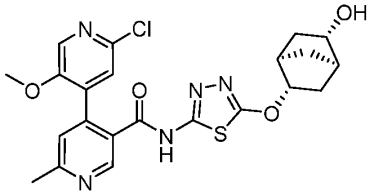
Example 255	 3'-fluoro-N-(5-(((1R,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not determined and the relative stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d6): δ 12.94 (s, 1H), 8.90 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 4.88-4.75 (m, 2H), 3.69 (s, 3H), 3.55-3.45 (m, 1H), 2.59 (s, 3H), 2.43 (d, J = 3.20 Hz, 3H), 2.42-2.37 (m, 1H), 2.15-2.07 (m, 1H), 1.83-1.67 (m, 2H), 1.35-1.20 (m, 3H), 1.15-1.00 (m, 1H).	MS (ESI) calculated for ($C_{22}H_{24}FN_5O_4S$) $(M)^+$, 474.16; found, 474.0.
Example 256	 3'-fluoro-N-(5-(((1S,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not determined and the relative stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d^6): δ 12.95 (s, 1H), 8.90 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 5.21-5.13 (m, 1H), 4.63 (d, J = 4.00 Hz, 1H), 3.92-3.83 (m, 1H), 3.69 (s, 3H), 2.58 (s, 3H), 2.42 (d, J = 3.2 Hz, 3H), 1.92-1.88 (m, 1H), 1.87-1.75 (m, 2H), 1.72-1.49 (m, 4H), 1.42-1.32 (m, 1H).	MS (ESI) calculated for ($C_{22}H_{24}FN_5O_4S$) $(M+1)^+$, 474.16; found, 474.0.

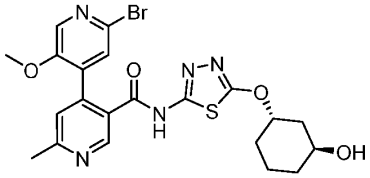
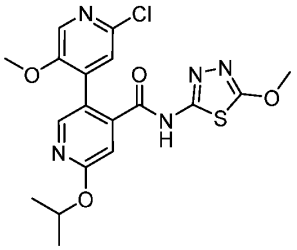
Example 257	 3'-fluoro-N-(5-(((1s,4s)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide . The relative stereochemistry was determined as synthesis used starting material with known relative stereochemistry.	1H-NMR (400 MHz, DMSO-d^6): δ 12.95 (s, 1H), 8.89 (s, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 5.08 (s, 1H), 4.44 (t, J = 5.60 Hz, 1H), 3.69 (s, 3H), 3.26 (t, J = 6.00 Hz, 2H), 2.59 (s, 3H), 2.43 (d, J = 3.20 Hz, 3H), 2.07-1.96 (m, 2H), 1.70-1.40 (m, 5H), 1.38-1.20 (m, 2H).	MS (ESI) calculated for ($C_{23}H_{26}FN_5O_4S$) $(M+1)^+$, 488.18; found, 488.0.
Example 258	 3'-fluoro-5'-methoxy-2',6-dimethyl-N-(5-(2-(methyl(2,2,2-trifluoroethyl) amino)ethoxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.97 – 8.75 (m, 1H), 8.17 (s, 1H), 7.39 (s, 1H), 4.49 (t, *J* = 5.4 Hz, 2H), 3.67 (s, 3H), 3.33 – 3.24 (m, 2H), 2.98 (t, *J* = 5.6 Hz, 2H), 2.58 (s, 3H), 2.44 (s, 3H), 2.42 (d, *J* = 3.4 Hz, 3H)	MS (ESI) calc'd for ($C_{21}H_{22}F4N_6O_3S$) $(M+1)^+$, 515.1, found 515.1.

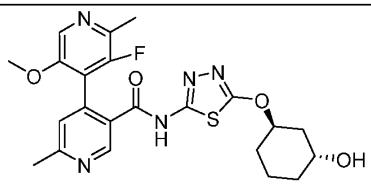
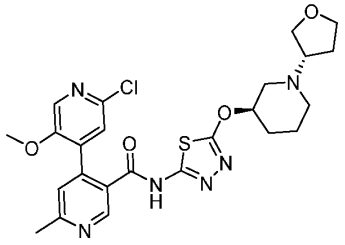
Example 260	 2'-chloro-N-(5-(((3R,5S)-5-fluoro-1-(oxetan-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.80 (s, 1H), 8.10 (s, 1H), 7.50 (s, 1H), 7.45 (s, 1H), 5.17 – 5.05 (m, 1H), 4.86 – 4.79 (m, 1H), 4.70 (td, J = 6.7, 1.7 Hz, 2H), 4.62 (dt, J = 12.7, 6.4 Hz, 2H), 3.74 (s, 3H), 3.72 – 3.65 (m, 1H), 2.93 – 2.84 (m, 1H), 2.82 – 2.71 (m, 1H), 2.69 (s, 3H), 2.60 – 2.40 (m, 3H), 2.15 – 2.02 (m, 1H)	MS (ESI) calc'd for ($C_{23}H_{24}ClFN_6O_4S$) $(M+1)^+$, 535.0, found 535.3
Example 261	 3'-fluoro-N-(5-(((1R,2S,4R,5S)-5-hydroxybicyclo[2.2.1]heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d_6): δ 12.97 (brs, 1H), 8.94 (s, 1H), 8.16 (s, 1H), 7.33 (s, 1H), 4.67-4.49 (m, 2H), 3.68 (d, J = 0.8 Hz, 3H), 3.58-3.53 (m, 1H), 2.57 (s, 3H), 2.46-2.42 (m, 1H), 2.42 (d, J = 2.8 Hz, 3H), 2.09 (d, J = 4.4 Hz, 1H), 1.67-1.59 (m, 2H), 1.56-1.49 (m, 1H), 1.48-1.40 (m, 2H), 1.24-1.19 (m, 1H).	MS (ESI) calculated for ($C_{23}H_{24}FN_5O_4S$) $(M+1)^+$ 486.16; found, 486.2

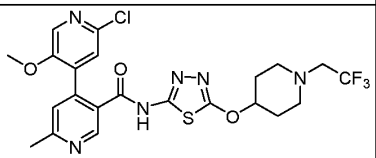
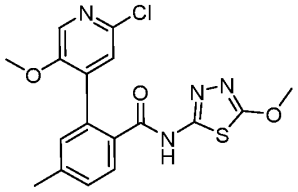
Example 263	 2'-chloro-N-(5-(((1S,2R,4S,5R)-5-hydroxybicyclo[2.2.1]heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.42 (s, 1H), 4.69-4.61 (m, 2H), 3.63 (s, 3H), 3.59-3.54 (m, 1H), 2.59 (s, 3H), 2.49-2.46 (m, 1H), 2.13-2.08 (m, 1H), 1.70-1.59 (m, 2H), 1.58-1.50 (m, 1H), 1.49-1.40 (m, 2H), 1.27-1.17 (m, 1H).	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$ 488.12; found, 488.0
Example 264	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((R)-1-((R)-tetrahydrofuran-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3- carboxamide. The stereochemistry determined using VCD.	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.97 (s, 1H), 8.04 (s, 1H), 7.28 (s, 1H), 7.18 (s, 1H), 5.09 – 4.99 (m, 1H), 3.96 – 3.89 (m, 1H), 3.84 (dd, J = 8.8, 6.8 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.74 (s, 3H), 3.65 (dd, J = 8.8, 6.4 Hz, 1H), 3.13 – 3.04 (m, 1H), 3.02 – 2.95 (m, 1H), 2.72 (s, 3H), 2.55 – 2.35 (m, 3H), 2.09 – 1.98 (m, 2H),	MS (ESI) calc'd for ($C_{24}H_{27}ClN_6O_4S$) $(M+1)^+$, 531.0, found 531.1

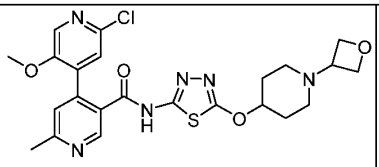
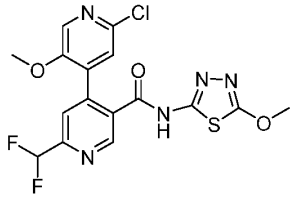
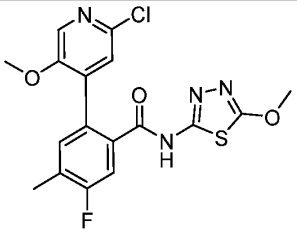
		1.92 – 1.80 (m, 2H), 1.76 – 1.59 (m, 2H)	
Example 265	 2'-chloro-6-(difluoromethoxy)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 13.10 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 7.83 (t, J = 72 Hz, 1H), 7.59 (s, 1H), 7.51 (s, 1H), 4.09 (s, 3H), 3.62 (s, 3H)	MS (ESI) calculated for ($C_{16}H_{12}ClF_2N_5O_4S$) $(M+1)^+$, 444.04; found, 444.0.
Example 266	 2-(2-chloro-5-methoxypyridin-4-yl)-4-fluoro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)benzamide	^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.74 (br s, 1H), 8.12 (s, 1H), 7.84 (dd, 1H, *J*=5.6, 8.6 Hz), 7.50 (s, 1H), 7.4-7.5 (m, 2H), 4.06 (s, 3H), 3.61 (s, 3H)	MS (ESI) calc'd for ($C_{16}H_{12}ClFN_4O_3S$) $(M+1)^+$, 395.0, found 395.2.
Example 267	 2'-chloro-N-(5-(((3R,5S)-5-fluoro-1-methylpiperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-	^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.80 (s, 1H), 8.10 (s, 1H), 7.53 – 7.49 (m, 1H), 7.48 – 7.38 (m, 1H), 5.21 – 5.11 (m, 1H), 4.85 – 4.70 (m, 1H), 3.74 (s, 3H), 2.88 – 2.81 (m, 1H), 2.81 –	MS (ESI) calc'd for ($C_{21}H_{22}ClFN_6O_3S$) $(M+1)^+$, 493.0, found 493.3

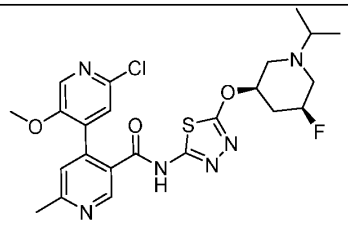
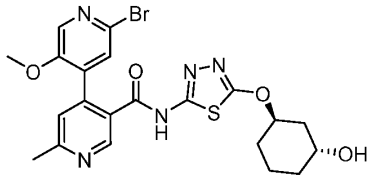
	6-methyl-[4,4'-bipyridine]-3-carboxamide	2.71 (m, 2H), 2.69 (s, 3H), 2.67 – 2.58 (m, 1H), 2.36 (s, 3H), 2.34 – 2.17 (m, 2H)	
Example 268	 2'-bromo-N-(5-(((1s,4s)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide.	1H-NMR (400 MHz, DMSO-d^6): δ 12.88 (s, 1H), 8.84 (s, 1H), 8.16 (s, 1H), 7.58 (s, 1H), 7.36 (s, 1H), 5.05 (s, 1H), 4.45-4.38 (m, 1H), 3.63 (s, 3H), 3.30-3.20 (m, 2H), 2.57 (s, 3H), 2.08-1.98 (m, 2H), 1.70-1.42 (m, 5H), 1.32-1.20 (m, 2H).	MS (ESI) calculated for ($C_{22}H_{24}BrN_5O_4S$) $(M+1)^+$, 534.08; found, 534.0.
Example 269	 2'-chloro-N-(5-(((1R,2S,4R,5S)-5-hydroxybicyclo[2.2.1]heptan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.68-4.61 (m, 2H), 3.63 (s, 3H), 3.59-3.54 (m, 1H), 2.59 (s, 3H), 2.49-2.46 (m, 1H), 2.13-2.08 (m, 1H), 1.70-1.59 (m, 2H), 1.58-1.50 (m, 1H), 1.48-1.40 (m,	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$ 488.12; found, 488.0

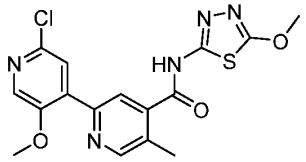
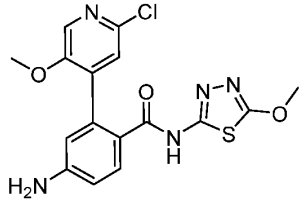
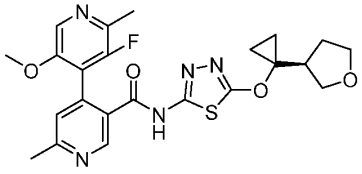
		2H), 1.27-1.17 (m, 1H).	
Example 271	 2'-bromo-N-(5-(((1S,3S)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d^6): δ 12.88 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.62 (s, 1H), 7.40 (s, 1H), 5.22-5.15 (m, 1H), 4.63 (d, J = 4.00 Hz, 1H), 3.91-3.83 (m, 1H), 3.63 (s, 3H), 2.58 (s, 3H), 1.95-1.89 (m, 1H), 1.88-1.75 (m, 2H), 1.74-1.50 (m, 4H), 1.42-1.35 (m, 1H).	MS (ESI) calculated for ($C_{21}H_{22}BrN_5O_4S$) $(M)^+$, 520.4; found, 519.8.
Example 273	 2'-chloro-6-isopropoxy-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 12.92 (s, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.53 (s, 1H), 7.10 (s, 1H), 5.37-5.31 (m, 1H), 4.08 (s, 3H), 3.59 (s, 3H), 1.36 (d, J = 6.40 Hz, 6H).	MS (ESI) calculated for ($C_{18}H_{18}ClN_5O_4S$) $(M+1)^+$, 436.08; found, 435.8.

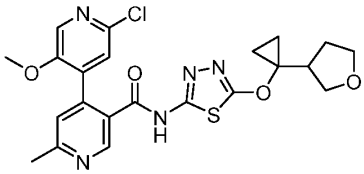
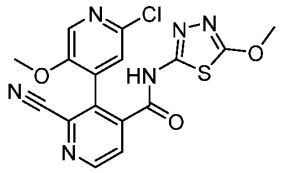
Example 274	 3'-fluoro-N-(5-(((1R,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The absolute stereochemistry was not determined and the relative stereochemistry was determined by X-ray crystallography.	1H-NMR (400 MHz, DMSO-d^6): δ 12.95 (s, 1H), 8.94 (s, 1H), 8.17 (s, 1H), 7.34 (s, 1H), 5.21-5.11 (m, 1H), 4.62 (d, J = 3.60 Hz, 1H), 3.91-3.83 (m, 1H), 3.69 (s, 3H), 2.58 (s, 3H), 2.42 (d, J = 3.2 Hz, 3H), 1.95-1.88 (m, 1H), 1.87-1.73 (m, 2H), 1.72-1.49 (m, 4H), 1.44-1.32 (m, 1H).	MS (ESI) calculated for ($C_{22}H_{24}FN_5O_4S$) $(M+1)^+$, 474.16; found, 474.0.
Example 275	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((R)-1-((S)-tetrahydrofuran-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3- carboxamide. The stereochemistry was dertermined using VCD.	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.97 (s, 1H), 8.04 (s, 1H), 7.28 (s, 1H), 7.18 (s, 1H), 5.12 – 4.98 (m, 1H), 3.94 (td, *J* = 8.7, 4.6 Hz, 1H), 3.85 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.75 (s, 3H), 3.67 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.14 – 3.05 (m, 1H), 2.81 (br dd, *J* = 11.2, 2.9 Hz, 1H), 2.72 (s, 3H), 2.67 – 2.57 (m, 2H), 2.40 – 2.30 (m, 1H), 2.09 – 1.98 (m, 2H), 1.92 –	MS (ESI) calc'd for ($C_{24}H_{27}ClN_6O_4S$) $(M+1)^+$, 531.0, found 531.1

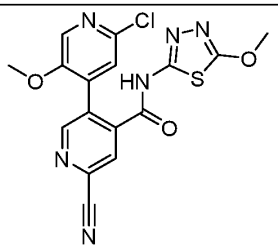
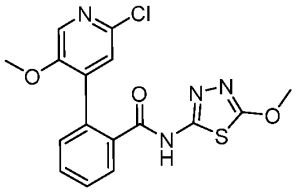
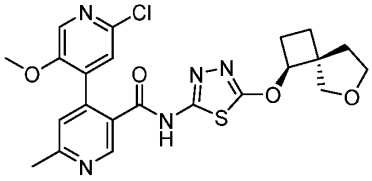
		1.80 (m, 2H), 1.78 – 1.58 (m, 2H)	
Example 278	 2'-chloro-5'-methoxy-6-methyl-N-(5-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.89 (br s, 1H), 8.85 – 8.77 (m, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 4.09 (q, *J* = 5.2 Hz, 1H), 3.61 (s, 3H), 3.24 – 3.18 (m, 2H), 2.89 – 2.78 (m, 2H), 2.61 (br d, *J* = 2.9 Hz, 1H), 2.58 (s, 3H), 2.56 (br d, *J* = 3.4 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.83 – 1.70 (m, 2H)	MS (ESI) calc'd for ($C_{22}H_{22}ClF_3N_6O_3S$) $(M+1)^+$, 543.1, found 543.0.
Example 279	 2-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-methylbenzamide	^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 12.72 (br s, 1H), 8.17 (s, 1H), 7.75 .(d, 1H, *J*=7.8 Hz), 7.52 (s, 1H), 7.48 (dd, 1H, *J*=2.0, 8.3 Hz), 7.38 (s, 1H), 4.15 (s, 3H), 3.68 (s, 3H), 2.50 (s, 3H)	MS (ESI) calc'd for ($C_{17}H_{15}ClN_4O_3S$) $(M+1)^+$, 391.1, found 391.1

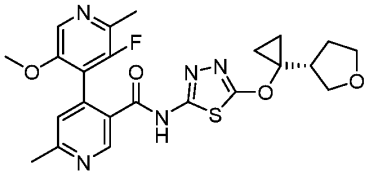
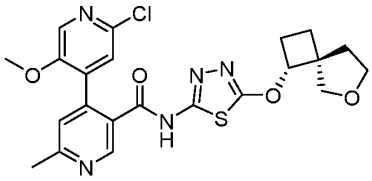
Example 280	 2'-chloro-5'-methoxy-6-methyl-N-(5-((1-(oxetan-3-yl)piperidin-4-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.82 – 8.78 (m, 1H), 8.10 (s, 1H), 7.52 – 7.49 (m, 1H), 7.45 (s, 1H), 5.13 (br s, 1H), 4.81 – 4.74 (m, 2H), 4.68 (t, J = 6.4 Hz, 2H), 3.89 – 3.79 (m, 1H), 3.74 (s, 3H), 2.84 (br d, J = 5.9 Hz, 2H), 2.69 (s, 3H), 2.66 – 2.57 (m, 2H), 2.28 – 2.17 (m, 2H), 2.13 – 2.02 (m, 2H)	MS (ESI) calc'd for ($C_{23}H_{25}ClN_6O_4S$) $(M+1)^+$, 517.1, found 517.0.
Example 281	 2'-chloro-6-(difluoromethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (br s, 1H), 9.06 (s, 1H), 8.22 (s, 1H), 7.87 (s, 1H), 7.66 (s, 1H), 7.10 (t, J = 54.5 Hz, 1H), 4.09 (s, 3H), 3.65 (s, 3H).	MS (ESI) calc'd for ($C_{16}H_{12}ClF_2N_5O_3S$) $(M+1)^+$, 428.0; found 428.1
Example 282	 2-(2-chloro-5-methoxypyridin-4-yl)-5-fluoro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-methyl	^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.74 (br s, 1H), 8.09 (s, 1H), 7.60 (d, 1H, J=9.8 Hz), 7.4-7.5 (m, 2H), 4.07 (s, 3H), 3.59 (s, 3H), 2.33 (s, 3H)	MS (ESI) calc'd for ($C_{17}H_{14}ClFN_4O_3S$) $(M+1)^+$, 409.0, found 409.1

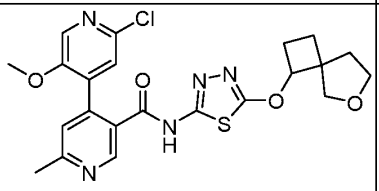
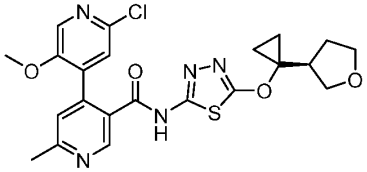
	benzamide		
Example 283	 2'-chloro-N-(5-(((3R,5S)-5-fluoro-1-isopropylpiperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, METHANOL-d$_4$) δ 8.80 (s, 1H), 8.10 (s, 1H), 7.55 – 7.47 (m, 1H), 7.45 (s, 1H), 5.16 – 5.01 (m, 1H), 4.80 – 4.65 (m, 1H), 3.74 (s, 3H), 3.14 (br d, *J* = 11.7 Hz, 1H), 3.07 – 2.91 (m, 2H), 2.71 – 2.62 (m, 4H), 2.58 – 2.40 (m, 2H), 2.06 – 1.88 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 6H)	MS (ESI) calc'd for ($C_{23}H_{26}ClFN_6O_3S$) $(M+1)^+$, 521.0, found 521.3
Example 284	 2'-bromo-N-(5-(((1R,3R)-3-hydroxycyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The stereochemistry	1H-NMR (400 MHz, DMSO-*d*^{6}): δ 12.87 (s, 1H), 8.80 (s, 1H), 8.18 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 5.24-5.15 (m, 1H), 4.63 (d, J = 4.00 Hz, 1H), 3.91-3.83 (m, 1H), 3.63 (s, 3H), 2.59 (s, 3H), 1.95-1.89 (m, 1H), 1.87-1.75 (m, 2H), 1.74-1.50 (m,	MS (ESI) calculated for ($C_{21}H_{22}BrN_5O_4S$) $(M)^+$, 520.4; found, 520.0.

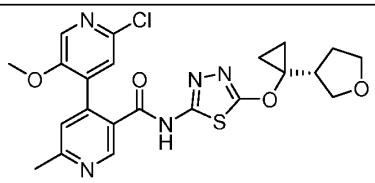
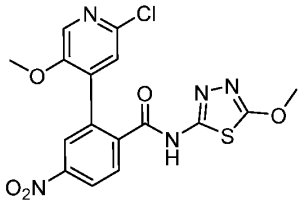
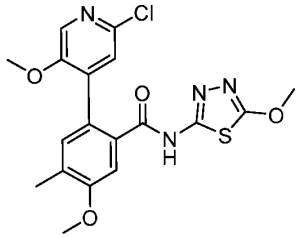
	was determined by X-ray crystallography.	4H), 1.42-1.35 (m, 1H).	
Example 285	 2'-chloro-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-5-methyl-[2,4'-bipyridine]-4-carboxamide.	1H-NMR (400 MHz, DMSO-d6): δ 13.07 (s, 1H), 8.74 (s, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 4.11 (s, 3H), 3.99 (s, 3H), 2.44 (s, 3H).	MS (ESI) calculated for ($C_{16}H_{14}ClN_5O_3S$) $(M+1)^+$, 392.06; found, 392.0.
Example 286	 4-amino-2-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)benzamide	^1H NMR (METHANOL-d_4, 400 MHz) δ 7.96 (s, 1H), 7.53 (d, 1H, *J*=8.8 Hz), 7.34 (s, 1H), 6.75 (dd, 1H, *J*=2.2, 8.6 Hz), 6.60 (d, 1H, *J*=2.4 Hz), 4.10 (s, 3H), 3.69 (s, 3H)	MS (ESI) calc'd for ($C_{16}H_{14}ClN_5O_3S$) $(M+1)^+$, 392.1, found 392.1.
Example 287	 3'-fluoro-5'-methoxy-2',6-dimethyl-N-(5-(1-((S)-tetrahydrofuran-3-yl)cyclopropoxy)-1,3,4-thiadiazol-	1H-NMR (400 MHz, DMSO-d^6): δ 13.03 (s, 1H), 8.90 (s, 1H), 8.19 (s, 1H), 7.40 (s, 1H), 3.79-3.71 (m, 2H), 3.69 (s, 3H), 3.62 (q, J = 7.60 Hz, 1H), 3.42-3.36 (m, 1H),	MS (ESI) calculated for ($C_{23}H_{24}FN_5O_4S$) $(M+1)^+$, 486.16; found, 486.0.

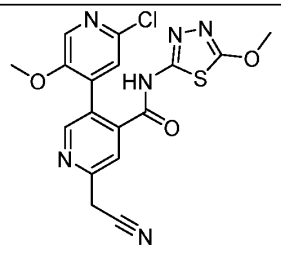
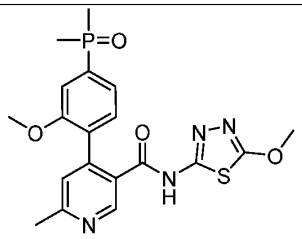
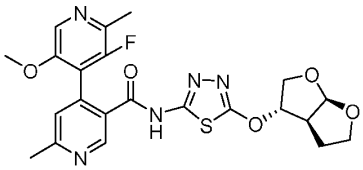
	2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	3.10 (t, J = 7.60 Hz, 1H), 2.59 (s, 3H), 2.43 (d, J = 2.80 Hz, 3H), 2.00-1.90 (m, 1H), 1.61-1.50 (m, 1H), 1.10 -1.02 (m, 2H), 0.98-0.90 (m, 2H),	
Example 288	 2'-chloro-5'-methoxy-6-methyl-N-(5-(1-(tetrahydrofuran-3-yl)cyclopropoxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 12.98 (brs, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 7.53 (s, 1H), 7.44 (s, 1H), 3.80-3.70 (m, 2H), 3.68-3.59 (m, 4H), 3.42-3.38 (m, 1H), 3.15-3.05 (m, 1H), 2.59 (s, 3H), 2.01-1.90 (m, 1H), 1.61-1.51 (m, 1H), 1.12-1.05 (m, 2H), 0.98-0.89 (m, 2H).	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$, 488.12; found, 488.0.
Example 289	 2'-chloro-2-cyano-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide.	1H-NMR (400 MHz, DMSO-d^6): δ 13.39 (brs, 1H), 9.01 (d, J = 4.80 Hz, 1H), 8.32 (s, 1H), 8.18 (d, J = 5.20 Hz, 1H), 7.75 (s, 1H), 4.07 (s, 3H), 3.73 (s, 3H).	MS (ESI) calculated for ($C_{16}H_{11}ClN_6O_3S$) $(M+1)^+$, 403.04; found, 403.0

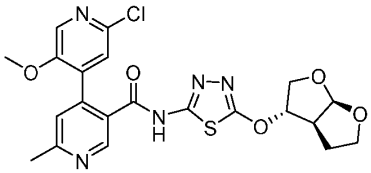
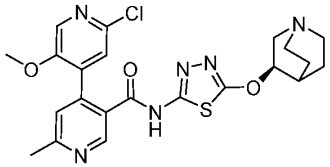
Example 290	 2'-chloro-6-cyano-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide	1H-NMR (400 MHz, DMSO-d6): δ 13.24 (brs, 1H), 8.93 (s, 1H), 8.48 (s, 1H), 8.22 (s, 1H), 7.70 (s, 1H), 4.09 (s, 3H), 3.63 (s, 3H).	MS (ESI) calculated for ($C_{16}H_{11}ClN_6O_3S$) $(M+1)^+$, 403.04; found, 403.0
Example 291	 2-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)benzamide	^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.73 (br s, 1H), 8.10 (s, 1H), 7.77 (dd, 1H, *J*=1.2, 7.6 Hz), 7.6-7.7 (m, 1H), 7.6-7.6 (m, 1H), 7.48 (dd, 1H, *J*=1.0, 7.3 Hz), 7.44 (s, 1H), 4.07 (s, 3H), 3.61 (s, 3H)	MS (ESI) calc'd for ($C_{16}H_{13}ClN_4O_3S$) $(M+1)^+$, 377.0, found 377.1.
Example 292	 rac-N-(5-(((1S,4S)-6-oxaspiro[3.4]octan-1-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.89 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.23 (t, *J* = 7.6 Hz, 1H), 4.02 (d, J = 8.8 Hz, 1H), 3.64-3.52 (m, 3H), 3.63 (s, 3H), 2.59 (s, 3H), 2.40-2.32 (m, 1H), 2.31-2.21 (m, 1H), 2.05-1.97 (m, 1H), 1.97-	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$, 488.12; found, 488.0.

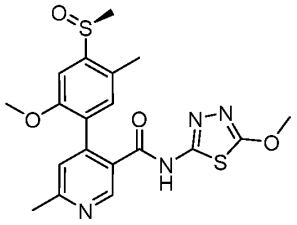
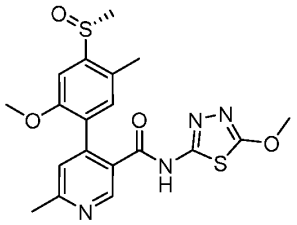
		1.85 (m, 2H), 1.82-1.72 (m, 1H).	
Example 293	 3'-fluoro-5'-methoxy-2',6-dimethyl-N-(5-(1-((R)-tetrahydrofuran-3-yl)cyclopropoxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 13.06 (s, 1H), 8.93 (s, 1H), 8.18 (s, 1H), 7.37 (s, 1H), 3.79-3.71 (m, 2H), 3.69 (s, 3H), 3.61 (q, J = 7.60 Hz, 1H), 3.42-3.36 (m, 1H), 3.10 (t, J = 7.60 Hz, 1H), 2.58 (s, 3H), 2.43 (d, J = 2.80 Hz, 3H), 2.00-1.90 (m, 1H), 1.60-1.50 (m, 1H), 1.10 -1.02 (m, 2H), 0.98-0.90 (m, 2H),	MS (ESI) calculated for ($C_{23}H_{24}FN_5O_4S$) $(M+1)^+$, 486.16; found, 486.2.
Example 295	 rac-N-(5-(((1R,4S)-6-oxaspiro[3.4]octan-1-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The	1H-NMR (400 MHz, DMSO-d^6): δ 8.80 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.19 (t, J = 7.6 Hz, 1H), 3.91 (d, J = 8.8 Hz, 1H), 3.72-3.58 (m, 3H), 3.63 (s, 3H), 2.59 (s, 3H), 2.40-2.30 (m, 1H), 2.28-2.19 (m, 1H), 2.12-	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$, 488.12; found, 488.0.

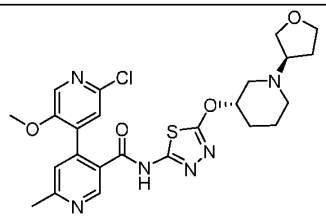
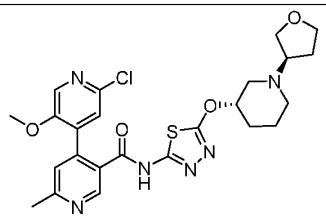
	stereochemistry was not determined.	2.00 (m, 1H), 1.90-1.80 (m, 2H), 1.78-1.69 (m, 1H).	
Example 296	 N-(5-((6-oxaspiro[3.4]octan-1-yl)oxy)-1,3,4-thiadiazol-2-yl)-2'-chloro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide		MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$, 488.12; found, 488.0.
Example 297	 (S)-2'-chloro-5'-methoxy-6-methyl-N-(5-(1-(tetrahydrofuran-3-yl)cyclopropoxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 13.05 (brs, 1H), 8.81 (s, 1H), 8.19 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 3.79-3.70 (m, 2H), 3.69-3.58 (m, 4H), 3.42-3.35 (m, 1H), 3.15-3.05 (m, 1H), 2.59 (s, 3H), 2.02-1.90 (m, 1H), 1.62-1.51 (m, 1H), 1.14-1.04 (m, 2H), 0.99-0.89 (m, 2H),	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$, 488.12; found, 488.0.

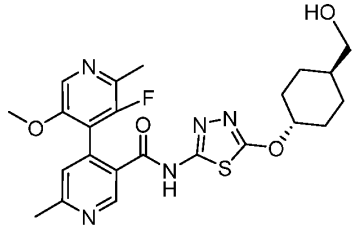
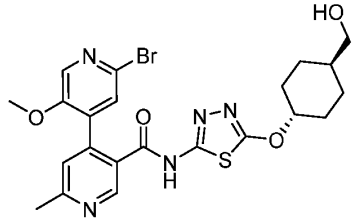
Example 299	 (R)-2'-chloro-5'-methoxy-6-methyl-N-(5-(1-(tetrahydrofuran-3-yl)cyclopropoxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.98 (brs, 1H), 8.81 (s, 1H), 8.19 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 3.80-3.70 (m, 2H), 3.69-3.58 (m, 4H), 3.42-3.36 (m, 1H), 3.15-3.05 (m, 1H), 2.59 (s, 3H), 2.02-1.90 (m, 1H), 1.62-1.51 (m, 1H), 1.13-1.05 (m, 2H), 0.99-0.89 (m, 2H).	MS (ESI) calculated for ($C_{22}H_{22}ClN_5O_4S$) $(M+1)^+$, 488.12; found, 488.0.
Example 300	 2-(2-chloro-5-methoxypyridin-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-nitrobenzamide	^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.09 (br s, 1H), 8.42 (dd, 1H, *J*=2.2, 8.6 Hz), 8.29 (d, 1H, *J*=2.4 Hz), 8.17 (s, 1H), 8.04 (d, 1H, *J*=8.8 Hz), 7.62 (s, 1H), 4.08 (s, 3H), 3.63 (s, 3H)	MS (ESI) calc'd for ($C_{16}H_{12}ClN_5O_5S$) $(M+1)^+$, 422.0, found 422.1.
Example 301	 2-(2-chloro-5-methoxypyridin-4-yl)-5-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-methylbenzamide	^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.65 (s, 1H), 8.05 (s, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.26 (d, 1H, *J*=1.0 Hz), 4.07 (s, 3H), 3.94 (s, 3H), 3.58 (s, 3H), 2.23 (s, 3H)	MS (ESI) calc'd for ($C_{18}H_{17}ClN_4O_4S$) $(M+1)^+$, 421.1, found 421.1.

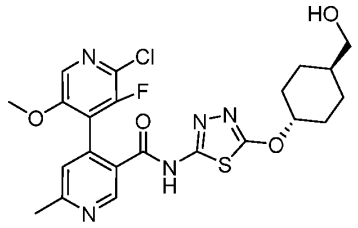
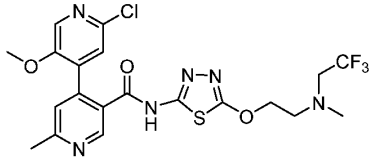
Example 302	 2'-chloro-6-(cyanomethyl)-5'-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-[3,4'-bipyridine]-4-carboxamide	1H-NMR (400 MHz, DMSO-d^6): δ 13.08 (s, 1H), 8.72 (s, 1H), 8.17 (s, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 4.40 (s, 2H), 4.09 (s, 3H), 3.62 (s, 3H).	MS (ESI) calculated for ($C_{17}H_{13}ClN_6O_3S$) $(M+1)^+$, 417.05; found, 417.0.
Example 303	 4-(4-(dimethylphosphoryl)-2-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	1H-NMR (400 MHz, DMSO-d^6): δ 12.82 (brs, 1H), 8.71 (s, 1H), 7.49-7.45 (m, 2H), 7.33-7.29 (m, 2H), 4.07 (s, 3H), 3.58 (s, 3H), 2.58 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H)	MS (ESI) calculated for ($C_{19}H_{21}N_4O_4PS$) $(M+1)^+$, 433.11; found, 433.2
Example 304	 3'-fluoro-N-(5-(((3S,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 – 12.89 (m, 1H), 8.89 (s, 1H), 8.17 (s, 1H), 7.40 (s, 1H), 5.77 (d, J = 4.9 Hz, 1H), 5.36 (s, 1H), 4.04 (d, J = 2.4 Hz, 2H), 3.84 – 3.69 (m, 2H), 3.68 (s, 3H), 3.08 – 2.99 (m, 1H), 2.58 (s, 3H), 2.42 (d, J = 2.9 Hz,	MS (ESI) calc'd for ($C_{22}H_{22}FN_5O_5S$) $(M+1)^+$, 488.1, found 488.1.

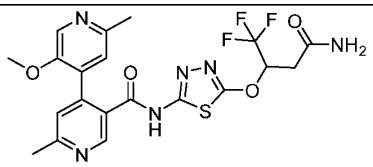
		3H), 2.18 – 2.06 (m, 1H), 1.95 (ddt, *J* = 13.1, 6.6, 3.4 Hz, 1H)	
Example 305	 2'-chloro-N-(5-(((3S,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 – 12.76 (m, 1H), 8.79 (s, 1H), 8.17 (s, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 5.78 (d, *J* = 5.4 Hz, 1H), 5.37 (d, *J* = 2.0 Hz, 1H), 4.08 – 4.02 (m, 2H), 3.85 – 3.69 (m, 2H), 3.62 (s, 3H), 3.09 – 2.98 (m, 1H), 2.59 (s, 3H), 2.18 – 2.08 (m, 1H), 1.95 (ddt, *J* = 13.1, 6.6, 3.4 Hz, 1H)	MS (ESI) calc'd for ($C_{21}H_{20}ClN_5O_5S$) $(M+1)^+$, 490.1, found 490.1.
Example 306	 (R)-2'-chloro-5'-methoxy-6-methyl-N-(5-(quinuclidin-3-yloxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide.	1H NMR (400 MHz, METHANOL-d4) δ ppm 1.59 - 1.73 (m, 1 H), 1.73 - 1.86 (m, 1 H), 1.86 - 1.99 (m, 1 H), 2.00 - 2.13 (m, 1 H), 2.37 - 2.46 (m, 1 H), 2.66 (s, 3 H), 2.89 - 3.14 (m, 5 H), 3.46 - 3.58 (m, 1 H) ,3.73 (s, 3 H), 5.05 - 5.17	MS (ESI) calculated for ($C_{22}H_{23}ClN_6O_3S$)($M+1)^+$, 487.1; found, 487.0, 489.0

		(m, 1 H), 7.38 (s, 1 H), 7.44 - 7.48 (m, 1 H),8.03 - 8.09 (m, 1 H), 8.79 - 8.85 (m, 1 H)	
Example 307	 (S)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxy-5-methyl-4-(methylsulfinyl)phenyl)-6-methylnicotinamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.72 (brs, 1H), 8.73 (s, 1H), 7.34-7.25 (m, 3H), 4.05 (s, 3H), 3.56 (s, 3H), 2.74 (s, 3H), 2.57 (s, 3H), 2.33 (s, 3H).	MS (ESI) calculated for ($C_{19}H_{20}N_4O_4S_2$) $(M+1)^+$, 433.10; found, 433.0
Example 308	 (R)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(2-methoxy-5-methyl-4-(methylsulfinyl)phenyl)-6-methylnicotinamide. The stereochemistry was not determined.	1H-NMR (400 MHz, DMSO-d^6): δ 12.83 (brs, 1H), 8.73 (s, 1H), 7.35-7.26 (m, 3H), 4.05 (s, 3H), 3.56 (s, 3H), 2.74 (s, 3H), 2.57 (s, 3H), 2.33 (s, 3H).	MS (ESI) calculated for ($C_{19}H_{20}N_4O_4S_2$) $(M+1)^+$, 433.10; found, 433.1

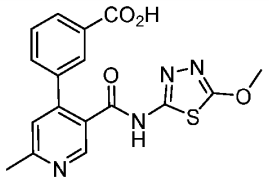
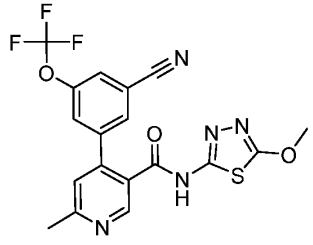
Example 309	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((S)-1-((R)-tetrahydrofuran-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3- carboxamide. The stereochemistry was determined using VCD..	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 4.91 (dt, 1H), 3.81 – 3.68 (m, 2H), 3.63 (s, 3H), 3.62 – 3.57 (m, 1H), 3.48 (dd, J = 8.6, 6.1 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.91 – 2.79 (m, 1H), 2.59 (s, 4H), 2.48 – 2.41 (m, 1H), 2.28 – 2.16 (m, 1H), 2.07 – 1.89 (m, 2H), 1.82 – 1.65 (m, 2H), 1.63 – 1.44 (m, 2H)	MS (ESI) calc'd for ($C_{24}H_{27}ClN_6O_4S$) $(M+1)^+$, 531.0, found 531.1
Example 310	 2'-chloro-5'-methoxy-6-methyl-N-(5-(((S)-1-((S)-tetrahydrofuran-3-yl)piperidin-3-yl)oxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3- carboxamide. The stereochemistry was determined using VCD.	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (br d, J = 4.4 Hz, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 5.00 – 4.86 (m, 1H), 3.78 (td, J = 8.4, 4.2 Hz, 1H), 3.74 – 3.69 (m, 1H), 3.63 (s, 3H), 3.62 – 3.57 (m, 1H), 3.46 (dd, J = 8.6, 6.1 Hz, 1H), 3.10 – 2.94 (m, 2H), 2.59 (s, 3H),	MS (ESI) calc'd for ($C_{24}H_{27}ClN_6O_4S$) $(M+1)^+$, 531.0, found 531.1

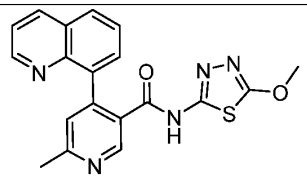
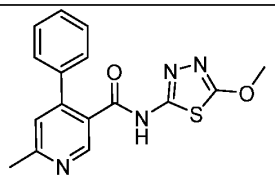
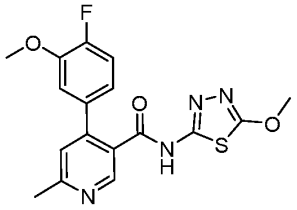
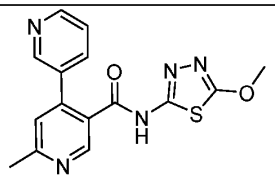
		2.49 – 2.42 (m, 1H), 2.41 – 2.16 (m, 2H), 2.08 – 1.89 (m, 2H), 1.82 – 1.68 (m, 2H), 1.65 – 1.42 (m, 2H)	
Example 314	 3'-fluoro-N-(5-(((1r,4r)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide. The relative stereochemistry was determined as synthesis used starting material with known relative stereochemistry.	1H-NMR (400 MHz, DMSO-d^6): δ 12.96 (s, 1H), 8.89 (s, 1H), 8.18 (s, 1H), 7.40 (s, 1H), 4.85-4.75 (m, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.68 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 2.59 (s, 3H), 2.43 (d, J = 2.80 Hz, 3H), 2.23-2.15 (m, 2H), 1.85-1.77 (m, 2H), 1.50-1.32 (m, 3H), 1.10-0.98 (m, 2H).	MS (ESI) calculated for ($C_{23}H_{26}FN_5O_4S$) $(M+1)^+$, 488.18; found, 488.2.
Example 315,	 2'-bromo-N-(5-(((1r,4r)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The relative stereochemistry was determined as	1H-NMR (400 MHz, DMSO-d^6): δ 12.88 (s, 1H), 8.79 (s, 1H), 8.18 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 4.85-4.75 (m, 1H), 4.46 (t, J = 5.20 Hz, 1H), 3.62 (s, 3H), 3.18 (t, J = 5.20 Hz, 2H), 2.69 (s, 3H), 2.25-2.15 (m, 2H), 1.87-	MS (ESI) calculated for ($C_{22}H_{24}BrN_5O_4S$) $(M+1)^+$, 534.08; found, 534.0.

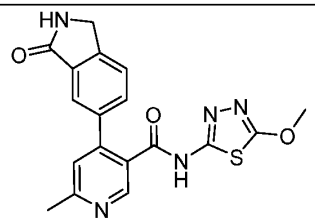
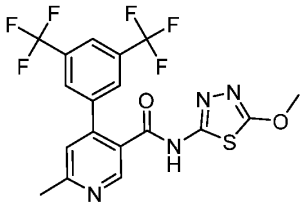
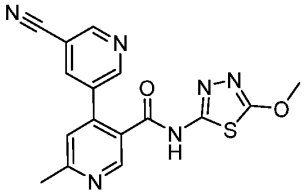
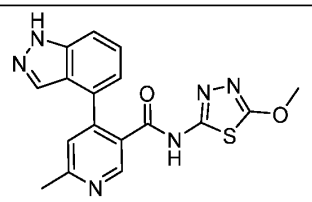
	synthesis used starting material with known relative stereochemistry.	1.76 (m, 2H), 1.50-1.35 (m, 3H), 1.11-0.98 (m, 2H).	
Example 316	 2'-chloro-3'-fluoro-N-(5-(((1r,4r)-4-(hydroxymethyl)cyclohexyl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide. The relative stereochemistry was determined as synthesis used starting material with known relative stereochemistry.	1H-NMR (400 MHz, DMSO-d^6): δ 13.03 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 7.46 (s, 1H), 4.82-4.73 (m, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.74 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 2.59 (s, 3H), 2.25-2.15 (m, 2H), 1.85-1.77 (m, 2H), 1.50-1.31 (m, 3H), 1.11-0.99 (m, 2H).	MS (ESI) calculated for ($C_{22}H_{23}ClFN_5O_4S$) $(M+1)^+$, 508.12; found, 508.1.
Example 317	 2'-chloro-5'-methoxy-6-methyl-N-(5-(2-(methyl(2,2,2-trifluoroethyl)amino)ethoxy)-1,3,4-thiadiazol-2-yl)-[4,4'-bipyridine]-3-carboxamide	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.71 (s, 1H), 8.08 (s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 4.41 (t, J = 5.6 Hz, 2H), 3.54 (s, 3H), 3.22 – 3.16 (m, 2H), 2.90 (t, J = 5.6 Hz, 2H), 2.41 (t, J = 2.0 Hz, 3H), 2.36 (s, 3H).	MS (ESI) calc'd for ($C_{20}H_{20}ClF_3N_6O_3S$) $(M+1)^+$, 517.1, found 517.2.

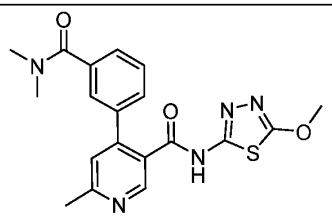
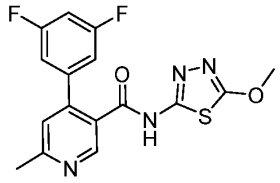
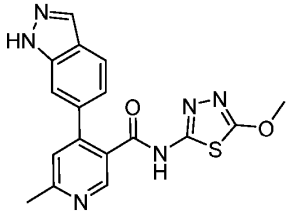
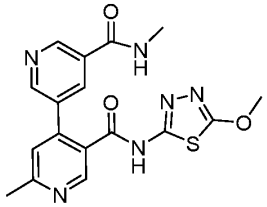
Example 324	 N-(5-((4-amino-1,1,1-trifluoro-4-oxobutan-2-yl)oxy)-1,3,4-thiadiazol-2-yl)-5'-methoxy-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide.	^{1}H NMR (700 MHz, DMSO-d_6) δ ppm 13.48 (br s, 1 H), 12.31 - 12.86 (m, 2 H), 8.79 (s, 1 H), 8.18 (s, 1 H), 7.40 (s, 1 H), 7.28 (s, 1 H), 6.42 - 6.46 (m,1 H), 3.54 (s, 3 H), 2.60 (s, 5 H), 2.48 (s, 3 H).	MS (ESI) calc'd for ($C_{20}H_{19}F_3N_6O_4S$) $(M+1)^+$, 497.47, found 497.2

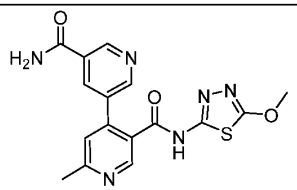
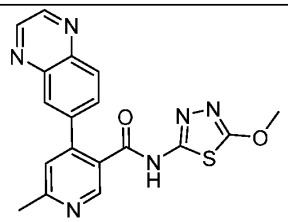
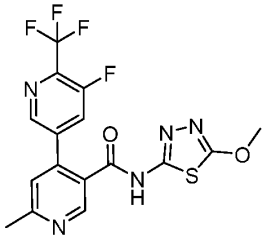
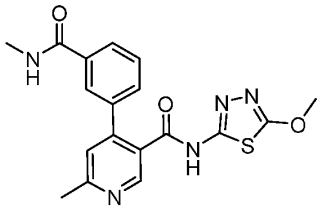
Following procedures similar to the palladium-catalyzed coupling procedure described in Example 377, Step 3, the following examples were synthesized.

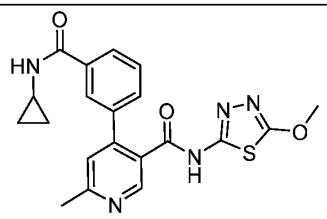
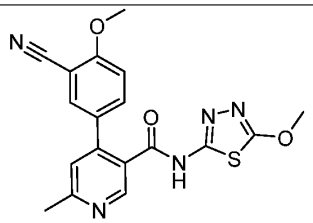
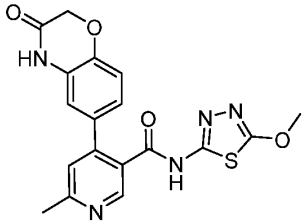
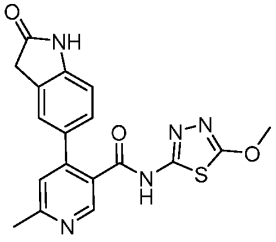
Example	Structure / Name	LCMS
Example 326	 3-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)benzoic acid	MS (ESI) calculated for ($C_{17}H_{14}N_4O_4S$) $(M+1)^+$, 371.1; found, 371.1.
Example 327		MS (ESI) calculated for ($C_{18}H_{12}F_3N_5O_3S$) $(M+1)^+$, 436.1; found, 436.1.

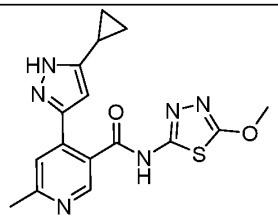
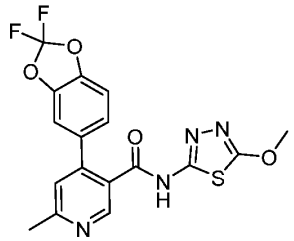
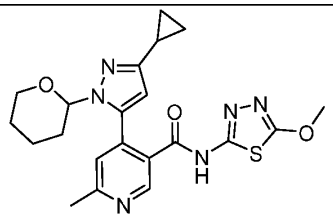
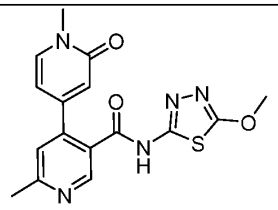
	4-[3-cyano-5-(trifluoromethoxy)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	
Example 328	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(quinolin-8-yl)nicotinamide	MS (ESI) calc'd for ($C_{19}H_{15}N_5O_2S$) $(M+1)^+$, 378.1, found 378.0.
Example 329	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{14}N_4O_2S$) $(M+1)^+$, 327.1, found 327.1
Example 330	 4-(4-fluoro-3-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_3S$) $(M+Na)^+$, 397.1 found 397.2 $[M+Na]^+$
Example 331	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{15}H_{13}N_5O_2S$) $(M+1)^+$, 328.1, found 328.2.

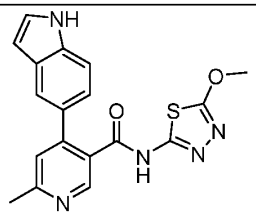
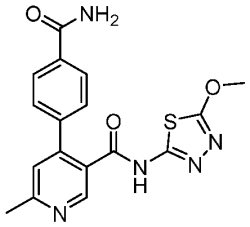
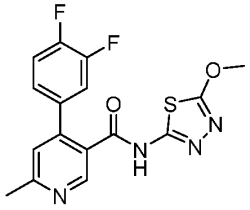
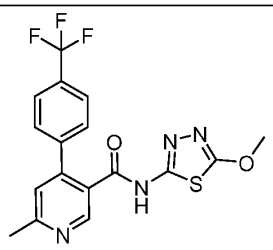
Example 332	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_3S$) $(M+1)^+$, 328.1, found 328.1.
Example 333	 4-[3,5-bis(trifluoromethyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{12}F_6N_4O_2S$) $(M+1)^+$, 463.1, found 463.2.
Example 334	 5-cyano-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{12}N_6O_2S$) $(M+1)^+$, 353.1, found 353.1.
Example 335	 4-(1H-indazol-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.1.

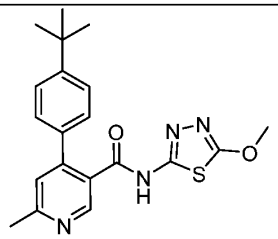
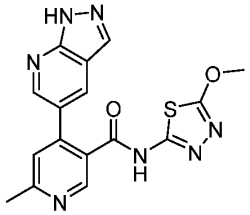
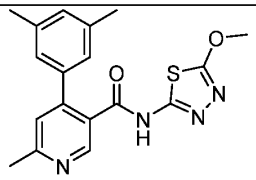
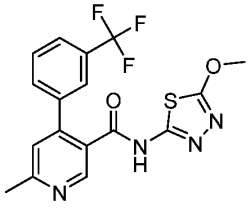
Example 336	 4-[3-(dimethylcarbamoyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{19}N_5O_3S$) $(M+1)^+$, 398.1, found 398.2.
Example 337	 4-(3,5-difluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{12}F_2N4O2S$) $(M+1)^+$, 363.1, found 363.1.
Example 338	 4-(1H-indazol-6-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.1.
Example 339	 N3'-(5-methoxy-1,3,4-thiadiazol-2-yl)-N5,6'-dimethyl-[3,4'-bipyridine]-3',5-dicarboxamide	MS (ESI) calc'd for ($C_{17}H_{16}N_6O_3S$) $(M+1)^+$, 385.1, found 385.1.

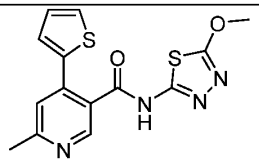
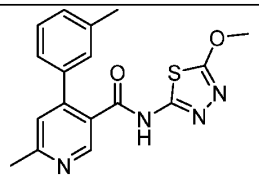
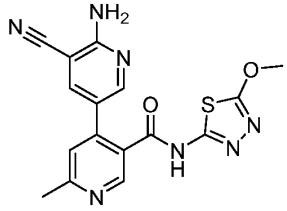
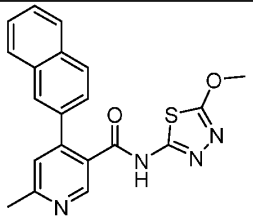
Example 340	 N3'-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3',5-dicarboxamide	MS (ESI) calc'd for ($C_{16}H_{14}N_6O_3S$) $(M+1)^+$, 371.1, found 371.1.
Example 341	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(quinoxalin-6-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{14}N_6O_2S$) $(M+1)^+$, 379.1, found 379.1.
Example 342	 5-fluoro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-6-(trifluoromethyl)-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{11}F_4N_5O_2S$) $(M+1)^+$, 414.1, found 414.1.
Example 343	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(methylcarbamoyl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{17}N_5O_3S$) $(M+1)^+$, 384.1, found 384.1.

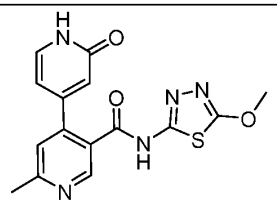
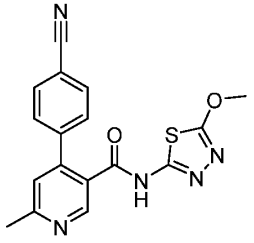
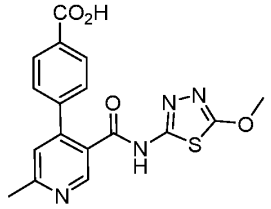
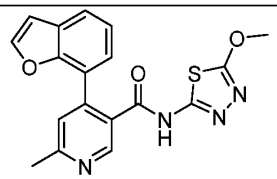
Example 344	 4-[3(cyclopropylcarbamoyl)phenyl] -N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3carboxamide	MS (ESI) calc'd for ($C_{20}H_{19}N_5O_3S$) $(M+1)^+$, 410.1, found 410.1.
Example 345	 4-(3-cyano-4-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_3S$) $(M+1)^+$, 382.1, found 382.0.
Example 346	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_4S$) $(M+1)^+$, 398.1, found 398.1.
Example 347	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_3S$) $(M+1)^+$, 382.1, found 382.1.

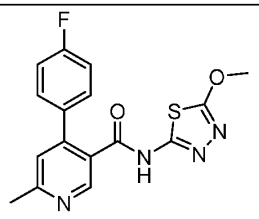
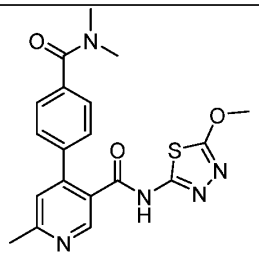
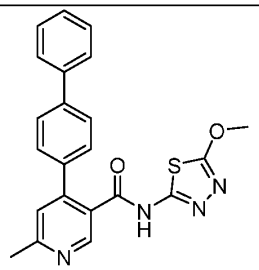
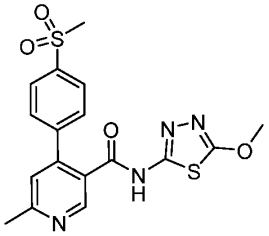
Example 348	 4-(3-cyclopropyl-1H-pyrazol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{16}N_6O_2S$) $(M+1)^+$, 357.1, found 357.1.
Example 349	 4-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{12}F_2N_4O_4S$) $(M+1)^+$, 407.1, found 407.0.
Example 350	 4-(3-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{21}H_{24}N_6O_3S$) $(M+1)^+$, 441.1 , found 441.1.
Example 351	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-1',6-dimethyl-2'-oxo-1',2'-dihydro-[4,4'-bipyridine]-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_3S$) $(M+1)^+$, 358.1, found 358.1.

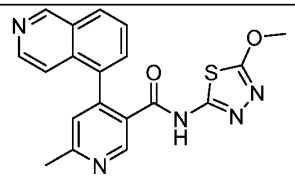
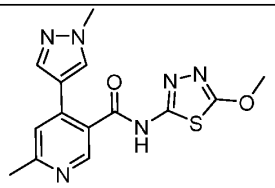
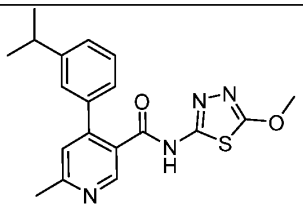
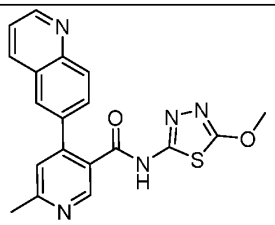
Example 352	 4-(1H-indol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_2S$) $(M+1)^+$, 366.1, found 366.1.
Example 353	 4-(4-carbamoylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}N_5O_3S$) $(M+1)^+$, 370.1, found 370.1.
Example 354	 4-(3,4-difluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{12}F_2N_4O_2S$) $(M+1)^+$, 363.1, found 363.1.
Example 355	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-methyl4-(4-(trifluoromethyl) phenyl) nicotinamide	MS (ESI) calc'd for ($C_{17}H_{13}F_3N_4O_2S$) $(M+Na)^+$, 417.1, found 417.0.

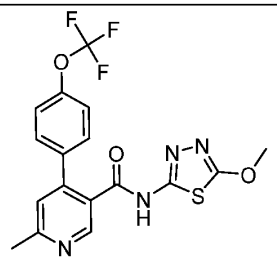
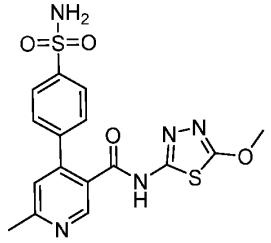
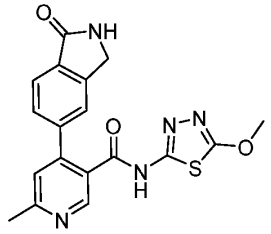
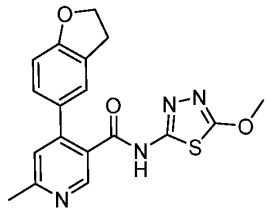
Example 356	 4-(4-(tert-butyl)phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{20}H_{22}N_4O_2S$) $(M+1)^+$, 383.2, found 383.2.
Example 357	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1H-pyrazolo[3,4-b]pyridin-5-yl)nicotinamide	MS (ESI) calc'd for ($C_{16}H_{13}N_7O_2S$) $(M+1)^+$, 368.1, found 368.1.
Example 358	 4-(3,5-dimethylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_2S$) $(M+1)^+$, 355.1, found 355.2.
Example 359	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{13}F_3N_4O_2S$) $(M+1)^+$, 395.1, found 395.2.

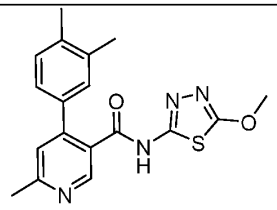
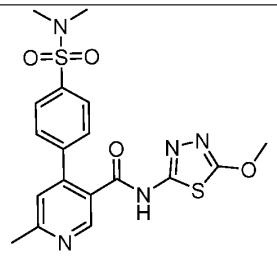
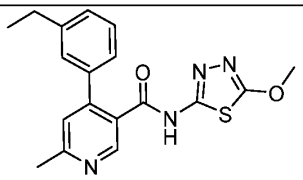
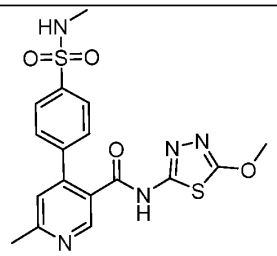
Example 360	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(thiophen-2-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{14}H_{13}N_4O_2S_2$) $(M+1)^+$, 333.0, found 333.1.
Example 361	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(3-methylphenyl) pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{16}N_4O_2S$) $(M+1)^+$, 341.1, found 341.1.
Example 362	 6-amino-5-cyano-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{13}N_7O_2S$) $(M+1)^+$, 368.1, found 368.1.
Example 363	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(naphthalen-2-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{16}N_4O_2S$) $(M+1)^+$, 377.1, found 377.1.

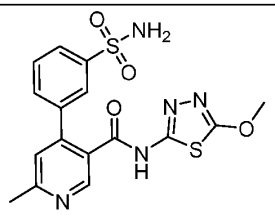
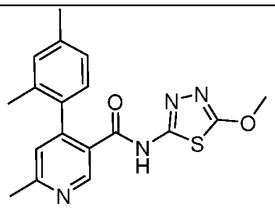
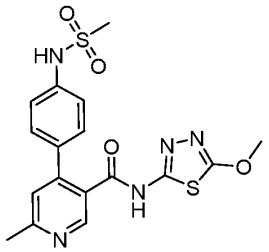
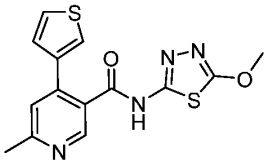
Example 364	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-2'-oxo-1',2'-dihydro-[4,4'-bipyridine]-3-carboxamide	MS (ESI) calc'd for ($C_{15}H_{13}N_5O_3S$) $(M+1)^+$, 344.1, found 344.2.
Example 365	 4-(4-cyanophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{13}N_5O_2S$) $(M+1)^+$, 352.1, found 352.1.
Example 366	 4-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)benzoic acid	MS (ESI) calc'd for ($C_{17}H_{14}N_4O_4S$) $(M+1)^+$, 371.1, found 371.1.
Example 367	 4-(1-benzofuran-7-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{14}N_4O_3S$) $(M+1)^+$, 367.1, found 367.1.

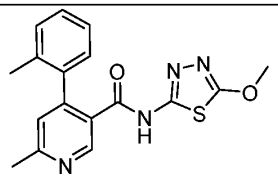
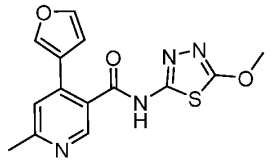
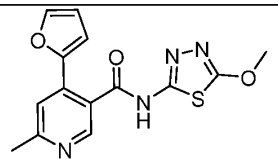
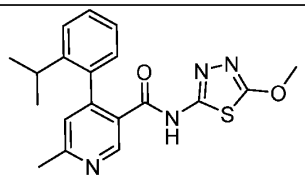
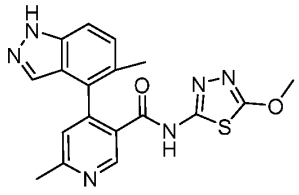
Example 368	 4-(4-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{13}FN_4O_2S$) $(M+1)^+$, 345.1, found 345.1.
Example 369	 4-[4-(dimethylcarbamoyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{19}N_5O_3S$) $(M+1)^+$, 398.1, found 398.2.
Example 370	 4-{[1,1'-biphenyl]-4-yl}-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{22}H_{18}N_4O_2S$) $(M+1)^+$, 403.1, found 403.2.
Example 371	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(4-(methylsulfonyl) phenyl)nicotinamide	MS (ESI) calc'd for ($C_{17}H_{16}N_4O_4S_2$) $(M+1)^+$, 405.1, found 405.1.

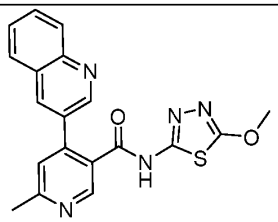
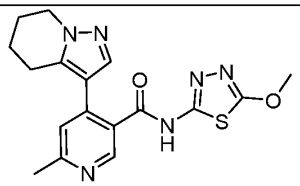
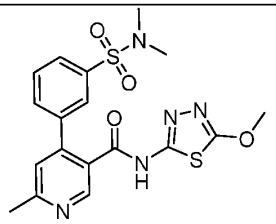
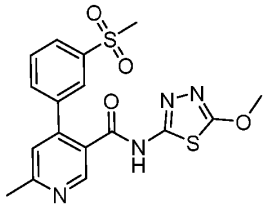
Example 372	 4-(isoquinolin-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{15}N_5O_2S$) $(M+1)^+$, 378.1, found 378.1.
Example 373	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-methyl-1H-pyrazol-4-yl)nicotinamide	MS (ESI) calc'd for ($C_{14}H_{14}N_6O_2S$) $(M+1)^+$, 331.1, found 331.1.
Example 374	 4-(3-isopropylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{19}H_{20}N_4O_2S$) $(M+1)^+$, 369.1, found 369.2.
Example 375	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(quinolin-6-yl)nicotinamide	MS (ESI) calc'd for ($C_{19}H_{15}N_5O_2S$) $(M+1)^+$, 378.1, found 378.1.

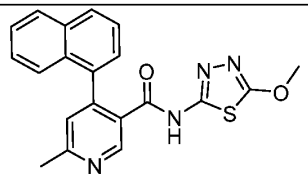
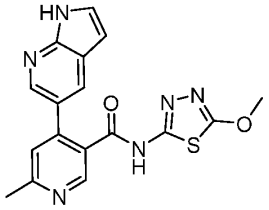
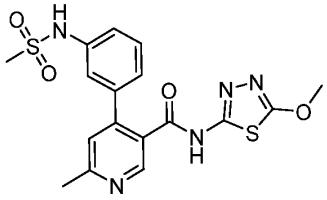
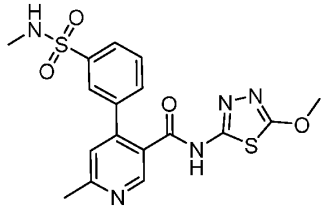
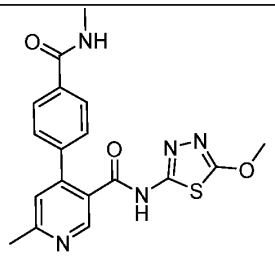
Example 376	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[4-(trifluoromethoxy)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{13}F_3N_4O_3S$) $(M+1)^+$, 411.1, found 411.1.
Example 378	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(4-sulfamoylphenyl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_4S_2$) $(M+1)^+$, 406.1, found 406.1.
Example 379	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_3S$) $(M+1)^+$, 382.1, found 382.1.
Example 380	 4-(2,3-dihydro-1-benzofuran-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{16}N_4O_3S$) $(M+1)^+$, 369.1, found 369.1.

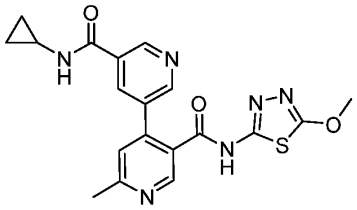
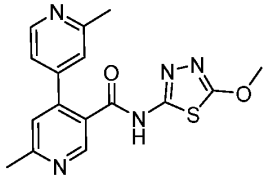
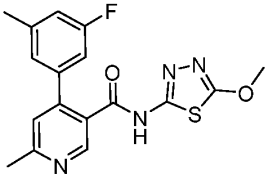
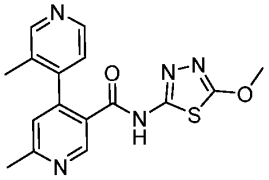
Example 381	 4-(3,4-dimethylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_2S$) $(M+1)^+$, 355.1, found 355.2.
Example 382	 4-[4-(dimethylsulfamoyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{19}N_5O_4S_2$) $(M+1)^+$, 434.1, found 434.0.
Example 383	 4-(3-ethylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_2S$) $(M+1)^+$, 355.1, found 355.0.
Example 384	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[4-(methylsulfamoyl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_4S_2$) $(M+1)^+$, 420.1, found 420.1.

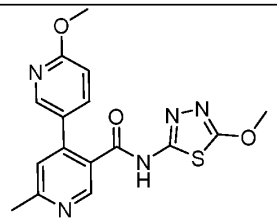
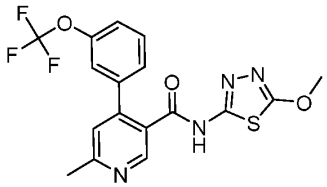
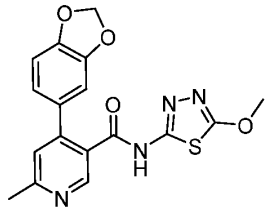
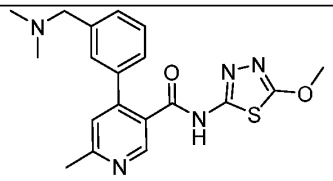
Example 385	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(3-sulfamoylphenyl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_4S_2$) $(M+1)^+$, 406.1, found 406.0.
Example 386	 4-(2,4-dimethylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_2S$) $(M+1)^+$, 355.1, found 355.1.
Example 387	 4-(4-methanesulfonamidophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_4S_2$) $(M+1)^+$, 420.1, found 420.1.
Example 388	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(thiophen-3-yl)nicotinamide	MS (ESI) calc'd for ($C_{14}H_{12}N_4O_2S_2$) $(M+1)^+$, 333.0, found 333.1.

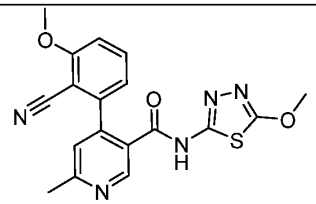
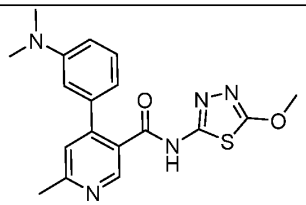
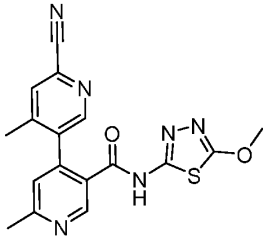
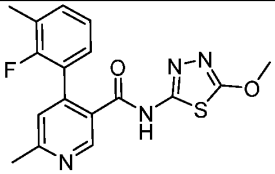
Example 389	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-methylphenyl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{16}N_4O_2S$) $(M+1)^+$, 341.1, found 341.1.
Example 390	 4-(furan-3-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{14}H_{12}N_4O_3S$) $(M+1)^+$, 317.1, found 317.1.
Example 391	 4-(furan-2-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{14}H_{12}N_4O_3S$) $(M+1)^+$, 317.1, found 317.0.
Example 392	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[2-(propan-2-yl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{20}N_4O_2S$) $(M+1)^+$, 369.1, found 369.2.
Example 393	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(5-methyl-1H-indazol-4-yl)nicotinamide	MS (ESI) calc'd for ($C_{18}H_{16}N_6O_2S$) $(M+1)^+$, 381.1, found 381.1.

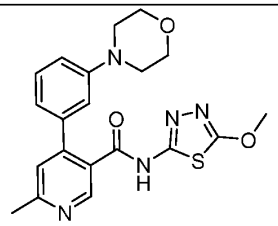
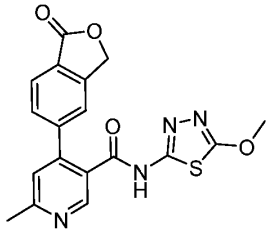
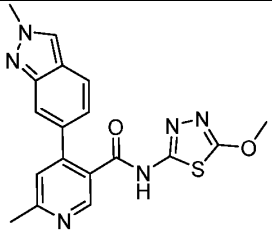
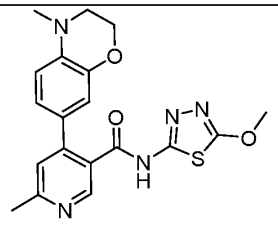
Example 394	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(quinolin-3-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{15}N_5O_2S$) $(M+1)^+$, 378.1, found 378.0.
Example 395	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-{4H,5H,6H,7H-pyrazolo[1,5-a]pyridin-3-yl}pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{18}N_6O_2S$) $(M+1)^+$, 371.1, found 371.1.
Example 396	 4-[3-(dimethylsulfamoyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{19}N_5O_4S_2$) $(M+1)^+$, 434.1, found 434.1.
Example 397	 4-(3-methanesulfonylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{16}N_4O_4S_2$) $(M+1)^+$, 405.1, found 405.0.

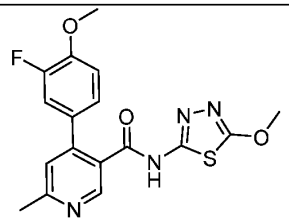
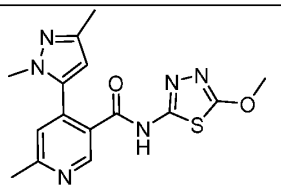
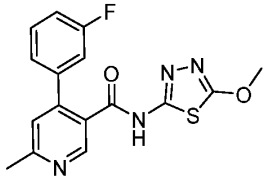
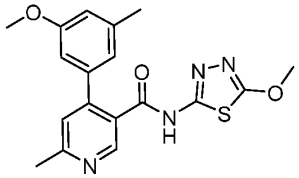
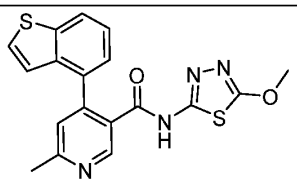
Example 398	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(naphthalen-1-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{16}N_4O_2S$) $(M+1)^+$, 377.1, found 377.1.
Example 399	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-{1H-pyrrolo[2,3-b]pyridin-5-yl}pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.0.
Example 400	 4-(3-methanesulfonamidophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_4S_2$) $(M+1)^+$, 420.1, found 420.1.
Example 401	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(methylsulfamoyl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_4S_2$) $(M+1)^+$, 420.1, found 420.1.
Example 402		MS (ESI) calc'd for ($C_{18}H_{17}N_5O_3S$) $(M+1)^+$, 384.1, found 384.1.

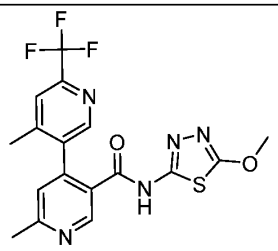
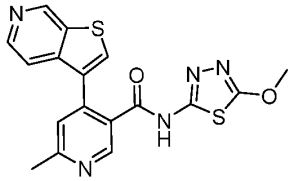
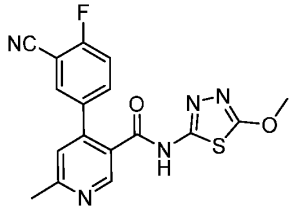
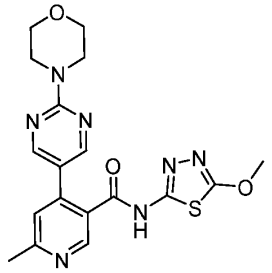
	N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[4-(methylcarbamoyl)phenyl]pyridine-3-carboxamide	
Example 403	 N5-cyclopropyl-N3'-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3',5-dicarboxamide	MS (ESI) calc'd for ($C_{19}H_{18}N_6O_3S$) $(M+1)^+$, 411.1, found 411.2.
Example 404	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_2S$) $(M+1)^+$, 342.1, found 342.0.
Example 405	 4-(3-fluoro-5-methylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_2S$) $(M+1)^+$, 359.1, found 359.0.
Example 406	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-3',6-dimethyl-[4,4'-bipyridine]-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_2S$) $(M+1)^+$, 342.1, found 342.0.

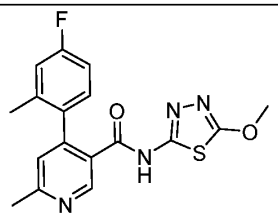
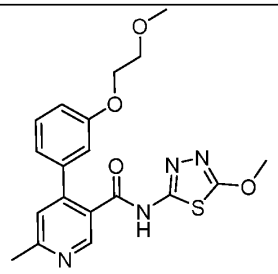
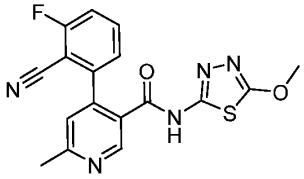
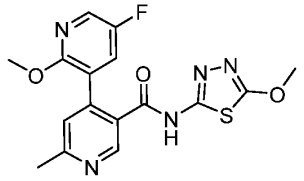
Example 407	 6-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_3S$) $(M+1)^+$, 358.1, found 358.0.
Example 408	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(trifluoromethoxy)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{13}F_3N_4O_3S$) $(M+1)^+$, 411.1, found 411.1.
Example 409	 4-(2H-1,3-benzodioxol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}N_4O_4S$) $(M+1)^+$, 371.1, found 371.1.
Example 410	 4-(3-((dimethylamino)methyl) phenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6 methylnicotinamide	MS (ESI) calc'd for ($C_{19}H_{21}N_5O_2S$) $(M+1)^+$, 384.1, found 384.2 .

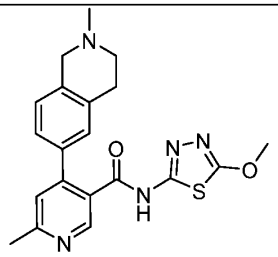
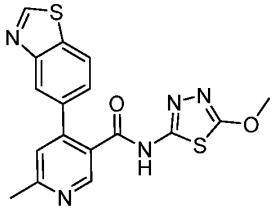
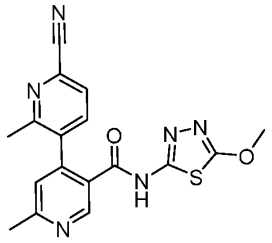
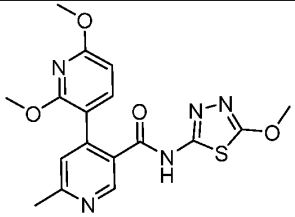
Example 411	 4-(2-cyano-3-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_3S$) $(M+1)^+$, 382.1, found 382.0.
Example 412	 4-[3-(dimethylamino)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{19}N_5O_2S$) $(M+1)^+$, 370.1, found 370.1.
Example 413	 6-cyano-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4,6'-dimethyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.1.
Example 414	 4-(2-fluoro-3-methylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_2S$) $(M+1)^+$, 359.1, found 359.1.

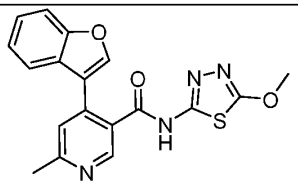
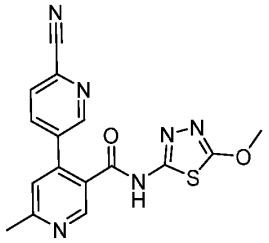
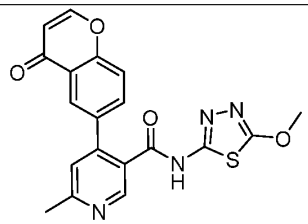
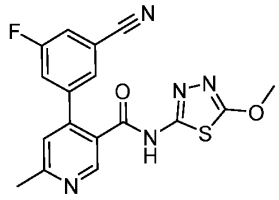
Example 415	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(morpholin-4-yl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{21}N_5O_3S$) $(M+1)^+$, 412.1, found 412.2.
Example 416	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-oxo-1,3-dihydro-2-benzofuran-5-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{14}N_4O_4S$) $(M+1)^+$, 383.1, found 383.1.
Example 417	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-methyl-2H-indazol-6-yl)nicotinamide	MS (ESI) calc'd for ($C_{18}H_{16}N_6O_2S$) $(M+1)^+$, 381.1, found 381.1.
Example 418	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{19}N_5O_3S$) $(M+1)^+$, 398.1, found 398.2.

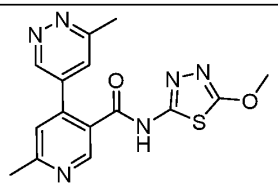
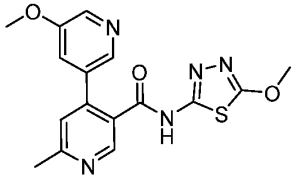
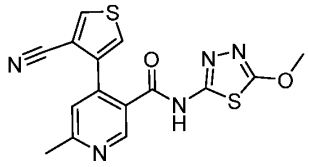
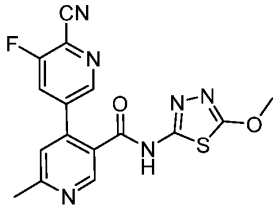
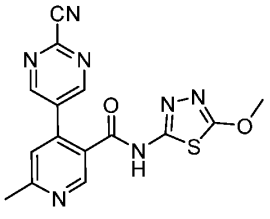
Example 419	 4-(3-fluoro-4-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_3S$) $(M+Na)^+$, 397.1, found 397.1.
Example 420	 4-(1,3-dimethyl-1H-pyrazol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{15}H_{16}N_6O_2S$) $(M+1)^+$, 345.1, found 345.2.
Example 421	 4-(3-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{13}FN_4O_2S$) $(M+1)^+$, 345.1, found 345.1.
Example 422	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-(3-methoxy-5-methylphenyl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_3S$) $(M+1)^+$, 371.1, found 371.2.
Example 423	 4-(1-benzothiophen-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{14}N_4O_2S_2$) $(M+1)^+$, 383.1, found 383.1.

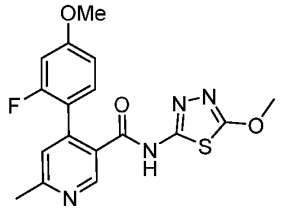
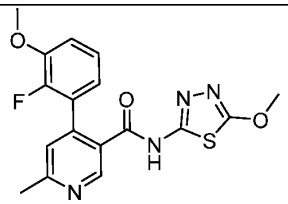
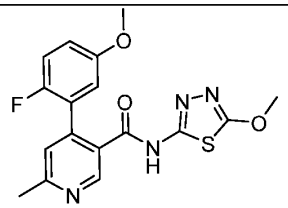
Example 424	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4,6'-dimethyl-6-(trifluoromethyl)-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}F_3N_5O_2S$) $(M+1)^+$, 410.1, found 410.2.
Example 425	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-{thieno[2,3-c]pyridin-3-yl}pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{13}N_5O_2S_2$) $(M+1)^+$, 384.1, found 384.1.
Example 426	 4-(3-cyano-4-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{17}H_{12}FN_5O_2S$) $(M+1)^+$, 370.1, found 370.1.
Example 427	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[2-(morpholin-4-yl)pyrimidin-5-yl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{19}N_7O_3S$) $(M+1)^+$, 414.1, found 414.2.

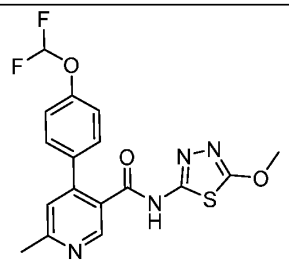
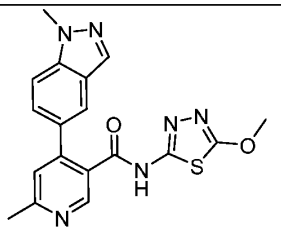
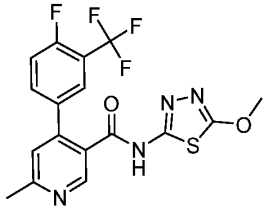
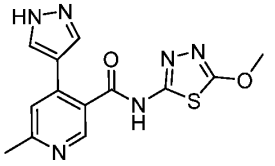
Example 428	 4-(4-fluoro-2-methylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_2S$) $(M+1)^+$, 359.1, found 359.1.
Example 429	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4-[3-(2-methoxyethoxy)phenyl]-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{20}N_4O_4S$) $(M+1)^+$, 401.1, found 401.2.
Example 430	 4-(2-cyano-3-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{12}FN_5O_2S$) $(M+1)^+$, 370.1, found 370.1.
Example 431	 5-fluoro-2-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{14}FN_5O_3S$) $(M+1)^+$, 376.1, found 376.1.

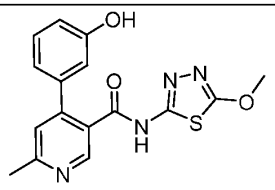
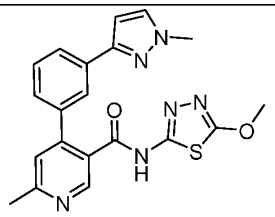
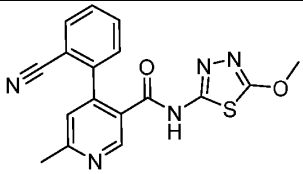
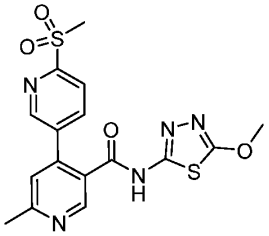
Example 432	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)nicotinamide	MS (ESI) calc'd for ($C_{20}H_{21}N_5O_2S$) $(M+1)^+$, 396.2, found 396.2.
Example 433	 4-(benzo[d]thiazol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{17}H_{13}N_5O_2S_2$) $(M+1)^+$, 384.1, found 384.1.
Example 434	 6-cyano-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2,6'-dimethyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.1.
Example 435	 2,6-dimethoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_4S$) $(M+1)^+$, 388.1, found 388.1.

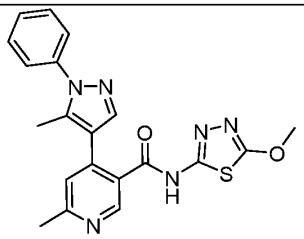
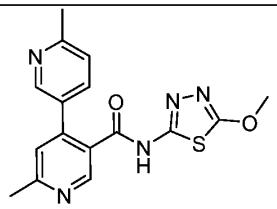
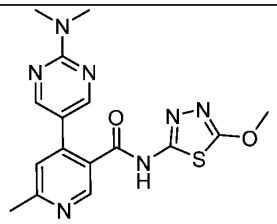
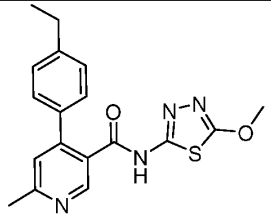
Example 436	 4-(1-benzofuran-3-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{14}N_4O_3S$) $(M+1)^+$, 367.1, found 367.0.
Example 437	 6-cyano-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{12}N_6O_2S$) $(M+1)^+$, 353.1, found 353.0.
Example 438	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(4-oxo-4H-chromen-6-yl)nicotinamide	MS (ESI) calc'd for ($C_{19}H_{14}N_4O_4S$) $(M+1)^+$, 395.1, found 395.1.
Example 439	 4-(3-cyano-5-fluorophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{12}FN_5O_2S$) $(M+1)^+$, 370.1, found 370.1.

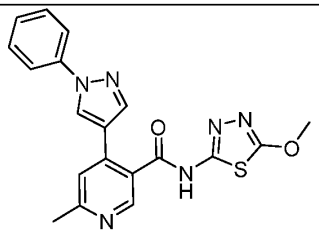
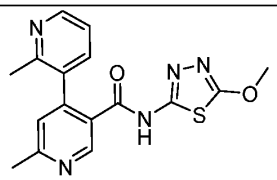
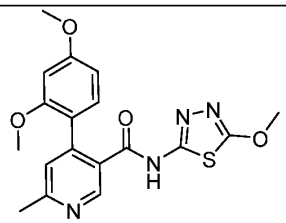
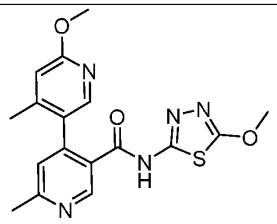
Example 440	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(6-methylpyridazin-4-yl)nicotinamide	MS (ESI) calc'd for ($C_{15}H_{14}N_6O_2S$) $(M+1)^+$, 343.1, found 343.1.
Example 441	 5-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_3S$) $(M+1)^+$, 358.1, found 358.1.
Example 442	 4-(4-cyanothiophen-3-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{15}H_{11}N_5O_2S_2$) $(M+1)^+$, 358.0, found 358.1.
Example 443	 6-cyano-5-fluoro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{11}FN_6O_2S$) $(M+1)^+$, 371.1, found 371.1.
Example 444		MS (ESI) calc'd for ($C_{15}H_{11}N_7O_2S$) $(M+1)^+$, 354.1, found 354.1.

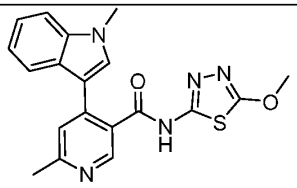
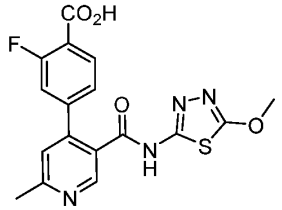
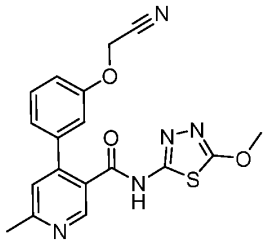
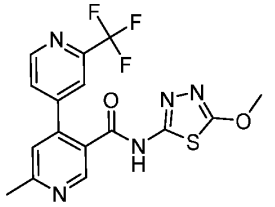
	4-(2-cyanopyrimidin-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	
Example 445	 4-(2-fluoro-4-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_3S$) $(M+1)^+$, 375.1, found 375.1.
Example 446	 4-(2-fluoro-3-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_3S$) $(M+1)^+$, 375.1, found 375.1.
Example 447	 4-(2-fluoro-5-methoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{15}FN_4O_3S$) $(M+1)^+$, 375.1, found 375.2.

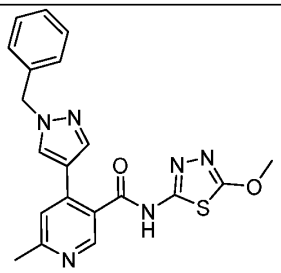
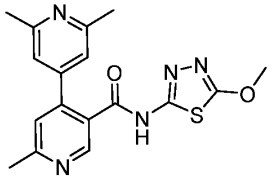
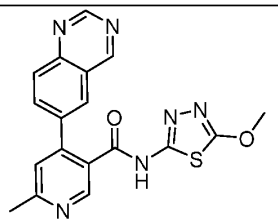
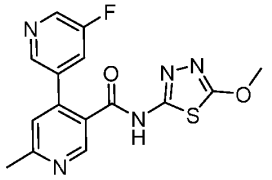
Example 448	 4-[4-(difluoromethoxy)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}F_2N_4O_3S$) $(M+1)^+$, 393.1, found 393.1.
Example 449	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-methyl-1H-indazol-5-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{16}N_6O_2S$) $(M+1)^+$, 381.1, found 381.2.
Example 450	 4-[4-fluoro-3-(trifluoromethyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{12}F_4N_4O_2S$) $(M+1)^+$, 413.1, found 413.1.
Example 451	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1H-pyrazol-4-yl)nicotinamide	MS (ESI) calc'd for ($C_{13}H_{12}N_6O_2S$) $(M+1)^+$, 317.1, found 317.2.

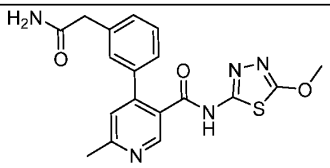
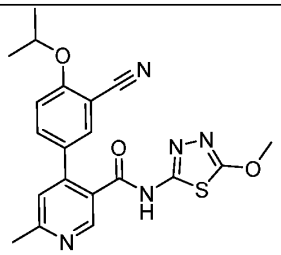
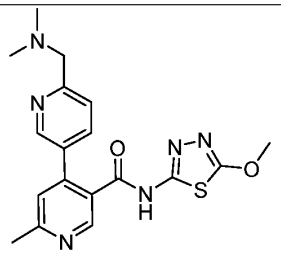
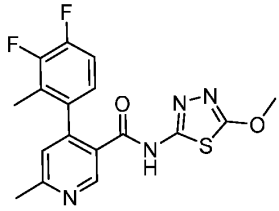
Example 452	 4-(3-hydroxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{14}N_4O_3S$) $(M+1)^+$, 343.1, found 343.1.
Example 453	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(1-methyl-1H-pyrazol-3-yl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{18}N_6O_2S$) $(M+1)^+$, 407.1, found 407.2.
Example 454	 4-(2-cyanophenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{13}N_5O_2S$) $(M+1)^+$, 352.1, found 352.2.
Example 455	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-6-(methylsulfonyl)-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_4S_2$) $(M+1)^+$, 406.1, found 406.1.

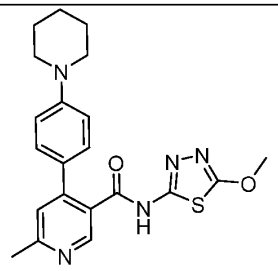
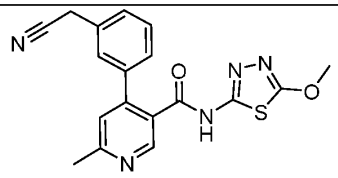
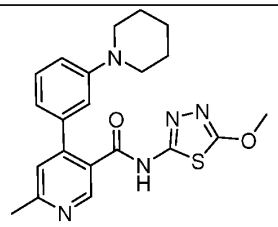
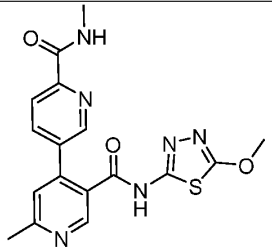
Example 456	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{18}N_6O_2S$) $(M+1)^+$, 407.1, found 407.2.
Example 457	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6,6'-dimethyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_2S$) $(M+1)^+$, 342.1, found 342.15.
Example 458	 4-(2-(dimethylamino)pyrimidin-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{16}H_{17}N_7O_2S$) $(M+1)^+$, 372.1, found 372.1.
Example 459	 4-(4-ethylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_2S$) $(M+1)^+$, 355.1, found 355.2.

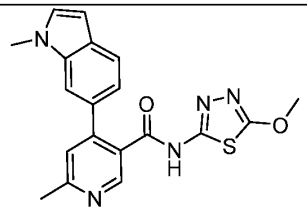
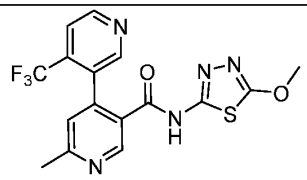
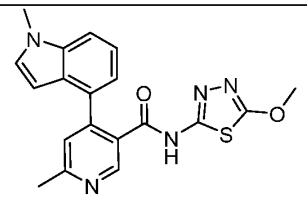
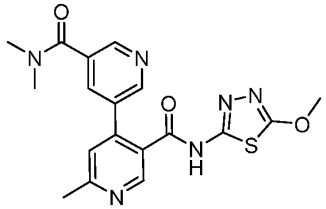
Example 460	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-phenyl-1H-pyrazol-4-yl)nicotinamide	MS (ESI) calc'd for ($C_{19}H_{16}N_6O_2S$) $(M+1)^+$, 393.1, found 393.2.
Example 461	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2,6'-dimethyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{15}N_5O_2S$) $(M+1)^+$, 342.1, found 342.2.
Example 462	 4-(2,4-dimethoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_4S$) $(M+1)^+$, 387.1, found 387.2.
Example 463	 6-methoxy-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-4,6'-dimethyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_3S$) $(M+1)^+$, 372.1, found 372.1.

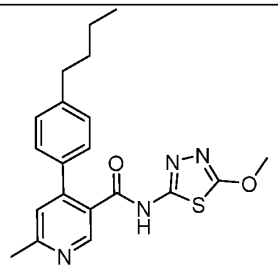
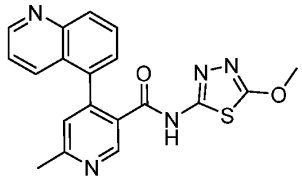
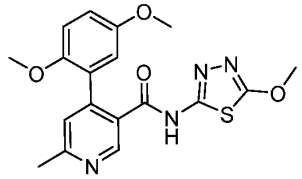
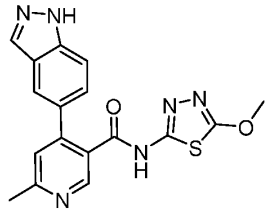
Example 464	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-methyl-1H-indol-3-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{17}N_5O_2S$) $(M+1)^+$, 380.1, found 380.2.
Example 465	 2-fluoro-4-(5-((5-methoxy-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)benzoic acid	MS (ESI) calc'd for ($C_{17}H_{13}FN_4O_4S$) $(M+1)^+$, 389.1, found 389.1.
Example 466	 4-[3-(cyanomethoxy)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_3S$) $(M+1)^+$, 382.1, found 382.1.
Example 467	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-2'-(trifluoromethyl)-[4,4'-bipyridine]-3-carboxamide	MS (ESI) calc'd for ($C_{16}H_{12}F_3N_5O_2S$) $(M+1)^+$, 396.1, found 396.1.

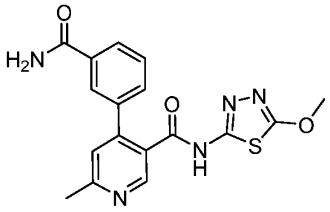
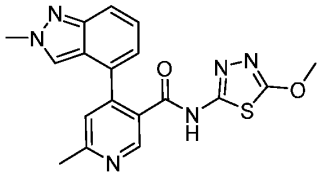
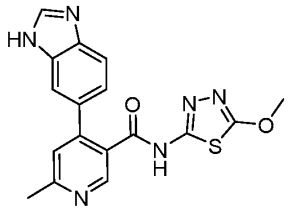
Example 468	 4-(1-benzyl-1H-pyrazol-4-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{20}H_{18}N_6O_2S$) $(M+1)^+$, 407.1, found 407.1.
Example 469	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-2',6,6'-trimethyl-[4,4'-bipyridine]-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{17}N_5O_2S$) $(M+1)^+$, 356.1, found 356.2.
Example 470	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(quinazolin-6-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{14}N_6O_2S$) $(M+Na)^+$, 401.1, found 401.1
Example 471	 5-fluoro-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{15}H_{12}FN_5O_2S$) $(M+1)^+$, 346.0, found 346.1

Example 472	 4-[3-(carbamoylmethyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{17}N_5O_3S$) $(M+1)^+$, 384.1, found 384.2
Example 473	 4-[3-cyano-4-(propan-2-yloxy)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{19}N_5O_3S$) $(M+1)^+$, 410.1, found 410.2
Example 474	 6-((dimethylamino)methyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{18}H_{20}N_6O_2S$) $(M+1)^+$, 384.1, found 384.2
Example 475	 4-(3,4-difluoro-2-methylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}F_2N_4O_2S$) $(M+1)^+$, 377.1, found 377.1

Example 476	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[4-(piperidin-1-yl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{21}H_{23}N_5O_2S$) $(M+1)^+$, 410.2, found 410.2
Example 477	 4-[3-(cyanomethyl)phenyl]-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{15}N_5O_2S$) $(M+1)^+$, 366.1, found 366.2
Example 478	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-[3-(piperidin-1-yl)phenyl]pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{21}H_{23}N_5O_2S$) $(M+1)^+$, 410.2, found 410.2
Example 479	 N3'-(5-methoxy-1,3,4-thiadiazol-2-yl)-N6,6'-dimethyl-[3,4'-bipyridine]-3',6-dicarboxamide	MS (ESI) calc'd for ($C_{17}H_{16}N_6O_3S$) $(M+1)^+$, 385.1, found 385.1

Example 480	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-methyl-1H-indol-6-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{17}N_5O_2S$) $(M+1)^+$, 380.1, found 380.2
Example 481	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6'-methyl-4-(trifluoromethyl)-[3,4'-bipyridine]-3'-carboxamide	MS (ESI) calc'd for ($C_{16}H_{12}F_3N_5O_2S$) $(M+1)^+$, 396.1, found 396.1
Example 482	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(1-methyl-1H-indol-4-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{19}H_{17}N_5O_2S$) $(M+1)^+$, 380.1, found 380.2
Example 483	 N3'-(5-methoxy-1,3,4-thiadiazol-2-yl)-N5,N5,6'-trimethyl-[3,4'-bipyridine]-3',5-dicarboxamide	MS (ESI) calc'd for ($C_{18}H_{18}N_6O_3S$) $(M+1)^+$, 399.1, found 399.1

Example 484	 4-(4-butylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{20}H_{22}N_4O_2S$) $(M+Na)^+$, 405.2, found 405.2
Example 485	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(quinolin-5-yl)nicotinamide	MS (ESI) calc'd for ($C_{19}H_{15}N_5O_2S$) $(M+1)^+$, 378.1, found 378.0
Example 486	 4-(2,5-dimethoxyphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{18}H_{18}N_4O_4S$) $(M+1)^+$, 387.1, found 387.1
Example 487	 4-(1H-indazol-5-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotin amide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.0

Example 488	 4-(3-carbamoylphenyl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	MS (ESI) calc'd for ($C_{17}H_{15}N_5O_3S$) $(M+1)^+$, 370.1, found 370.1
Example 489	 N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methyl-4-(2-methyl-2H-indazol-4-yl)pyridine-3-carboxamide	MS (ESI) calc'd for ($C_{18}H_{16}N_6O_2S$) $(M+1)^+$, 381.1, found 381.1
Example 490	 4-(1H-1,3-benzodiazol-6-yl)-N-(5-methoxy-1,3,4-thiadiazol-2-yl)-6-methylpyridine-3-carboxamide	MS (ESI) calc'd for ($C_{17}H_{14}N_6O_2S$) $(M+1)^+$, 367.1, found 367.1

Biological Assay

The ability of the compounds of Formula (I) or Table 1 to inhibit ATPase activity of Pol theta (1-899) was determined using the assay described below.

Pol Theta ATPase activity was determined by measuring the rate of ATP turn over in a NADH oxidation-coupled enzymatic assay. 10-point dilution series of compounds were used in a 384 well format for the inhibition assays. Pol theta (1-899) (5 nM) in assay buffer (20 mM Tris HCl (pH 7.80), 80 mM KCl, 10 mM $MgCl_2$, 1 mM DTT, 0.01% BSA, 0.01% Tween, 5% glycerol) was transferred to the test wells (20 µL), except the low control wells (20 µL of assay buffer was added to the low control wells). The plate was then incubated at room temperature for 15 min. An equal volume (20 µL) of 100 µM ATP, 300 nM dT_{50} (single-stranded DNA (ssDNA) containing 50 thymine bases), 300 µM NADH, 6 mM PEP,

10 U/mL lactate dehydrogenase and 20 U/mL pyruvate kinase in assay buffer was added to all the test wells. The plate was then centrifuged at 1000 rpm for 1 min. The reaction was monitored for 60 min by measuring absorbance (λ= 340 nm) in a Tecan Spark multimode plate reader every minute. The high control (DMSO with enzyme) with low absorbance intensity represents no inhibition of ATPase reaction while the low control (DMSO with buffer) with high absorbance intensity represents full inhibition of ATPase activity. Slope of the reaction progress curves were used to calculate the rate of ATP hydrolysis. The rates were used to determine the percent inhibition using a four-parameter inhibition model to generate IC_{50}, Hill slope and max inhibition.

The IC_{50} of the compounds in Table 1 above are disclosed in Table 4, below:

IC_{50}: 10 uM ≥ (+) > 1 uM ; 1 uM ≥ (++) > 500 nM;
500 nM ≥ (+++) > 200 nM; 200 nM ≥ (++++)

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
1	++++	40	+
2	++++	41	++++
3	+	42	+++
4	+++	43	+++
5	++++	44	++++
6	++++	45	++++
7	++++	46	++++
8	++++	47	++++
9	++++	48	++++
10	++++	49	++++
11	++++	50	+
12	++++	51	++++
13	++++	52	++++
14	++++	53	+++
15	++++	54	++
16	++++	55	+++
17	++++	56	+++
18	++++	57	++++
19	++++	58	++++
20	++++	59	++++
21	++++	60	++++
22	++++	61	++++
23	++++	62	++++
24	++++	63	++++
25	++++	64	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
26	++++	65	++
27	++++	66	+++
28	++++	67	+
29	++++	68	+
30	++++	69	+
31	+++	70	++++
32	++++	71	+
33	++++	72	++
34	++	73	++
35	+++	74	++++
36	++++	75	++++
37	++++	76	++++
38	++++	77	++++
39	++++	78	++

The IC_{50} of the compounds in Table 2 above are disclosed in Table 5, below:

IC_{50}: 10 uM ≥ (+) > 1 uM ; 1 uM ≥ (++) > 500 nM;
500 nM ≥ (+++) > 200 nM; 200 nM ≥ (++++)

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
79	+++	164	++++
80	++++	165	++++
81	++++	166	++++
82	++++	167	++++
83	++++	168	++++
84	++++	169	++++
85	+	170	++++
88	+	171	++++
91	+	172	++++
92	+++	173	++++
93	++++	174	++++
98	> 10 uM	175	++++
99	> 10 uM	176	++++
100	+++	177	+++
101	+	178	++++
102	+++	179	++++
103	++++	180	+++
104	+++	181	++++
105	+	182	++++
107	> 10 uM	183	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
109	+	184	++++
110	> 10 uM	185	++++
112	+++	186	++++
114	++++	187	++++
115	++++	188	++++
116	++++	189	++++
117	++++	190	++++
118	++++	191	++++
119	++++	192	++++
120	> 10 uM	193	++
121	> 10 uM	194	++++
122	++++	195	++++
123	> 10 uM	196	++
124	++++	197	++++
125	++++	198	++++
126	+	199	++++
127	++++	200	++++
128	++++	201	++++
129	++++	202	++++
130	++++	203	++++
131	++++	204	++++
132	++++	205	++++
133	++++	206	++++
134	++	207	++++
135	++++	208	++++
136	++++	209	++++
137	++++	210	++++
138	++++	211	++++
139	+++	212	++++
140	++++	213	++++
141	++++	214	++++
142	++++	215	++++
143	+++	216	++++
144	> 10 uM	217	++++
145	++++	218	++++
146	++++	219	++++
147	++++	220	++++
148	++++	221	++++
149	++++	222	++++
150	++++	223	++++
151	++++	224	++++
152	++++	225	++++
153	++++	226	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
154	++++	227	++++
155	++++	228	++++
156	++++	229	++++
157	++++	230	++++
158	++++	231	++++
159	++++	232	++++
160	++++	233	++++
161	++++	234	> 10 uM
162	++++	235	> 10 uM
163	++++		

The IC_{50} of the compounds in Table 3 above are disclosed in Table 6, below:

IC_{50}: 10 uM ≥ (+) > 1 uM ; 1 uM ≥ (++) > 500 nM;
500 nM ≥ (+++) > 200 nM; 200 nM ≥ (++++)

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
236	++++	364	+
237	++++	365	+
238	++++	366	+
239	++++	367	+++
240	++++	368	+
241	++++	369	+
242	++++	370	+
243	++++	371	+
244	++++	372	+++
245	++++	373	ND
246	++++	374	ND
247	++++	375	ND
248	++++	376	+
249	++++	377	+
250	++++	378	+
251	++++	379	+
252	++++	380	+
253	++++	381	+
254	++++	382	+
255	++++	383	++
256	++++	384	+
257	++++	385	+
258	++++	386	++
259	++++	387	+

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
260	++++	388	+
261	++++	389	++
262	++++	390	+
263	++++	391	+
264	++++	392	+
265	++++	393	ND
266	++++	394	+
267	++++	395	+
268	++++	396	+
269	++++	397	++
270	+++	398	++++
271	++++	399	+
272	++++	400	+
273	+++	401	+
274	++++	402	+
275	++++	403	+
276	++++	404	+
277	++++	405	+++
278	+++	406	+
279	++++	407	+
280	++++	408	++
281	++++	409	++
282	++++	410	+
283	+++	411	+
284	++++	412	+
285	+	413	+
286	++++	414	++++
287	++++	415	+
288	++++	416	+
289	+	417	+
290	+++	418	+
291	++++	419	+
292	++++	420	+
293	++++	421	++
294	+++	422	++
295	++++	423	+++
296	++++	424	+
297	++++	425	++
298	++	426	ND
299	++++	427	+
300	++++	428	++
301	++++	429	+
302	++++	430	++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
303	+	431	++
304	++++	432	+
305	++++	433	ND
306	+	434	+
307	+++	435	+++
308	+	436	+
309	++++	437	+
310	++++	438	+
311	+++	439	++
312	++	440	+
313	++++	441	ND
314	++++	442	+
315	++++	443	ND
316	++++	444	+
317	++++	445	+
318	++++	446	+
319	++++	447	++
320	++++	448	+
321	+	449	++
322	++	450	++++
323	++++	451	+
324	++++	452	+
325	+	453	+
326	+	454	+
327	+	455	+
328	ND	456	+
329	+	458	+
330	+	458	+
331	+	459	+
332	+	460	+
333	+	461	+
334	+	462	+++
335	++	463	+
336	+	464	+
337	++	465	+
338	+	466	+
339	+	467	++
340	+	468	+
341	++	469	+++
342	+	470	+
343	+	471	+
344	+	472	+
345	+	473	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50
346	+	474	+
347	+	475	++
348	ND	476	+
349	+	477	+
350	+	478	+
351	+	479	+
352	+	480	+
353	+	481	+
354	+	482	+
355	+	483	+
356	+	484	+
357	+	485	+++
358	++	486	++
359	++++	487	++
360	+	488	+
361	++	489	+
362	+	490	+
363	++		

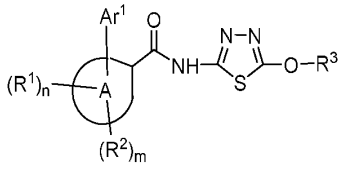
* ND means “not determined.”

Particular embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Upon reading the foregoing, description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as specifically described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

All patent applications, patents, and printed publications cited herein are incorporated herein by reference in the entireties, except for any definitions, subject matter disclaimers or disavowals, and except to the extent that the incorporated material is inconsistent with the express disclosure herein, in which case the language in this disclosure controls.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 6- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl,

C_{1-6} haloalkoxy, $–X^1–$cyano, $–NO_2$, $–C(O)OR^a$, $–NR^aC(O)R^b$, $–X^1–C(O)NR^aR^b$, $–X^1–$OH, C_{3-6} cycloalkyl, $–X^1–O–$ C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $–X^1–NR^aR^b$, $–X^1–S(O)_2R^a$,$–X^1–S(O)_2NR^aR^b$, $X^1–X^{1a}–OR^a$, and a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and

$–X^1–$cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene,

X^{1a} is 3- to 6- membered heterocycloalkylene having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl, naphthyl, pyridin-2-one, and a 5- to 10-membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–C(O)_2R^c$, $–NR^cC(O)R^d$, $–O–C_{1-4}$ alkylene$–O–C_{1-4}$ alkyl , $–X^2$-$C(O)NR^cR^d$, $–X^2$-$S(O)_2NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2–$cyano, $–O$-$X^2–$cyano, $–X^2–S(O)R^c$, $–X^2–S(O)_2R^c$, $–X^2–N(R^d)S(O)_2R^c$, $–P(O)R^cR^d$, -Y and $–X^2–OH$; or

two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered cycloalkyl or heterocycloalkyl, having 0 to 2 heteroatoms as ring vertices independently selected from N, O, and S, and which is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

wherein

each Y is independently selected from phenyl, benzyl, 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl;

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-5} cycloalkyl and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl, C_{6-11} bridged cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $-ONO_2$, 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$,$–X^3–$cyano, and oxo; and

R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-3} haloalkyl, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, –OH, –

NR^eR^f,

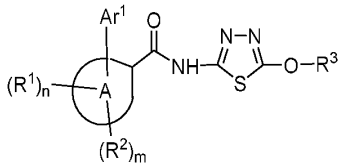
$-CONR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

each R^e and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl and -C_{1-3}alkylene-C_{3-6} cycloalkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I):



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-X^1-O-C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $-X^1$–cyano, $-C(O)OR^a$, $-NR^aC(O)R^b$, $-X^1-C(O)NR^aR^b$, $-X^1$–OH, C_{3-6} cycloalkyl, $-X^1-O-$ C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $-X^1-NR^aR^b$, $-X^1-S(O)_2R^a$,$-X^1-S(O)_2NR^aR^b$, and $X^1-X^{1a}-OR^a$;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and

$-X^1$–cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene,

X^{1a} is 3- to 6- membered heterocycloalkylene having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–NR^cC(O)R^d$, $–NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2–$cyano, $–X^2–S(O)R^c$ and $–X^2–OH$; or

two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered heterocycloalkyl having 1 to 2 heteroatoms as ring vertices independently selected from N, O, and S,

wherein

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$,$–X^3–$cyano, and oxo; and

R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, $–OH$, $–NR^eR^f$, and oxo,

wherein

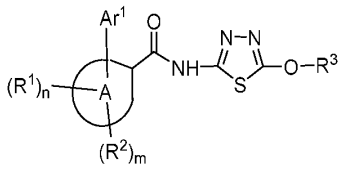
each X^3 is independently selected from a bond and C_{1-4} alkylene, and

each R^e and R^f is independently selected from H and C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

aims for O-Linked Thiadiazole Application (PolQ)
Ideaya Ref. 2021-007-A-USP1
Mintz Ref. 052326-542P01US

3. A compound of Formula (I):



(I)

wherein:

ring A is selected from the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S;

the subscripts m and n are each independently 0 or 1;

R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^1–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $–X^1$–cyano, $–C(O)OR^a$, $–NR^aC(O)R^b$, $–X^1–C(O)NR^aR^b$, $–X^1$–OH, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkynyl, $–X^1–NR^aR^b$, $–X^1–S(O)_2R^a$, and $–X^1–S(O)_2NR^aR^b$;

R^2 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and

$–X^1$–cyano, wherein

each X^1 is independently selected from a bond and C_{1-4} alkylene, and

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Ar^1 is selected form the group consisting of phenyl and a 5- to 10- membered heteroaryl ring having 1 to 4 heteroatoms independently selected from N, O, and S, wherein Ar^1 is substituted with 0 to 4 R^{1a} substituents;

each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $–X^2–O–C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, $–C(O)R^c$, $–NR^cC(O)R^d$, $–NR^cR^d$, $–X^2–NR^cR^d$, $–C(O)NR^cR^d$, $–X^2$–cyano, and $–X^2$–OH, wherein

each X^2 is independently selected from a bond and C_{1-4} alkylene; and

each R^c and R^d are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^3 is a member selected from the group consisting of

(i) C_{3-6} cycloalkyl and C_{6-12} spirocycloalkyl;

(ii) 3- to 6- membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iii) 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(iv) 6- to 10-membered bridged heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(v) 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S;

(vi) hydrogen;

(vii) C_{1-6} alkyl, or C_{2-6} alkynyl,

wherein

each R^3 member of (i) through (v) is substituted with 0 to 4 R^{3a} substituents, each of which is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $–X^3–O–C_{1-6}$ alkyl, $–X^3–OH$, $–NR^eR^f$, $–NR^eC(O)R^f$, $–X^3–NR^eR^f$, $–X^3–$cyano, and oxo; and

R^3 member (vii) is substituted with from 0 to 3 R^{3b} substituents selected from the group consisting of halo, C_{1-6} haloalkoxy, $–O–C_{1-6}$ alkyl, cyano, $–OH$, $–NR^eR^f$, and oxo, wherein

each X^3 is independently selected from a bond and C_{1-4} alkylene, and

each R^e and R^f is independently selected from H and C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims **1** to **3**, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, imidazo[1,2-a]pyridinyl, 1,2,3-triazole, pyrazolyl, isoxazolyl, and imidazo[1,5-a]pyridinyl.

5. The compound of any one of claims **1** to **3**, or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, and imidazo[1,2-a]pyridinyl.

6. The compound of any one of claims **1** to **3**, or a pharmaceutically acceptable salt thereof, wherein ring A is pyridinyl.

7. The compound of any one of claims **1** to **3**, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl.

8. The compound of any one of claims **1** to **7**, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^1 is a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S.

9. The compound of any one of claims **1** to **7**, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^1 is selected from the group consisting of C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-X^1-O-C_{1-6}$ alkyl, C_{1-6} haloalkoxy, $-X^1-$cyano, $-X^1-OH$,C_{3-6} cycloalkyl, $-X^1-NR^aR^b$.

10. The compound of any one of claims **1** to **7**, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^1 is selected from the group consisting of C_{1-6} alkyl and $-X^1-OH$.

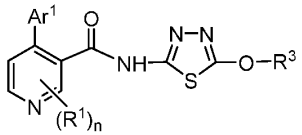
11. The compound of any one of claims **1** to **7**, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^1 is selected from the group consisting of methyl and hydroxymethyl.

12. The compound of any one of claims **1** to **7**, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^1 is methyl.

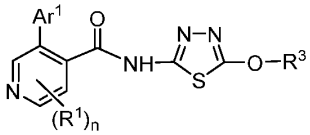
13. The compound of any one of claims **1** to **12**, or a pharmaceutically acceptable salt thereof, wherein m is 0.

14. The compound of any one of claims **1** to **12**, or a pharmaceutically acceptable salt thereof, wherein m is 1 and R^2 is C_{1-6} alkyl, halo, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy.

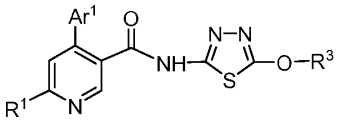
15. The compound of any one of claims **1** to **14**, or a pharmaceutically acceptable salt thereof, having Formula (Ia), (Ib), or (Ic):



(Ia)



(Ib)



(Ic).

16. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is naphthyl or pyridin-2-one, each of which is substituted with 0 to 4 R^{1a}.

17. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is selected from the group consisting of phenyl, pyridinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, pyridazyl, imidazo[1,2-a]pyrimidinyl, oxazolo[4,5-b]pyridinyl, oxazolo[5,4-b]pyridinyl, thiazolo[4,5-b]pyridinyl, benzo[d]thiazole, indazolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, and tetrazolo[1,5-a]pyridinyl, each of which is substituted with 0 to 4 R^{1a}.

18. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is selected from the group consisting of phenyl, pyridinyl, benzopyrazolyl, benzimidazolyl, imidazolyl, and pyridazyl each of which is substituted with 0 to 4 R^{1a}.

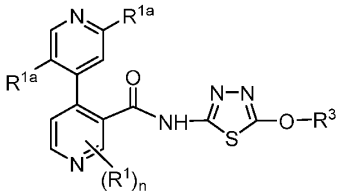
19. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is pyridinyl substituted with 0 to 4 R^{1a}.

20. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is phenyl substituted with 0 to 4 R^{1a}.

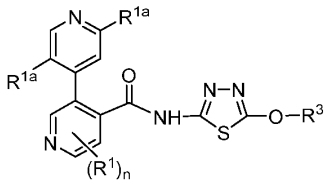
21. The compound of any one of claims **1** to **20**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is substituted with 0 to 3 R^{1a}.

22. The compound of any one of claims **1** to **20**, or a pharmaceutically acceptable salt thereof, wherein Ar^1 is substituted with 0 to 2 R^{1a}.

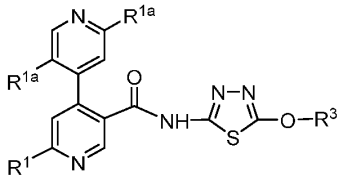
23. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, having Formula (Ia2), (Ib2), or (Ic2):



(Ia2)

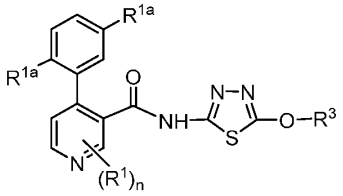


(Ib2)

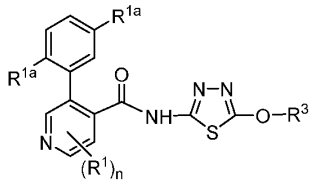


(Ic2).

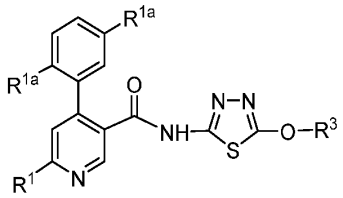
24. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, having Formula (Ia1), (Ib1), or (Ic1):



(Ia1)



(Ib1)



(Ic1).

25. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-X^2-O-C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, $-NR^aR^b$, $-X^2-$cyano, and $-X^2-$OH.

26. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein each R^{1a} is independently selected from C_{1-6} alkyl, halo, –O–

C_{1-6} alkyl, $-C(O)_2R^c$, $-C_{1-4}$ alkoxy-C_{1-4} alkoxy, $-X^2$-$C(O)NR^cR^d$, $-X^2$-$S(O)_2NR^cR^d$, $-O$-X^2- cyano, $-X^2-S(O)_2R^c$, and $-X^2-N(R^d)S(O)_2R^c$.

27. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein each R^{1a} is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, $-NR^aR^b$, and $-X^2-OH$.

28. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein each R^{1a} is independently selected from methyl, ethyl, fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, cyclopropyl, $-NH_2$, hydroxymethyl, and 1-hydroxyethyl.

29. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein each R^{1a} is independently selected from methyl, fluoro, chloro, trifluoromethyl, difluoromethyl, methoxy, ethoxy, difluoromethoxy, and cyclopropyl.

30. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein at least one R^{1a} is Y and Y is selected from phenyl, benzyl, 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

31. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein at leaste one R^{1a} is Y and Y is phenyl or benzyl; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

32. The compound of any one of claims **1** to **24**, or a pharmaceutically acceptable salt thereof, wherein at least one R^{1a} is Y and Y is 4- to 6-membered heterocycloalkyl, and 5- or 6-membered heteroaryl, wherein each heterocycloalkyl and heteroaryl has 1 or 2 ring members independently selected from O, N and S; and each Y is substituted with 0, 1 or 2 groups independently selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

33. The compound of any one of claims **1** to **22**, or a pharmaceutically acceptable salt thereof, wherein two R^{1a} groups on adjacent ring vertices combine to form a 4 to 6 membered cycloalkyl or heterocycloalkyl, having 0 to 2 heteroatoms as ring vertices independently selected from N, O, and S, and which is substituted with 0 to 4 groups independently selected from oxo, halo, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} haloalkyl.

34. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

35. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl or C_{2-6} alkynyl, and is substituted with 0 to 4 R^{3b}.

36. The compound of claim **35**, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of 2-propynyl, ethyl, methyl, 2,2,-dimethylpropyl, isobutyl, isopropyl, and n-propyl, and is substituted with 0 to 4 R^{3b}.

37. The compound of claim **35**, or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl and is substituted with 0 to 3 R^{3b}.

38. The compound of claims **35** or **36**, or a pharmaceutically acceptable salt thereof, wherein R^3 is substituted with 0 to 3 R^{3b}.

39. The compound of claims **35** or **37**, or a pharmaceutically acceptable salt thereof, wherein R^3 is substituted with 0 to 2 R^{3b}.

40. The compound of any one of claims **35** to **39**, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is selected from the group consisting of halo, C_{1-3} haloalkyl, –O–C_{1-6} alkyl, cyano,–OH, and –$CONR^eR^f$.

41. The compound of any one of claims **35** to **39**, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is selected from the group consisting of halo, –O–C_{1-6} alkyl, cyano, and –OH.

42. The compound of any one of claims **35** to **39**, or a pharmaceutically acceptable salt thereof, wherein each R^{3b} is selected from the group consisting of fluoro, methoxy, cyano, and –OH.

43. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{6-12} spirocyclyl or C_{3-6} cycloalkyl, each of which is substituted with 0 to 4 R^{3a}.

44. The compound of claim **43**, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

45. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{6-11} bridged cycloalkyl, each of which is substituted with 0 to 4 R^{3a}.

46. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 3- to 6-membered heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}.

47. The compound of claim **46**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 5- membered heterocycloalkyl substituted with 0 to 4 R^{3a}.

48. The compound of claim **46**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 6- membered heterocycloalkyl substituted with 0 to 4 R^{3a}.

49. The compound of claim **46**, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of tetrahydropyran, oxetanyl, tetrahydrofuranyl, and tetrahydrothiopyranyl, each of which is substituted with 0 to 4 R^{3a}.

50. The compound of claim **46**, or a pharmaceutically acceptable salt thereof, wherein R^3 is tetrahydrothiopyranyl substituted with 2 oxo groups.

51. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 6- to 10-membered bicyclic heterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}.

52. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 6- to 10-membered bridged heterocyclyl having 1 to 4

heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}.

53. The compound of any one of claims **1** to **33**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 6- to 12-membered spiroheterocyclyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S, and is substituted with 0 to 4 R^{3a}.

54. The compound of any one of claims **43** to **49** or **51** to **53**, or a pharmaceutically acceptable salt thereof, wherein R^3 is substituted with 0 to 2 R^{3a}.

55. The compound of any one of claims **43** to **49** or **51** to **54**, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} is selected from the group consisting of $C_{1\text{-}6}$ alkyl, halo, $–X^3–O–C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkoxy, $–X^3–OH$, $-ONO_2$, 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S and oxo.

56. The compound of any one of claims **43** to **49** or **51** to **54**, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} is selected from the group consisting of $C_{1\text{-}6}$ alkyl, halo, $–X^3–O–C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkoxy, $–X^3–OH$, and oxo.

57. The compound of any one of claims **43** to **49** or **51** to **54**, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} is selected from the group consisting of $C_{1\text{-}6}$ alkyl, halo, $–X^3–OH$, and oxo.

58. The compound of any one of claims **43** to **49** or **51** to **54**, or a pharmaceutically acceptable salt thereof, wherein each R^{3a} is selected from the group consisting of methyl, –OH, and oxo.

59. The compound of any one of claims **43** to **49** or **51** to **54**, or a pharmaceutically acceptable salt thereof, wherein at least one R^{3a} is a 4- to 6-member heterocycloalkyl having 1 to 4 heteroatoms as ring vertices independently selected from N, O, and S and oxo.

60. A compound selected from those in Table 1 or a pharmaceutically acceptable salt thereof, in Table 2 or a pharmaceutically acceptable salt thereof, Table 3 or a

pharmaceutically acceptable salt thereof, or in the Examples or a pharmaceutically acceptable salt thereof.

61. A pharmaceutical composition comprising a compound of any one of claims **1** to **60**, and at least one pharmaceutically acceptable excipient.

62. A method for treating a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**.

63. The method of claim **62**, wherein the patient is in recognized need of such treatment and the disease is a cancer.

64. A method of treating a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**.

65. The method of claim **64**, wherein the patient is in recognized need of such treatment.

66. A method for treating a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**.

67. The method of any one of claims **62** to **66**, wherein the cancer is lymphoma, rhabdoid tumor, multiple myeloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, breast cancer, ovarian cancer, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer, and pancreatic cancer.

68. Use of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**, in the manufacture of a medicament for treating a disease characterized by overexpression of Polθ.

69. Use of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**, in the manufacture of a medicament for treating a homologous recombinant (HR) deficient cancer.

70. Use of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**, in the manufacture of a medicament for treating cancer characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein.

71. Use of a compound of any one of claims **1** to **60**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **61**, in the manufacture of a medicament for treating cancer.