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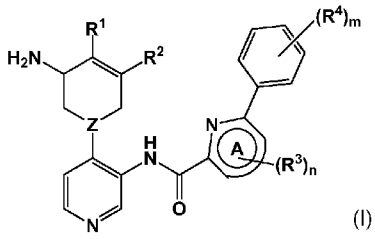
(54) Title: N-(3-PYRIDYL) BIARYLAMIDES AS KINASE INHIBITORS



(I)

(57) Abstract: The present invention provides a compound of formula (I): as described herein, and pharmaceutically acceptable salts, enantiomers, rotamers, tautomers, or racemates thereof. Also provided are methods of treating a disease or condition mediated by PIM kinase using the compounds of Formula (I), and pharmaceutical compositions comprising such compounds.

N-(3-PYRIDYL) BIARYLAMIDES AS KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to new compounds and compositions of the new compounds together with pharmaceutically acceptable carriers, and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of cancer and other cellular proliferation disorders.

BACKGROUND

Infection with the Moloney retrovirus and genome integration in the host cell genome results in development of lymphomas in mice. Provirus Integration of Moloney Kinase (PIM-Kinase) was identified as one of the frequent proto-oncogenes capable of being transcriptionally activated by this retrovirus integration event (Cuypers HT et al., "Murine leukemia virus-induced T-cell lymphomagenesis: integration of proviruses in a distinct chromosomal region," *Cell* **37(1):**141-50 (1984); Selten G, et al., "Proviral activation of the putative oncogene Pim-1 in MuLV induced T-cell lymphomas" *EMBO J* **4(7):**1793-8 (1985)), thus establishing a correlation between over-expression of this kinase and its oncogenic potential. Sequence homology analysis demonstrated that there are three highly homologous Pim-Kinases (Pim1, 2 & 3), Pim1 being the proto-oncogene originally identified by retrovirus integration. Furthermore, transgenic mice over-expressing Pim1 or Pim2 show increased incidence of T-cell lymphomas (Breuer M et al., "Very high frequency of lymphoma induction by a chemical carcinogen in pim-1 transgenic mice" *Nature* **340(6228):**61-3 (1989)), while over-expression in conjunction with c-myc is associated with incidence of B-cell lymphomas (Verbeek S et al., "Mice bearing the E mu-myc and E mu-pim-1 transgenes develop pre-B-cell leukemia prenatally" *Mol Cell Biol* **11(2):**1176-9 (1991)). Thus, these animal models establish a strong correlation between Pim over-expression and oncogenesis in hematopoietic malignancies. In addition to these animal models, Pim over-expression has been reported in many human malignancies, particularly in hematopoietic and in prostate cancer. Furthermore, mutational activation of several well known oncogenes in hematopoietic malignancies is thought to exert its effects at least in part through Pim(s). For example, targeted down-regulation of Pim expression impairs survival of hematopoietic cells transformed by Flt3 and BCR/ABL (Adam et al. 2006).

Pim1, 2 & 3 are Serine/Threonine kinases that normally function in survival and proliferation of hematopoietic cells in response to growth factors and cytokines. Substrates for Pim kinases include regulators of apoptosis such as the Bcl-2 family member BAD. The effects of Pim(s) in these regulators are consistent with a role in protection from apoptosis and promotion of cell proliferation and growth. Thus, over-expression of Pim(s) in cancer is thought to play a role in promoting survival and proliferation of cancer cells and, therefore, their inhibitions should be an effective way of treating cancers in which they are over-expressed. In fact several reports indicate that knocking down expression of Pim(s) with siRNA results in inhibition of proliferation and cell death (Dai JM, et al., "Antisense oligodeoxynucleotides targeting the serine/threonine kinase Pim-2 inhibited proliferation of DU-145 cells," *Acta Pharmacol Sin* **26(3):**364-8 (2005); Fujii et al. 2005; Li et al. 2006). Thus, inhibitors to Pim1, 2 and 3 would be useful in the treatment of these malignancies.

In addition to a potential role in cancer treatment and myeloproliferative diseases, such inhibitors could be useful to control expansion of immune cells in other pathologic condition such as autoimmune diseases, allergic reactions and in organ transplantation rejection syndromes. Recent reports demonstrate that Pim kinase inhibitors show activity in animal models of inflammation and autoimmune diseases. See JE Robinson "Targeting the Pim Kinase Pathway for Treatment of Autoimmune and Inflammatory Diseases," for the Second Annual Conference on Anti-Inflammatories: Small Molecule Approaches," San Diego, CA (Conf. April 2011; Abstract published earlier on-line).

A continuing need exists for compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, treat cancer, modulate cell cycle arrest, and/or inhibit molecules such as Pim1, Pim2 and Pim3, and pharmaceutical formulations and medicaments that contain such compounds. A need also exists for methods of administering such compounds, pharmaceutical formulations, and medicaments to patients or subjects in need thereof. The present invention addresses such needs.

Earlier patent applications have described compounds that inhibit Pims and function as anticancer therapeutics, see, e.g., WO2012/004217, WO2010/026124, WO 2008/106692 and WO2011/124580, and as treatment for inflammatory conditions such as Crohn's disease, inflammatory bowel disease, rheumatoid arthritis, and chronic inflammatory diseases, see e.g., WO 2008/022164. The present invention provides novel compounds that inhibit activity of one or more Pims, preferably two or more Pims, more

preferably Pim1, Pim2 and Pim3, at nanomolar levels (e.g., IC-50 under 50 nM) and exhibit distinctive characteristics that may provide improved therapeutic effects and pharmacokinetic properties, such as reduced drug-drug interactions associated with inhibition of cytochrome oxidases, relative to compounds previously disclosed. Compounds of the invention contain novel substitution combinations on one or more rings that provide these distinctive properties and are suitable for treating Pim-related conditions such as those described herein.

SUMMARY OF THE INVENTION

The invention provides unsaturated compounds of Formula (I) that inhibit one or more Pim kinases:

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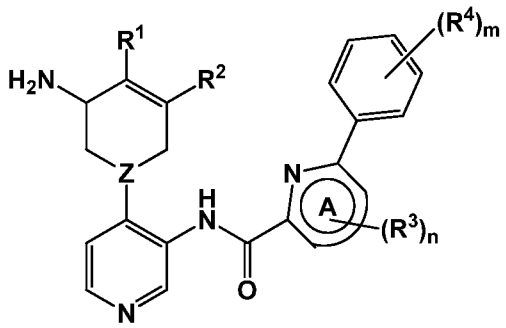


(I)

wherein:

Z is CH or N;

Aromatic ring A is a pyridine, pyrimidine, pyrazine, or thiazole ring with N located as shown;

R^1 is H, Me, Et, $-CH_2OH$, or $-CH_2OMe$;

R^2 is C_{1-4} alkyl, CF_3, or phenyl optionally substituted with 1-2 groups selected from halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and CN;

R^3 is halo, Me, CF_3, or NH_2 independently at each occurrence; and

each R^4 is independently selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, $-S(O)_p-R^*$, C_{1-4} haloalkoxy, $-(CH_2)_{0-3}-OR^*$, $-O-(CH_2)_{1-3}-OR^*$, $COOR^*$, $C(O)R^*$, $-CONR^*_2$, $-(CR'_2)_{1-3}-OR'$ or $-(CR'_2)_{1-3}-OR'$, and an optionally substituted member selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy,

C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl are each optionally substituted with up to two groups selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, and R*;

where each R' is independently H or Me

and each R* is independently H or a 4-7 membered cyclic ether, 4-6 membered cycloalkyl, or C_{1-6} alkyl, each of which is optionally substituted with up to three groups selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, OH, NH_2, COOH, COOMe, COOEt, OMe, OEt, and CN;

m is 1, 2 or 3;

n is 0, 1 or 2; and

p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

Additional embodiments of these compounds and pharmaceutical compositions and uses for these compounds and compositions are described below.

These compounds are inhibitors of Pim kinases as further discussed herein. These compounds and their pharmaceutically acceptable salts, and pharmaceutical compositions containing these compounds and salts, are useful for therapeutic methods such as treatment of cancers and autoimmune disorders that are caused by or exacerbated by excessive levels of Pim kinase activity.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

"PIM inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to PIM Kinase activity of no more than about 100 μM and more typically not more than about 5 μM, as measured in the PIM depletion assays described herein below for at least one of Pim1, Pim2 and Pim3. Preferred compounds have on IC_{50} below about 1 micromolar on at least one Pim, and generally have an IC_{50} below 100 nM on each of Pim1, Pim2 and Pim3.

The phrase "alkyl" refers to hydrocarbon groups that do not contain heteroatoms, i.e., they consist of carbon atoms and hydrogen atoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl,

decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: –$CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$CH(CH_2CH_3)_2$, -$C(CH_3)_3$, -$C(CH_2CH_3)_3$, -$CH_2CH(CH_3)_2$, -$CH_2CH(CH_3)(CH_2CH_3)$, -$CH_2CH(CH_2CH_3)_2$, -$CH_2C(CH_3)_3$, -$CH_2C(CH_2CH_3)_3$, -$CH(CH_3)$-$CH(CH_3)(CH_2CH_3)$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH(CH_3)(CH_2CH_3)$, -$CH_2CH_2CH(CH_2CH_3)_2$, -$CH_2CH_2C(CH_3)_3$, -$CH_2CH_2C(CH_2CH_3)_3$, -$CH(CH_3)CH_2$-$CH(CH_3)_2$, -$CH(CH_3)CH(CH_3)CH(CH_3)_2$, -$CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. Thus the term 'alkyl' includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Alkyl groups are described herein according to the number of carbon atoms they contain, e.g., an alkyl group containing up to six carbon atoms is described as a C1-6 or C_{1-6}, or C1-C6 alkyl. Typical alkyl groups include straight and branched chain alkyl groups having 1 to 12 carbon atoms, preferably 1-6 carbon atoms. The term 'lower alkyl' or "loweralkyl" and similar terms refer to alkyl groups containing up to 6 carbon atoms.

The term "alkenyl" refers to alkyl groups as defined above, wherein there is at least one carbon-carbon double bond, i.e., wherein two adjacent carbon atoms are attached by a double bond. The term "alkynyl" refers to alkyl groups wherein two adjacent carbon atoms are attached by a triple bond. Typical alkenyl and alkynyl groups contain 2-12 carbon atoms, preferably 2-6 carbon atoms. Lower alkenyl or lower alkynyl refers to groups having up to 6 carbon atoms. An alkenyl or alkynyl group may contain more than one unsaturated bond, and may include both double and triple bonds, but of course their bonding is consistent with well-known valence limitations.

The term 'alkoxy" refers to -OR, wherein R is alkyl.

As used herein, the term "halogen" or "halo" refers to chloro, bromo, fluoro and iodo groups. Typical halo substituents are F and/or Cl. "Haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms, typically 1-3 halogen atoms. The term "haloalkyl" thus includes monohalo alkyl, dihalo alkyl, trihalo alkyl, perhaloalkyl, and the like.

"Amino" refers herein to the group $–NH_2$. The term "alkylamino" refers herein to the group –NRR' where R and R' are each independently selected from hydrogen or a lower alkyl, provided –NRR' is not $–NH_2$. The term "arylamino" refers herein to the

group –NRR' where R is aryl and R' is hydrogen, a lower alkyl, or an aryl. The term "aralkylamino" refers herein to the group –NRR' where R is a lower aralkyl and R' is hydrogen, a loweralkyl, an aryl, or a loweraralkyl.

The term "alkoxyalkyl" refers to the group $–alk_1-O-alk_2$ where alk_1 is an alkyl linking group, and alk_2 is alkyl, e.g., a group such as $–O-(CH_2)_2-O-CH_3$. The term "loweralkoxyalkyl" refers to an alkoxyalkyl where alk_1 is loweralkyl and alk_2 is loweralkyl. The term "aryloxyalkyl" refers to the group –alkyl-O-aryl, where –alkyl- is a C_{1-12} straight or branched chain alkyl linking group, preferably C_{1-6}. The term "aralkoxyalkyl" refers to the group -alkyl-O-aralkyl, where aralkyl is preferably a loweraralkyl.

The term "aminocarbonyl" refers herein to the group $–C(O)-NH_2$. "Substituted aminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweralkyl and R' is hydrogen or a loweralkyl. In some embodiments, R and R', together with the N atom attached to them may be taken together to form a "heterocycloalkylcarbonyl" group. The term "arylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is an aryl and R' is hydrogen, loweralkyl or aryl. "aralkylaminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweraralkyl and R' is hydrogen, loweralkyl, aryl, or loweraralkyl.

"Aminosulfonyl" refers herein to the group $–S(O)_2-NH_2$. "Substituted aminosulfonyl" refers herein to the group $–S(O)_2-NRR'$ where R is loweralkyl and R' is hydrogen or a loweralkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group $–aryl-S(O)_2–NH-aralkyl$, where the aralkyl is loweraralkyl.

"Carbonyl" refers to the divalent group –C(O)-. "Carboxy" refers to–C(=O)–OH. "Alkoxycarbonyl" refers to ester –C(=O)–OR wherein R is optionally substituted lower alkyl. "Loweralkoxycarbonyl" refers to ester –C(=O)–OR wherein R is optionally substituted lower loweralkyl. "Cycloalkyloxycarbonyl" refers to –C(=O)–OR wherein R is optionally substituted C3-C8 cycloalkyl.

"Cycloalkyl" refers to a mono- di- or poly-cyclic, carbocyclic alkyl substituent in which all ring atoms are carbon. Typical cycloalkyl groups have from 3 to 8 backbone (i.e., ring) atoms. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures, including spirocyclic ring systems. The term "partially unsaturated cycloalkyl", "partially saturated cycloalkyl", and "cycloalkenyl" all refer to a cycloalkyl group wherein there is at least one unsaturated carbon-carbon bond in the ring, i.e., wherein two adjacent ring atoms are

connected by a double bond or a triple bond. Such rings typically contain 1 or 2 double bonds for 5-6 membered rings, and 1-2 double bonds or one triple bond for 7-8 membered rings. Illustrative examples include cyclohexenyl, cyclooctynyl, cyclopropenyl, cyclobutenyl, cyclohexadienyl, and the like.

The term "heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 3 heteroatoms as ring members in place of carbon atoms. Preferably, heterocycloalkyl or “heterocyclyl” groups contain one or two heteroatoms as ring members, typically only one heteroatom for 3-5 membered rings and 1-2 heteroatoms for 6-8 membered rings. Suitable heteroatoms employed in heterocyclic groups of the present invention are nitrogen, oxygen, and sulfur. Representative heterocycloalkyl moieties include, for example, pyrrolidinyl, tetrahydrofuranyl, oxirane, oxetane, oxepane, thiirane, thietane, azetidine, morpholino, piperazinyl, piperidinyl and the like.

The terms "substituted heterocycle", "heterocyclic group" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three heteroatoms, preferably 1-2 heteroatoms, selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms may be optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring or heteroaryl as described herein. Preferred heterocycles include, for example: diazapinyl, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, N-methylazetidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and oxiranyl. The heterocyclic groups may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.

Heterocyclic moieties can be unsubstituted or they can be substituted with one or more substituents independently selected from hydroxy, halo, oxo (C=O), alkylimino (RN=, wherein R is a loweralkyl or loweralkoxy group), amino, alkylamino, dialkylamino, acylaminoalkyl, alkoxy, thioalkoxy, lower alkoxyalkoxy, loweralkyl,

cycloalkyl or haloalkyl. Typically, substituted heterocyclic groups will have up to four substituent groups.

The term "cyclic ether" as used herein refers to a 3-7 membered ring containing one oxygen atom (O) as a ring member. Where the cyclic ether is "optionally substituted" it can be substituted at any carbon atom with a group suitable as a substituent for a heterocyclic group, typically up to three substituents selected from lower alkyl, lower alkoxy, halo, hydroxy, amino, -C(O)-lower alkyl, and -C(O)-lower alkoxy. In preferred embodiments, halo, hydroxy and lower alkoxy are not attached to the carbon atoms of the ring that are bonded directly to the oxygen atom in the cyclic ether ring. Specific examples include oxirane, oxetane (e.g., 3-oxetane), tetrahydrofuran (including 2-tetrahydrofuranyl and 3-tetrahydrofuranyl), tetrahydropyran (e.g., 4-tetrahydropyranyl), and oxepane.

"Aryl" refers to monocyclic and polycyclic aromatic groups having from 5 to 14 backbone carbon or hetero atoms, and includes both carbocyclic aryl groups and heteroaromatic aryl groups. Carbocyclic aryl groups are aryl groups in which all ring atoms in the aromatic ring are carbon, typically including phenyl and naphthyl. Exemplary aryl moieties employed as substituents in compounds of the present invention include phenyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like. When used in connection with aryl substituents, the term "polycyclic aryl" refers herein to fused and non-fused cyclic structures in which at least one cyclic structure is aromatic, such as, for example, benzodioxozolo (which has a heterocyclic structure fused to a phenyl group, naphthyl, and the like. Where "aryl" is used, the group is preferably a carbocyclic group; the term "heteroaryl" is used for aryl groups when ones containing one or more heteroatoms are preferred.

The term "heteroaryl" refers herein to aryl groups having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms, in a 5-14 atom aromatic ring system that can be monocyclic or polycyclic. Monocyclic heteroaryl rings are typically 5-6 atoms in size. Exemplary heteroaryl moieties employed as substituents in compounds of the present invention include pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl,

thiophenyl, furanyl, quinolinyl, purinyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like.

"Aralkyl" or "arylalkyl" refers to an aryl group connected to a structure through an alkylene linking group, e.g., a structure such as $-(CH_2)_{1-4}$-Ar, where Ar represents an aryl group. "Lower aralkyl" or similar terms indicate that the alkyl linking group has up to 6 carbon atoms.

"Optionally substituted" or "substituted" refers to the replacement of one or more hydrogen atoms with a non-hydrogen group. Alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups described herein may be substituted or unsubstituted. Suitable substitution groups include, for example, hydroxy, nitro, amino, imino, cyano, halo, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halololoweralkyl, loweralkylamino, halololoweralkylamino, lower alkoxy, lower haloalkoxy, lower alkoxyalkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like, provided that oxo, imidino or other divalent substitution groups are not placed on aryl or heteroaryl rings due to the well known valence limitations of such rings. In preferred embodiments, unless otherwise specified, optional substituents for alkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl groups are 1-3 groups selected from halo, hydroxy, amino, cyano, lower alkoxy, lower alkylsulfonyl, oxy, carboxy, and lower alkoxycarbonyl. In preferred embodiments, unless otherwise specified, optional substituents for aryl and heteroaryl groups are 1-3 groups selected from halo, hydroxy, amino, cyano, lower alkyl, lower alkoxy, lower alkylsulfonyl, carboxy, and lower alkoxycarbonyl.

The substitution group can itself be substituted where valence permits, i.e., where the substitution group contains at least one CH, NH or OH having a hydrogen atom that can be replaced. The group substituted onto the substitution group can be carboxyl, halo (on carbon only); nitro, amino, cyano, hydroxy, loweralkyl, loweralkoxy, C(O)R, -OC(O)R, -OC(O)OR, -NRCOR, $-CONR_2$, -NRCOOR, $-C(S)NR_2$, -NRC(S)R, $-OC(O)NR_2$, , -SR, $-SO_3H$, $-SO_2R$ or C3-8 cycloalkyl or 3-8 membered heterocycloalkyl, where each R is independently selected from hydrogen, lower haloalkyl, lower alkoxyalkyl, and loweralkyl, and where two R on the same atom or on directly connected

atoms can be linked together to form a 5-6 membered heterocyclic ring. Unless indicated as optionally substituted, these substitition groups are typically unsubstituted.

When a substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substituents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

It is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with five fluoro groups or a halogen atom substituted with another halogen atom). Such impermissible substitution patterns are well known to the skilled artisan.

"Syn" as used herein has its ordinary meaning, and is used in connection with Formula I to indicate that the specified groups are attached to sp^3 hybridized (tetrahedral) carbon centers and extend out from one face of the cyclohexyl or piperidinyl ring, i.e., those groups all project toward the 'alpha' face of the ring, or they all project toward the 'beta' face of the ring. This is thus used as a convenient way to define the relative orientations of two or more groups on a ring, without limiting the compounds to a specific absolute chiral configuration. This reflects the fact that the compounds of the invention have such groups in a specific relative orientation, but are not limited to either enantiomer of that specific relative orientation. Accordingly, unless described as optically active, such compounds may be racemic, but also include each of the two enantiomers having the specified relative stereochemistry. In some embodiments, the compounds of the invention are optically active form as further described herein, and in preferred embodiments of the invention, the compounds are obtained and used in optically active form. Preferably, the enantiomer having greater potency as an inhbitor of at least two of Pim1, Pim2 and Pim3 is selected.

It will also be apparent to those skilled in the art that the compounds of the invention, as well as the pharmaceutically acceptable salts, esters, metabolites and prodrugs of any of them, may be subject to tautomerization and may therefore exist in various tautomeric forms wherein a proton of one atom of a molecule shifts to another atom and the chemical bonds between the atoms of the molecules are consequently rearranged. See, e.g., March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992). As used herein, the

term "tautomer" refers to the compounds produced by the proton shift, and it should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

The compounds of the invention comprise one or more asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention existing in enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, such as in (R)- or (S)- forms. The compounds of the invention are sometimes depicted herein as single enantiomers, and are intended to encompass the specific configuration depicted and the enantiomer of that specific configuration (the mirror image isomer of the depicted configuration), unless otherwise specified—e.g., where a structure is labeled 'chiral', it represents the specified absolute stereochemistry as a single substantially pure (i.e., at least about 95% pure) enantiomer. The depicted structures herein describe the relative stereochemistry of the compounds where two or more chiral centers, but the invention is not limited to the depicted enantiomer's absolute stereochemistry unless otherwise stated. The invention includes both enantiomers, each of which will exhibit Pim inhibition, even though one enantiomer will be more potent than the other. In some instances, compounds of the invention have been synthesized in racemic form and separated into individual isomers by chiral chromatography or similar conventional methods, and the analytical data about the two enantiomers do not provide definitive information about absolute stereochemical configuration. In such cases, the absolute stereochemistry of the most active enantiomer has been identified based on correlation with similar compounds of known absolute stereochemistry, rather than by a definitive physical method such as X-ray crystallography. Therefore, in certain embodiments, the preferred enantiomer of a compound described herein is the specific isomer depicted or its opposite enantiomer, whichever has the lower IC-50 for Pim kinase inhibition using the assay methods described herein, i.e., the enantiomer that is more potent as a Pim inhibitor for at least two of Pim1, Pim2, and Pim3.

The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, *Pure Appl. Chem. 45*:13-30 (1976). The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred

substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) paragraph 203.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or base addition salts of the compounds of Formulas I, II, etc., wherein the compound acquires a positive or negative charge as a result of adding or removing a proton; the salt then includes a counterion of opposite charge from the compound itself, and the counterion is preferably one suitable for pharmaceutical administration under the conditions where the compound would be used. These salts can be prepared *in situ* during the final isolation and purification of the compounds of Formula I or II, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate.

Also, a basic nitrogen-containing group in compounds of the invention can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained. These quaternized ammonium salts when paired with a pharmaceutically acceptable anion can also serve as pharmaceutically acceptable salts.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and

phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Counterions for pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters, which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular pharmaceutically acceptable esters include formates, acetates, propionates, maleates, lactates, hydroxyacetates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, PRO-DRUGS AS NOVEL DELIVERY SYSTEMS, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., BIOREVERSIBLE CARRIERS IN DRUG DESIGN, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3H}, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an 18F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

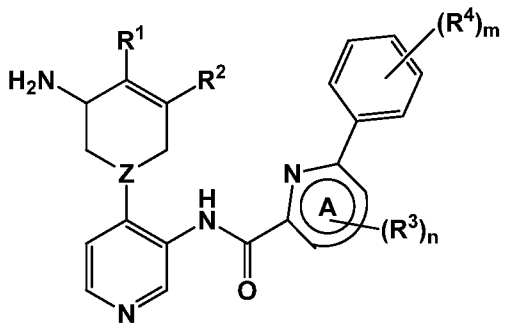
Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least

6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d^6-acetone, d^6-DMSO.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

In one aspect, the invention provides compounds of Formula I:



(I)

wherein:

Z is CH or N;

Aromatic ring A is a pyridine, pyrimidine, pyrazine, or thiazole ring with N located as shown;

R^1 is H, Me, Et, $-CH_2OH$, or $-CH_2OMe$;

R^2 is C_{1-4} alkyl, CF_3, or phenyl optionally substituted with 1-2 groups selected from halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and CN;

R^3 is halo, Me, CF_3, or NH_2 independently at each occurrence; and

each R^4 is independently selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, $-S(O)_p-R^*$, C_{1-4} haloalkoxy, $-(CH_2)_{0-3}-OR^*$, $-O-(CH_2)_{1-3}-OR^*$, COOR*,

C(O)R*, -CONR*$_2$, -(CR'$_2$)$_{1-3}$-OR' or -(CR'$_2$)$_{1-3}$-OR', and an optionally substituted member selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl are each optionally substituted with up to two groups selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, and R*;

where each R' is independently H or Me

and each R* is independently H or a 4-7 membered cyclic ether, 4-6 membered cycloalkyl, or C_{1-6} alkyl, each of which is optionally substituted with up to three groups selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, OH, NH_2, COOH, COOMe, COOEt, OMe, OEt, and CN;

m is 1, 2 or 3;

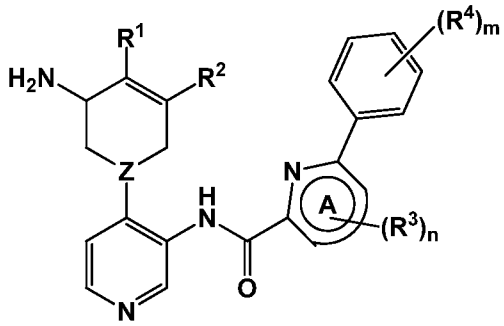
n is 0, 1 or 2; and

p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The following enumerated embodiments are representative of certain aspects of the invention:

1. A compound of Formula (I):



(I)

wherein:

Z is CH or N;

Aromatic ring A is a pyridine, pyrimidine, pyrazine, or thiazole ring with N located as shown;

R^1 is H, Me, Et, -CH_2OH, or -CH_2OMe;

R^2 is C_{1-4} alkyl, CF_3, or phenyl optionally substituted with 1-2 groups selected from halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and CN;

R^3 is halo, Me, CF_3, or NH_2 independently at each occurrence; and

each R^4 is independently selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, $-S(O)_p-R^*$, C_{1-4} haloalkoxy, $-(CH_2)_{0-3}-OR^*$, $-O-(CH_2)_{1-3}-OR^*$, $COOR^*$, $C(O)R^*$, $-CONR^*_2$, $-(CR'_2)_{1-3}-OR'$ or $-(CR'_2)_{1-3}-OR'$, and an optionally substituted member selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl are each optionally substituted with up to two groups selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, and R*;

where each R' is independently H or Me

and each R* is independently H or a 4-7 membered cyclic ether, 4-6 membered cycloalkyl, or C_{1-6} alkyl, each of which is optionally substituted with up to three groups selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, OH, NH_2, COOH, COOMe, COOEt, OMe, OEt, and CN;

m is 1, 2 or 3;

n is 0, 1 or 2; and

p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, wherein R^1 is H or Me.

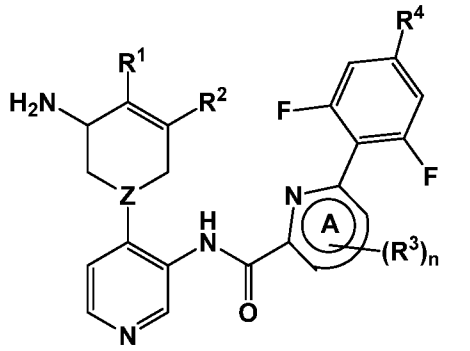
3. The compound of embodiment 1 or 2, wherein R^2 is Me or CF_3.

4. The compound of any of embodiments 1-3, wherein Z is CH.

5. The compound of any of embodiments 1-3, wherein Z is N.

6. The compound of any of embodiments 1-5, wherein two R^4 groups each represent F.

7. The compound of any of embodiments 1-6, wherein the compound is of the formula:



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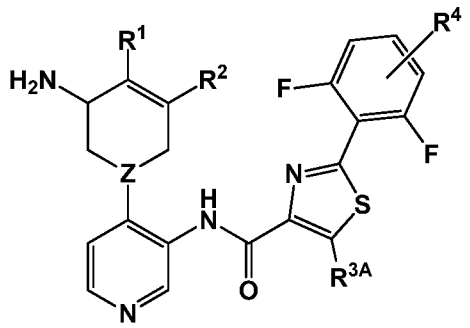
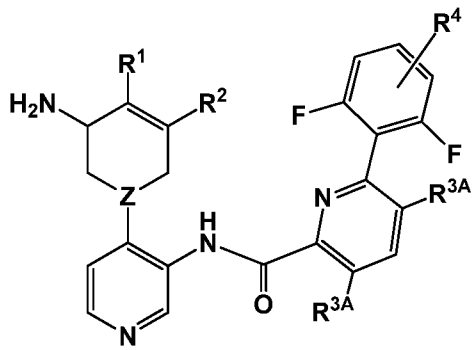
8. The compound of any of embodiments 1-7, wherein the compound is of the formula:



,

where R^{3A} (or R^3) is H, F or NH_2.

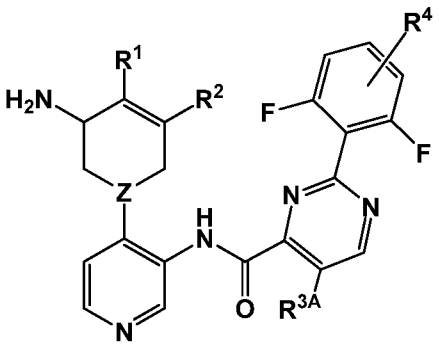
9. The compound of any one of embodiments 1-8, wherein the compound is of the formula:



,

where each R^{3A} (or R^3) is independently H, F or NH_2.

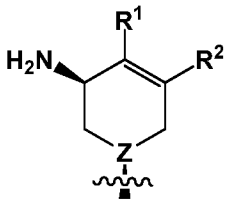
10. The compound of any of embodiments 1-8, which is of the formula:



,

where R^{3A} (or R^3) is H, F or NH_2.

11. The compound of any of the preceding embodiments, wherein the unsaturated ring has the relative stereochemistry of this formula:



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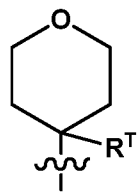
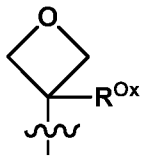
12. The compound of any of the preceding embodiments, wherein at least one R^3 or R^{3A} (or R^3) is F or NH_2.

13. The compound of any one of embodiments 1-12, wherein one R^4 is a



tetrahydropyranyl group of the formula: ,

wherein R^T is H, OH, OMe, or F.

14. The compound of any one of embodiments 1-12, wherein one R^4 is an oxetanyl group of the formula:  ,

wherein R^{Ox} is H, OH, OMe, or F.

15. The compound of any of embodiments 1-12, wherein one R^4 is OMe, OEt, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, or OPr.

16. The compound of any of embodiments 1-12, wherein one R^4 is $-CH_3$, $-CH_2OMe$, 1-hydroxycyclobutyl, $-SO_2Me$, or $-CH_2OEt$.

17. The compound of embodiment 1, which is selected from the compounds in Table I below.

18. A pharmaceutical composition comprising a compound of any of the preceding embodiments and at least one pharmaceutically acceptable excipient.

19. The pharmaceutical composition of embodiment 18, further comprising a co-therapeutic agent.

20. The pharmaceutical composition of embodiment 19, wherein the co-therapeutic agent is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, cytarabine, daunorubicin, PI3 Kinase inhibitors, mTOR inhibitors, DNA synthesis inhibitors, leucovorin, carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, and trastuzumab.

21. A method to treat a condition caused or exacerbated by excessive Pim kinase activity, which comprises administering to a subject in need thereof an effective amount of a compound of any one of claims 1-17.

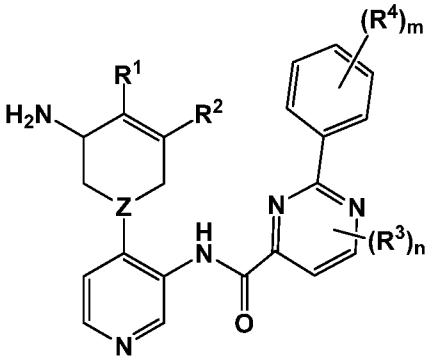
22. The method of embodiment 21, wherein the condition is a cancer.

23. The method of embodiment 21, wherein the cancer is selected from carcinoma of the lungs, pancreas, thyroid, ovary, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma, erythroleukemia, villous colon adenoma, and osteosarcoma; or the autoimmune disorder is selected from Crohn's disease, inflammatory bowel disease, rheumatoid arthritis, and chronic inflammatory diseases.

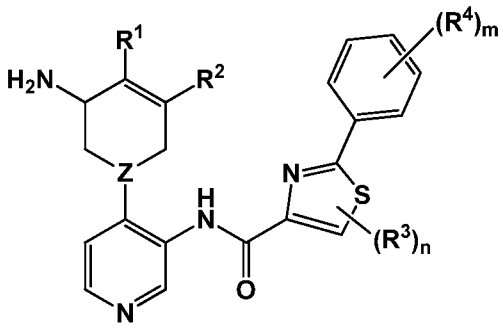
24. A compound according to any of embodiments 1-17 for use in therapy.

25. Use of a compound according to any of embodiments 1-17 for the preparation of a medicament.

In compounds of the invention (Formula I and the various embodiments described herein), Z can be N, but in preferred embodiments, Z is CH. Aromatic ring A can be pyridine, pyrimidine, pyrazine, or thiazole, provided the ring is oriented so a nitrogen atom is positioned as shown in Formula I. Pyridine is sometimes preferred. Preferred orientations for the pyrimidine and thiazole ring are these:



and



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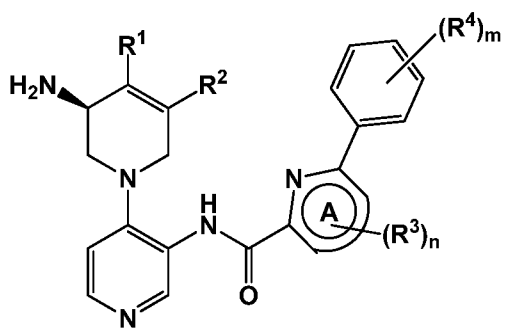
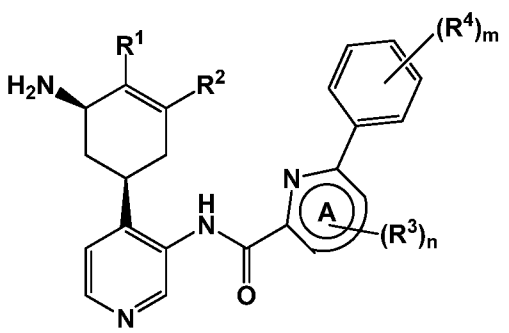
In the thiazole compounds, n is 0 or 1, preferably n is 1. In the pyrimidine and pyrazine compounds, n is preferably 0 or 1.

The compounds of the invention contain at least one chiral center: in some embodiments, the compounds have the following stereochemistry:



or



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Of the available options for R^1, H is preferred. From the various options for R^2, methyl is preferred.

When Ring A is thiazole, R^3 is often NH_2 when n is 1.

When Ring A is pyrimidine or pyrazine, n is often 0 or 1, and when present, R^3 is often NH_2.

When Ring A is pyridine, n can be 0, 1 or 2; and when present, each R^3 is often independently selected from halo and amino.

When Ring A is pyrazine, n can be 0 or 1 or 2 and is preferably 0 or 1; and when present, each R^3 is often independently selected from amino and halo.

In some embodiments, at least one R^4 is selected from F, Cl, NH_2, Me, Et, OMe, OEt, OCF_3, $OCHF_2$, OCH_2CF_3, CN, CF_3, SMe, SOMe, SO_2Me, -COOMe, -C(O)Me, -$C(Me)_2$-OH, $MeOCH_2$-, $HOCH_2$-, hydroxyethyl, hydroxyethoxy, methoxyethyl, methoxyethoxy, oxetanyl (e.g., 3-oxetanyl), tetrahydropyranyl, isopropoxy, tetrahydropyranyloxy (e.g., 4-tetrahydropyranyloxy), cyclopropyl, and CN; in these groups, the oxetane or tetrahydropyran rings can optionally be substituted with F, Me, OH, or OMe. At least one R^4 is preferably selected from Me, F, NH_2, OMe, $MeOCH_2$-, $HOCH_2$-, hydroxyethyl, hydroxyethoxy, methoxyethyl, methoxyethoxy, and CN. Typically, m is 2 or 3, and two of the R^4 groups are F, while the third if present is selected from Me, Et, OMe, OEt, OCF_3, $OCHF_2$, OCH_2CF_3, CN, CF_3, SMe, SOMe, SO_2Me, -COOMe, -C(O)Me, -$C(Me)_2$-OH, $MeOCH_2$-, $HOCH_2$-, hydroxyethyl, hydroxyethoxy, methoxyethyl, methoxyethoxy, oxetanyl (e.g., 3-oxetanyl), isopropoxy, tetrahydropyranyl (e.g., 4-tetrahydropyranyl), tetrahydropyranyloxy (e.g., 4-tetrahydropyranyloxy), cyclopropyl, and CN, where the oxetane or tetrahydropyran rings can optionally be substituted with F, Me, OH, or OMe.

Each of the species in Table 1 is a preferred embodiment of the invention.

The invention provides novel combinations of substituents on the cyclohexyl or piperidine ring and the phenyl ring that provide advantageous biological activities. Advantages provided by preferred compounds include reduced drug-drug interactions, due to reduction of time-dependent Cyp inhibition, or pharmacokinetic superiority based on improved clearance and/or metabolic properties.

These compounds may be used in racemic form, or the individual enantiomers may be used, or mixtures of the enantiomers or diastereomers may be used. Each enantiomer can be used, and preferably the compound to be used is the enantiomer that has greater activity as a Pim inhibitor.

For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily, typically 0.01 to 100 mg/kg per day, and more preferred from 0.1 to 30 mg/kg body weight daily. Generally, daily dosage amounts of 1 to 4000 mg, or from 5 to 3000, or from 10 to 2000 mg, or from 100 to 2000 mg are anticipated for human subjects. Dosage unit compositions may contain such amounts or submultiples thereof to make up the daily dose.

The compounds of the present invention may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. In preferred embodiments, the compound or composition of the invention is administered orally.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium

chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq.* (1976).

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents

used in the treatment of cancer. The compounds of the present invention are also useful in combination with known therapeutic agents and anti-cancer agents, and combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology*, V. T. Devita and S. Hellman (editors), 6th edition (Feb. 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: MEK inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The compounds of the invention are also useful when co-administered with radiation therapy.

Therefore, in one embodiment of the invention, the compounds of the invention are also used in combination with known therapeutic or anticancer agents including, for example, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

In certain presently preferred embodiments of the invention, representative therapeutic agents useful in combination with the compounds of the invention for the treatment of cancer include, for example, MEK inhibitors, irinotecan, topotecan, gemcitabine, 5-fluorouracil, cytarabine, daunorubicin, PI3 Kinase inhibitors, mTOR inhibitors, DNA synthesis inhibitors, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, trastuzumab, Revlimid, Velcade, dexamethasone, daunorubicin, cytaribine, clofarabine, Mylotarg, lenalidomide, bortezomib, as well as other cancer chemotherapeutic agents including targeted therapuetics.

The above compounds to be employed in combination with the compounds of the invention will be used in therapeutic amounts as indicated in the *Physicians' Desk Reference (PDR)* 47th Edition (1993), which is incorporated herein by reference, or such

therapeutically useful amounts as would be known to one of ordinary skill in the art, or provided in prescribing materials such as a drug label for the additional therapeutic agent.

The compounds of the invention and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

In one embodiment, the invention provides a method of inhibiting Pim1, Pim2 or Pim3 in a human or animal subject. The method includes administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any of the embodiments of compounds of Formula I or II to a subject in need thereof.

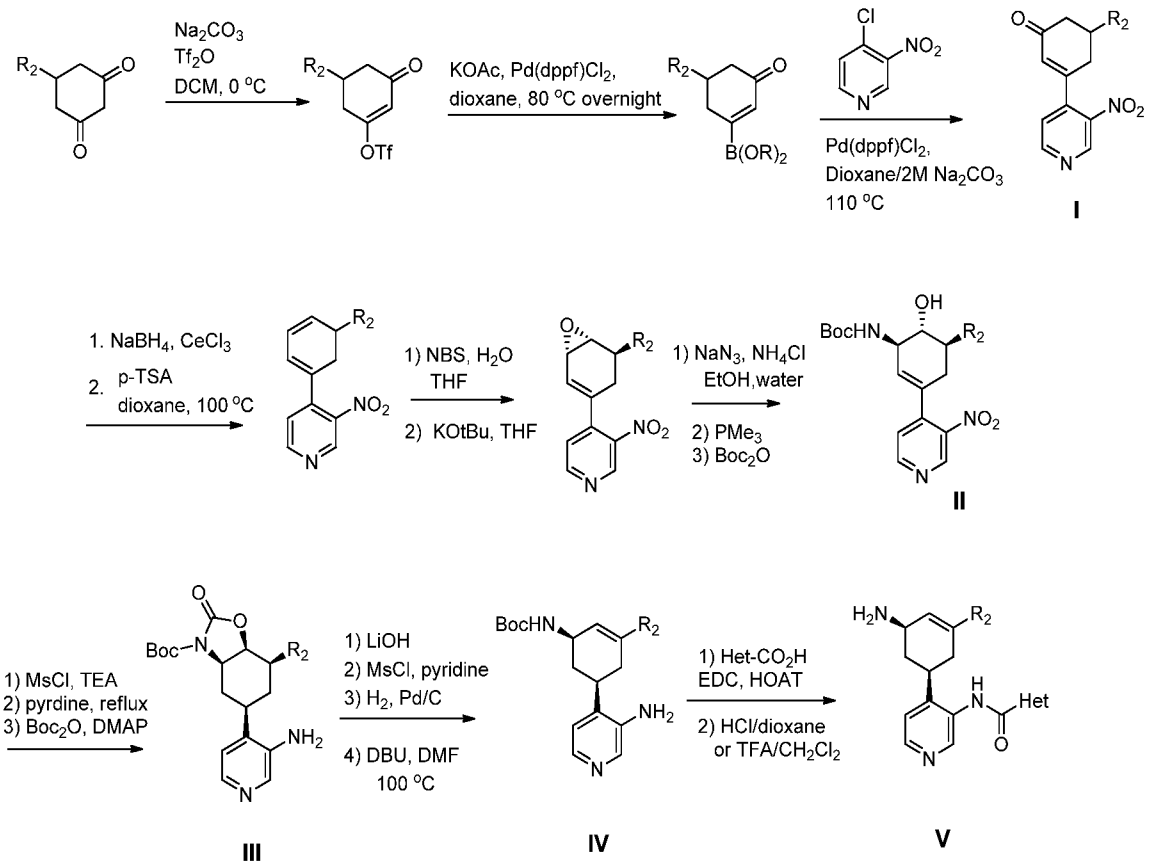
The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

Synthetic Methods

The compounds of the invention can be obtained through procedures known to those skilled in the art. As shown in Scheme 1, synthetic methods to prepare aminosubstituted aminocyclohexenylpyridyl amides **V** are depicted. Methyl cyclohexanedione can be converted via the monotriflate to the corresponding cyclohexenoneboronate ester which can undergo palladium mediated carbon bond formation with 4-chloro, 3-nitro pyridine to yield nitropyridine substituted cyclohexenone **I**. Ketone reduction followed by dehydration yields a cyclohexadiene which upon epoxidation (via bromohydrin formation and HBr elimination), azide epoxide opening, azide reduction and amine Boc protection yields cyclohexenyl Boc amino alcohol nitro pyridyl compound **II**. The alcohol moiety of nitropyridyl **II** can be inverted via a mesylation, cyclization and Boc protection sequence to provide the all cis substituted cyclohexyl pyridyl aniline **III**, where the cis hydroxy is protected in the form of a cylic carbamate. Hydrolysis of the cyclic carbamate, mesylation of the generated hydroxyl,

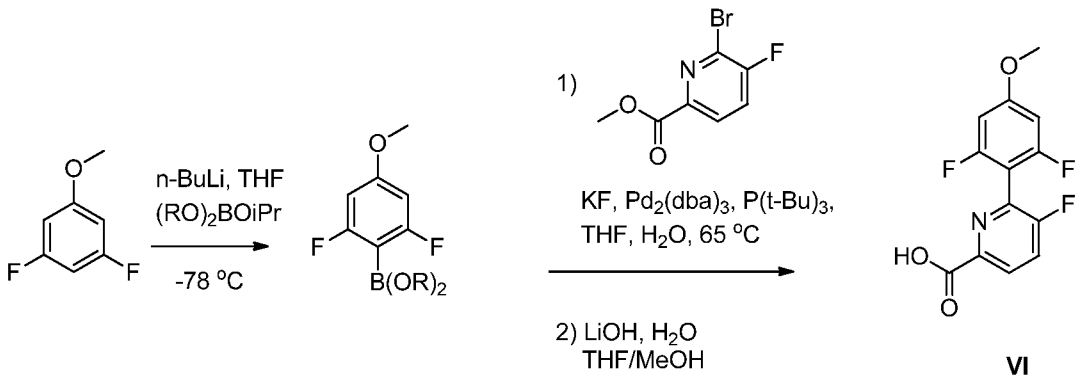
reduction of the trisubstituted alkene and nitro, followed by elimination of the mesylate yields the Bocamino protected cyclohexyenyl pyridyl aniline **IV**. Subsequent coupling with heterocylic acids and deprotection of the Boc group yields cyclohexenyl compounds **V** of the invention. By varying the input of the initial 5-substituted cyclohexanedione, the R_2 position of the compounds **V** of the invention can be varied.

Scheme 1



A representative route to a heterocyclic acid that can be incorporated into compounds **V** of the invention is depicted in Scheme 2. Lithiation of 5-methoxy, 1,3 difluorobenzene and reaction with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane yields a boranate ester which upon Suzuki coupling with the bromofluoro picolinate ester and subsequent ester hydrolysis yields the fluoro picolinic acid **VI.**

Scheme 2



EXAMPLES

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2695 Separation Module (Milford, MA). The analytical columns were reversed phase Phenomenex Luna C18 -5 μ, 4.6 x 50 mm, from Alltech (Deerfield, IL). A gradient elution was used (flow 2.5 mL/min), typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 10 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA).

In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well-known iodine vapor and other various staining techniques.

Mass spectrometric analysis was performed on one of three LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 4 min period; flow rate 0.8 mL/min; molecular weight range 200-1500; cone Voltage 20 V; column temperature 40°C),

another Waters System (ACQUITY UPLC system and a ZQ 2000 system; Column: ACQUITY UPLC HSS-C18, 1.8um, 2.1 x 50mm; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 1.3 min period; flow rate 1.2 mL/min; molecular weight range 150-850; cone Voltage 20 V; column temperature 50°C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% acetonitrile in water with 0.05% TFA over a 4 min period; flow rate 0.8 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses were reported as those of the protonated parent ions.

Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 400 MHz NMR (Palo Alto, CA). The spectral reference was either TMS or the known chemical shift of the solvent.

Preparative separations are carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material on ISCO or Analogix purification systems, or by HPLC using a Waters 2767 Sample Manager, C-18 reversed phase column, 30X50 mm, flow 75 mL/min. Typical solvents employed for the Flash 40 Biotage, ISCO or Analogixsystem for silica gel column chromatography are dichloromethane, methanol, ethyl acetate, hexane, n-heptanes, acetone, aqueous ammonia (or ammonium hydroxide), and triethyl amine. Typical solvents employed for the reverse phase HPLC are varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

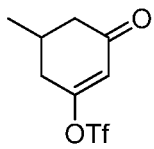
The examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

	ABBREVIATIONS
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Boc_2O	di-tert-butyl dicarbonate
Boc-OSu	*N*-(*tert*-Butoxycarbonyloxy)succinimide
DAST	(diethylamino)sulfurtrifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIAD	diisopropylazodicarboxylate
DIEA	diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
EtOH	Ethanol
HOAT	Hydroxyazabenzotriazole
K_2CO_3	Potassium carbonate
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione
LiOH	Lithium hydroxide
MCPBA	Meta-chloroperbenzoic acid
MeCN	Acetonitrile
methylDAST	(dimethylamino)sulfurtrifluoride
$MgSO_4$	Magnesium sulfate
MeOH	Methanol
MsCl	Methane sulfonyl chloride
Na_2CO_3	sodium carbonate

	ABBREVIATIONS
NaCl	Sodium chloride
$NaHCO_3$	sodium bicarbonate
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
oxone	Potassium peroxymonosulfate
p-TSA	*para*-toluene sulfonic acid
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphospine)palladium(0)
$Pd(dppf)Cl_2$-DCM	Dichloro-(1,2-bis(diphenylphosphino)ethan)-Palladium(II) – dichloromothethane adduct
RT or rt	room temperature
TBDMSCl	tert-butyldimethylsilylchloride
TEA	Triethylamine
THF	tetrahydrofuran

EXAMPLES

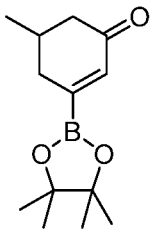
Synthesis of 5-methyl-3-oxocyclohex-1-enyltrifluoromethanesulfonate



To a solution of 5-methylcyclohexane-1,3-dione (1.0 equiv.) in DCM (0.5M) was added Na_2CO_3 (1.1 equiv.) and cooled to 0 °C. Added Tf_2O (1.0 equiv.) in DCM (5.0 M) dropwise over 1 hr at 0°C under a nitrogen atmosphere. Upon addition, the reaction was stirred for 1 hr at room temperature (dark red solution). The solution was filtered and the filtrate was quenched by careful addition of saturated $NaHCO_3$ with vigorous stirring until pH=7. The solution was transferred to a separatory funnel and the layers were

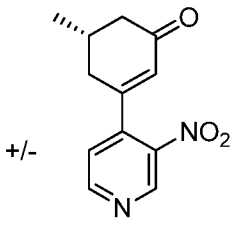
separated. The organic layer was washed with brine, dried with Na_2SO_4, filtered, concentrated under vacuo and dried under high vacuum for 15 min to yield 5-methyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate as light yellow oil in 78% yield. LC/MS=259.1/300.1 (M+H and M+CH_3CN); Rt = 0.86 min, LC = 3.84 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 6.05 (s, 1H), 2.70 (dd, J=17.2, 4.3, 1H), 2.53 (dd, J=16.6, 3.7, 1H), 2.48-2.31 (m, 2H), 2.16 (dd, J=16.4, 11.7, 1H), 1.16 (d, J=5.9, 3H).

Synthesis of 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone



To a solution of 5-methyl-3-oxocyclohex-1-enyl trifluoromethanesulfonate (1.0 equiv.) in degassed dioxane (0.7 M) was added bis(pinacolato)diboron (2.0 equiv.), KOAc (3.0 equiv.), and Pd(dppf)Cl_2-DCM (0.03 equiv.). The reaction was heated to 80 ^oC for 10 h then cooled to room temperature and filtered through a coarse frit glass funnel. The cake was rinsed with more dioxane and the filtrate solution was used for the next step without further purification. LC/MS = 155.1 (M+H of boronic acid); Rt = 0.41 min, LC = 1.37 min.

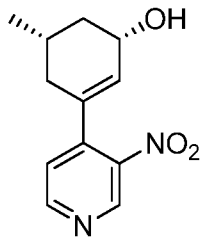
Synthesis of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone



To a solution of 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone (1.0 equiv.) in degassed dioxane (0.5 M) and 2M Na_2CO_3 (2 equiv.) was added 4-chloro-3-nitropyridine (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.). The

reaction was placed under a reflux condenser and heated in an oil bath to 110°C for 1 h. Cooled to room temperature, filtered through a pad of Celite, washed the pad with ethyl acetate and concentrated the filtrate under vacuo. The residue was further pumped at 80 °C on a rotary evaporator for one hour to remove boronate by-products (M+H = 101) via sublimation. The residue was partitioned between brine and ethyl acetate, and the layers were separated, the aqueous phase was further extracted with ethyl acetate (4x), the organics were combined, dried over sodium sulfate, filtered, and concentrated. The crude was purified via silica gel chromatography loading in DCM and eluting with 2-50% ethyl acetate and hexanes. The pure fractions were concentrated in vacuo to yield an orange oil. The oil was placed under high vacuum (~500 mtorr) with seed crystals overnight to yield an orange solid. The solid was further purified via trituration in hexanes to yield 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (48% 2 steps). LC/MS = 233.2 (M+H); Rt = 0.69 min, LC = 2.70 min. ^{1}H-NMR (400 MHz, $CdCl_3$) δ ppm: 9.31 (s, 1H), 8.88 (d, J=5.1, 1H), 7.30 (d, J=5.1, 1H), 6.00 (d, J=2.4, 1H), 2.62 (dd, J=16.4, 3.5, 1H), 2.53-2.34 (m, 3H), 2.23 (dd, J=16.1, 11.7, 1H), 1.16 (d, J=6.3, 3H).

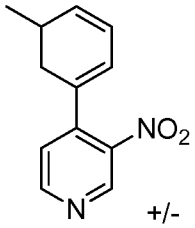
Synthesis of cis-(+/-)-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol



+/-

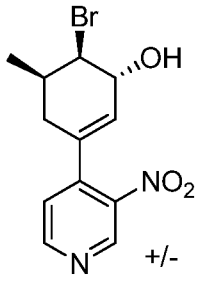
To a solution of 5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enone (1.0 equiv.) in EtOH (0.3 M) was added $CeCl_3$-$7H_2O$ (1.2 equiv.). The reaction was cooled to 0°C, then $NaBH_4$ (1.2 equiv.) was added in portions. Stirred for 1 h at 0°C, then quenched by adding water, concentrated to remove the EtOH, added EtOAc, extracted the organics, washed with brine, then dried with Na_2SO_4, filtered and concentrated to yield cis-(+/-)-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (94%). LC/MS = 235.2 (M+H), LC = 2.62 min.

Synthesis of (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine



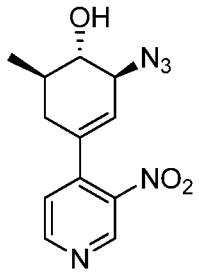
To a solution of (+/-)-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in dioxane (0.1M) was added p-TSA (1.0 equiv.), and the reaction was stirred at 100 °C for 3 h. The solution was cooled to room temperature, then passed through a pad of neutral alumina eluting with EtOAc to yield (+/-)-4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine as a yellow oil in 68% yield. LC/MS = 217.1 (M+H), LC = 3.908 min.

Synthesis of (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol



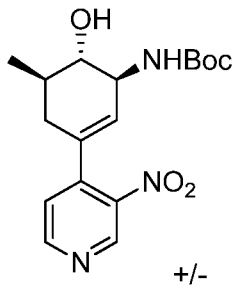
To a solution of 4-(5-methylcyclohexa-1,3-dienyl)-3-nitropyridine (1.0 equiv.) in THF and water (1:1, 0.13 M) was added NBS (1.5 equiv.) and the reaction was stirred at room temperature for 30 min. Upon completion, ethyl acetate and water were added to the reaction, the organic phase was dried with brine, then sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to give (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol as a yellow oil in 80% yield. LC/MS = 315.0/313.0 (M+H), LC = 2.966 min.

Synthesis of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol



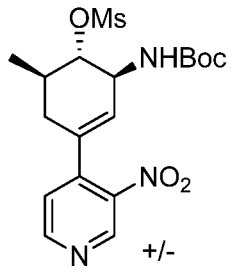
To a solution of (+/-)-6-bromo-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enol (1.0 equiv.) in THF (0.1 M) was added potassium tert-butoxide (1.5 equiv.). The reaction turned from orange to black almost immediately. By TLC, the formation of product is clean in 30 min. Quenched by adding saturated ammonium chloride and ethyl acetate. The organic phase was dried with brine, then sodium sulfate, filtered, and concentrated. The crude product was dissolved in ethanol and water (3:1, 0.1 M), and ammonium chloride (2.0 equiv) and sodium azide (2.0 equiv.) were added. The dark orange reaction was stirred at room temperature overnight. The conversion to product is clean as indicated by LC/MS. The reaction was concentrated to remove the ethanol, ethyl acetate and water were added, and the organic phase was dried with sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to give (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol in 55% yield. LC/MS = 276.0 (M+H), LC = 2.803 min.

Synthesis of (+/-)-tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate



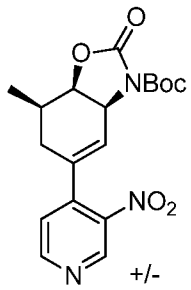
To a solution of (+/-)-2-azido-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enol (1.0 equiv.) in pyridine and ammonium hydroxide (8:1, 0.08 M) was added trimethylphosphine (3.0 equiv.) and the brown solution was stirred at room temperature for 2 h. Upon completion, EtOH was added and the solution was concentrated *in vacuo*. More ethanol was added and the reaction was concentrated again. Dioxane and sat. $NaHCO_3$ (1:1, 0.08 M) were added to the crude, followed by Boc_2O (1.0 equiv.). Stirred the reaction mixture at room temperature for 2h, then added water and ethyl acetate. The organic phase was dried with $MgSO_4$, and concentrated. The crude product was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford (+/-)-tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (59%). LC/MS = 350.1 (M+H), Rt: 0.76 min.

Synthesis of 2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate



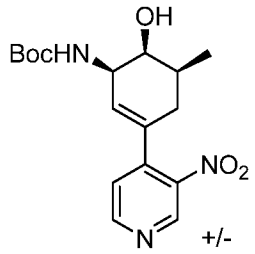
To a solution of tert-butyl 6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-enylcarbamate (1.0 equiv.) in DCM (0.09 M) was added triethylamine (1.5 equiv.) and the reaction was cooled to 0 °C. MsCl (1.2 equiv.) was added to the reaction and stirred for 3 h. Another 1.0 equiv. of MsCl was added to the reaction and stirred for another 2 h. Worked up the reaction by adding water, the organic phase was dried with brine, sodium sulfate, and concentrated. The crude product was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (1:1) to afford 2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate as a white foam in 65% yield. LC/MS = 428.2 (M+H), LC: 3.542 min.

Synthesis of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate



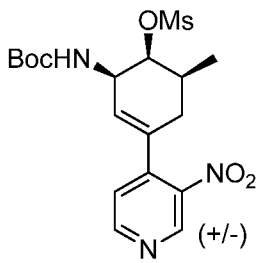
A solution of (+/-)-2-(tert-butoxycarbonylamino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-enyl methanesulfonate (1.0 equiv.) in pyridine (0.2 M) was heated in the microwave at 110 °C for 10 min (or refluxing in an oil bath for several hours). The orange reaction was then concentrated under vacuo, the crude was dissolved in ethyl acetate and water, the organic phase was dried with sodium sulfate and concentrated under vacuo. The crude material was dissolved in DCM (0.2 M), triethylamine (1.8 equiv.) was added, followed by Boc_2O (1.2 equiv.). The reaction was stirred for 40 min, then concentrated to dryness. The crude material was purified via silica gel column chromatography eluting with hexane and ethyl acetate (1:1) to afford (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate as a white foam in 66% yield. LC/MS = 376.0 (M+H), LC: 3.424 min.

Synthesis of (+/-)-tert-butyl ((1R,5S,6S)-6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-en-1-yl)carbamate



To a solution of (+/-)-tert-butyl 7-methyl-5-(3-nitropyridin-4-yl)-2-oxo-3a,6,7,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (1.0 equiv.) in tetrahydrofuran (0.2 M) was added 2M $LiOH_{(aq.)}$ (3.0 equiv). After stirring at rt for 20 hours the solution was diluted with EtOAc, washed with $NaHCO_{3(sat.)}$, the aqueous layer was further extracted with EtOAc (3x), the combined organics were washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated, and purified by ISCO SiO_2 chromatography to yield (+/-)-tert-butyl ((1R,5S,6S)-6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-en-1-yl)carbamate as a white foam in 84 % yield. LC/MS = 350.2 (M+H), R_t = 0.82 min.

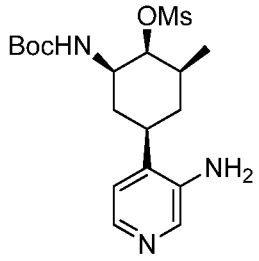
Synthesis of (+/-)-(1S,2R,6S)-2-((tert-butoxycarbonyl)amino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-en-1-yl methanesulfonate



To a solution of (+/-)-tert-butyl ((1R,5S,6S)-6-hydroxy-5-methyl-3-(3-nitropyridin-4-yl)cyclohex-2-en-1-yl)carbamate (1.0 equiv.) in pyridine (0.20 M) was added MsCl (5.0 equiv.). The capped solution was stirred for 5 minutes and then the homogeneous solution was left standing at rt for 5 hrs. The volatiles were removed in *vacuo* and the residue was partitioned between EtOAc and H_2O. The organic layer was

washed with 10% $CuSO_4$, H_2O, $Na_2CO_{3(sat.)}$, $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography to yield (+/-)-(1S,2R,6S)-2-((tert-butoxycarbonyl)amino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-en-1-yl methanesulfonate in 97% yield. LC/MS (*m/z*) = 428.1 (MH^+), R_t = 0.86 min.

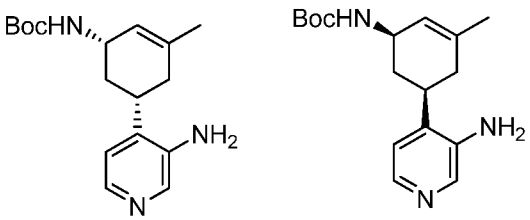
Synthesis of (+/-)-(1S,2R,4R,6S)-4-(3-aminopyridin-4-yl)-2-((tert-butoxycarbonyl)amino)-6-methylcyclohexyl methanesulfonate



+/-

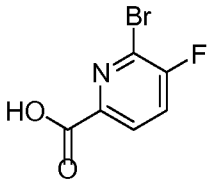
To a solution of (+/-)-(1S,2R,6S)-2-((tert-butoxycarbonyl)amino)-6-methyl-4-(3-nitropyridin-4-yl)cyclohex-3-en-1-yl methanesulfonate (1.0 equiv.) in isopropanol (0.20 M). To this solution was added Pd/C (0.2 equiv.) and after pulling vacuum and purging to H_2 3x the solution was left stirring under a balloon of H_2 for 16 hrs. The reaction was degassed, purged to Ar. filtered over celite, rinsed with CH_2Cl_2/i-PrOH, concentrated and purified by ISCO SiO_2 chromatography to yield (+/-)-(1S,2R,4R,6S)-4-(3-aminopyridin-4-yl)-2-((tert-butoxycarbonyl)amino)-6-methylcyclohexyl methanesulfonate in 72 % yield). LC/MS (*m/z*) = 400.2 (MH^+), R_t = 0.60 min.

Synthesis of tert-butyl ((1S,5S)-5-(3-aminopyridin-4-yl)-3-methylcyclohex-2-en-1-yl)carbamate and tert-butyl ((1R,5R)-5-(3-aminopyridin-4-yl)-3-methylcyclohex-2-en-1-yl)carbamate



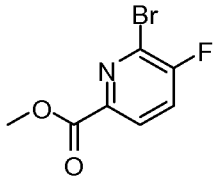
A solution of (+/-)-(1S,2R,4R,6S)-4-(3-aminopyridin-4-yl)-2-((tert-butoxycarbonyl)amino)-6-methylcyclohexyl methanesulfonate (1.0 equiv.) and DBU (3.0 equiv) in DMF (0.39 M) was heated at 100 °C for three hours. Upon cooling, the solution was diluted with EtOAc, washed with H_2O (4x), $Na_2CO_{3(sat.)}$, $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography to yield (+/-)-tert-butyl ((1R,5R)-5-(3-aminopyridin-4-yl)-3-methylcyclohex-2-en-1-yl)carbamate in 69 % yield. LC/MS (*m/z*) = 304.1 (MH^+), R_t = 0.63 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 8.06 (s, 1H), 8.02 (d, J=4.0, 1H), 6.97 (d, J=4.0, 1H), 5.37 (br. s, 1H), 4.35-4.52 (m, 2H), 3.62-3.68 (m, 2H), 2.70-2.90 (m, 1H), 2.16-2.32 (m, 2H), 2.02-2.12 (m, 1H), 1.45 (s, 3H), 1.45-1.48 (m, 1H). The racemic material was resolved using an AD-H chiral column (15% EtOH/n-heptanes, 20mL/min flow rate) to yield tert-butyl ((1S,5S)-5-(3-aminopyridin-4-yl)-3-methylcyclohex-2-en-1-yl)carbamate (peak#1, R_t =6.13 min on AD-H chiral analytical column, 15% EtOH/85% n-heptanes, 1 mL/min) and tert-butyl ((1R,5R)-5-(3-aminopyridin-4-yl)-3-methylcyclohex-2-en-1-yl)carbamate (peak#2, R_t =9.18 min on AD-H chiral analytical column, 15% EtOH/85% n-heptanes, 1 mL/min).

Synthesis of 6-bromo-5-fluoropicolinic acid



To 2-bromo-3-fluoro-6-methylpyridine (1.0 equiv.) in H_2O (30 mL) was added potassium permanganate (1.0 equiv.). The solution was heated at 100 °C for 5 hours at which time more potassium permanganate (1.0 equiv.) was added. After heating for an additional 48 hours the material was filtered through celite (4cm x 2 inches) and rinsed with H_2O (150 mL). The combined aqueous was acidified with 1N HCl to pH=4, extracted with ethyl acetate (200 mL), washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered and concentrated to yield 6-bromo-5-fluoropicolinic acid (17%) as a white solid. LCMS (m/z): 221.9 (MH+); LC Rt = 2.05 min.

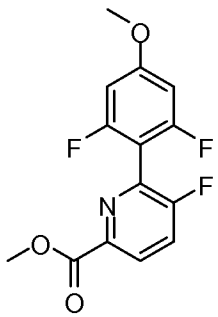
Synthesis of methyl 6-bromo-5-fluoropicolinate



To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in methanol (0.2 M) was added H_2SO_4 (4.2 equiv.) and the reaction was stirred at room temperature for two hours. Upon completion of the reaction as monitored by LC/MS, the reaction was diluted with ethyl acetate and quenched slowly with saturated aqueous $NaHCO_3$. The reaction was poured into a separatory funnel and extracted with ethyl acetate. The organic phase was dried with magnesium sulfate, filtered, and concentrated in vacuo to provide methyl 6-bromo-5-fluoropicolinate as a white solid (>99%). LC/MS = 233.9/235.9 (M+H), Rt = 0.69 min.

Method 1

Synthesis of methyl 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinate

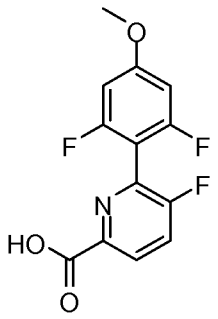


To a solution of methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) in THF and water (10:1, 0.1 M) was added 2,6-difluoro-4-methoxyphenylboronic acid (2.5 equiv.) and potassium fluoride (3.3 equiv.). The reaction was degassed with nitrogen, then $Pd_2(dba)_3$ (0.25 equiv.) and tri-tert-butylphosphine (0.5 equiv.) were added and the reaction was heated to 80 °C for one hour. LC/MS analysis indicated complete conversion of the starting material to product. The reaction was cooled to room temperature, then concentrated in vacuo and fused to silica gel. The crude product was purified by ISCO flash chromatography eluting with ethyl acetate and hexanes (0% to 30% ethyl acetate) to

provide methyl 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinate as a white solid in 85% yield. LC/MS = 298.0 (M+H), Rt = 0.89 min.

Method 2

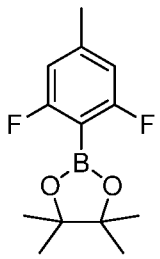
Synthesis of 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinic acid



To a solution of methyl 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinate (1.0 equiv.) in THF/MeOH (2:1, 0.09 M) was added LiOH (1.5 equiv.) and the reaction was stirred at room temperature for 1 hour. The solution was quenched with 1N HCl, extracted with ethyl acetate, washed with brine, dried with sodium sulfate, filtered and concentrated to give 6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinic acid in 84% yield. LC/MS = 284.1 (M+H), Rt = 0.76 min.

Method 3

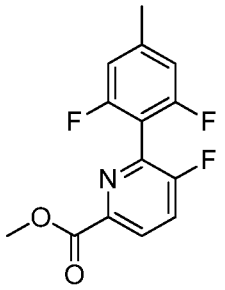
Synthesis of 2-(2,6-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaboroane



To a solution of 1,3-difluoro-5-methylbenzene (1.0eq) in dry THF (0.2M) under an atmosphere of N_2 at -78°C was added n-butyllithium (1eq, 1.6M in hexanes) slowly keeping the internal temperature below -65°C. The reaction was stirred for 2 hrs at -

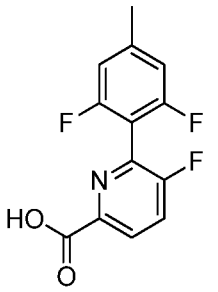
78°C, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.15eq). The reaction was allowed to warm to room temperature. Upon completion, the reaction was quenched with $NaHCO_{3\,(sat.)}$ and extracted with EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to yield 2-(2,6-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaboroane as a white solid in 92%. 1H NMR (400 MHz, <*cdcl3*>) δ ppm 6.67 (dd, *J*=9.39, 0.78 Hz, 2 H), 2.34 (s, 3 H), 1.38 (s, 12 H).

Synthesis of methyl 6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinate



Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 2-(2,6-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaboroane (1.75 equiv.) to give methyl 6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinate as a solid in 85% yield. LC/MS = 282.0 (M+H), Rt = 0.87 min.

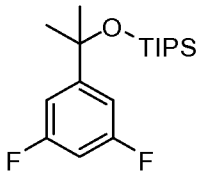
Synthesis of 6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinic acid



To a solution of methyl 6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinate (1.0eq) in THF (0.1M) was added LiOH (5.5eq, 2M) and allowed to stir at room temperature for 4hrs. The volatiles were removed *in vacuo*, and the residual aqueous was acidified with 2M HCl to pH 4. The precipitate was filtered and dried to yield 6-(2,6-

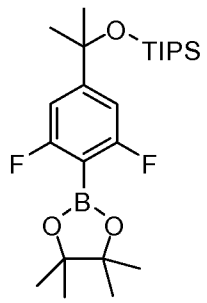
difluoro-4-methylphenyl)-5-fluoropicolinic acid as al light yellow solid in 73.5%. LCMS (m/z): 268.0 (MH^+), R_t = 0.76 min.

Synthesis of (2-(3,5-difluorophenyl)propan-2-yloxy)triisopropylsilane



To a solution of 1-(3,5-difluorophenyl)ethanone (1.0 equiv) in THF (0.2 M) at 0 °C was added methylmagnesium bromide (1.0 M in THF, 1.15 equiv). After stirring for 4 hours the reaction was quenched by addition of $NH_4Cl_{(sat.)}$, diluted with EtOAc, washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography to yield 2-(3,5-difluorophenyl)propan-2-ol. To a solution of 2-(3,5-difluorophenyl)propan-2-ol in CH_2Cl_2 (0.1 M) at 0 °C was added 2,6 lutidine (6 equiv.) and than triisopropylsilyl trifluoromethanesulfonate (3.0 equiv.). After stirring for 3 hours at 0 °C and six hours at rt the solution was partitioned between EtOAc and $NaHCO_{3(sat.)}$, separated, washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography to yield (2-(3,5-difluorophenyl)propan-2-yloxy)triisopropylsilane. (400 MHz, <*cdcl3*>) δ ppm 1.05 - 1.08 (m, 21 H) 1.57 (s, 6 H) 6.63 (s, 1 H) 7.00 (dd, *J*=9.39, 2.35 Hz, 2 H).

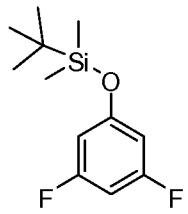
Synthesis of (2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yloxy)triisopropylsilane



To a solution of (2-(3,5-difluorophenyl)propan-2-yloxy)triisopropylsilane (1.0eq) in dry THF (0.2M) under an atmosphere of N_2 at -78°C was added n-butyllithium (1eq, 1.6M in hexanes) slowly keeping the internal temperature below -65°C. The reaction was stirred for 2 hrs at -78°C, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-

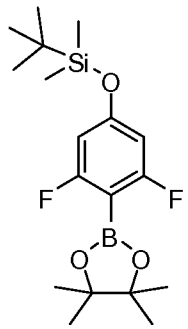
1,3,2-dioxaborolane (1.15eq). The reaction was allowed to warm to room temperature. Upon completion, the reaction was quenched with $NaHCO_{3\ (sat.)}$ and extracted with EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to yield (2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yloxy)triisopropylsilane in 99%. ^1H NMR (400 MHz, <*cdcl3*>) δ ppm 1.03-1.08 (m, 21 H) 1.24 (s, 12 H) 1.38 (s, 3 H) 1.57 (s, 3 H) 6.92 - 7.03 (m, 2 H).

Synthesis of tert-butyl(3,5-difluorophenoxy)dimethylsilane



To a solution of 3,5-difluorophenol (1.0 equiv.) and imidazole (2.2 equiv.) in DMF (0.8 M) at 0°C was added TBDMSCl (1.1 equiv.). The ice bath was removed and after stirring for 3 hours the solution was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, filtered, concentrated and purified by SiO_2 chromatography to yield tert-butyl(3,5-difluorophenoxy)dimethylsilane in 73% yield. ^1H NMR (400 MHz, <cdcl3>) δ ppm 0.23 (s, 6 H) 0.99 (s, 9 H) 6.33 - 6.40 (m, 2 H) 6.44 (tt 1 H).

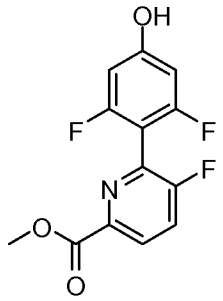
Synthesis of tert-butyl(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)dimethylsilane



To a solution of tert-butyl(3,5-difluorophenoxy)dimethylsilane (1.0eq) in dry THF (0.2M) under an atmosphere of N_2 at -78°C was added n-butyllithium (1eq, 1.6M in hexanes) slowly keeping the internal temperature below -65°C. The reaction was stirred for 1 hr at -78°C, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.1 eq). The reaction was allowed to warm to room temperature. Upon

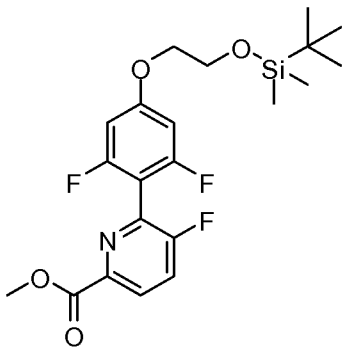
completion, the reaction was quenched with $NaHCO_{3\,(sat.)}$ and extracted with EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to yield tert-butyl(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)dimethylsilane in 91% yield. ^1H NMR (400 MHz, <cdcl3>) δ ppm 0.21 (s, 6 H) 0.97 (s, 9 H) 1.37 (s, 12 H) 6.33 (d, *J*=9.39 Hz, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinate



Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and tert-butyl(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)dimethylsilane (1.75 equiv.) to give methyl 6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinate in 65% yield. The reaction was heated for an additional 30 minutes at 100 °C in the microwave to drive to completion the deprotection of the TBDMS group. LC/MS = 283.9 (M+H), Rt = 0.69 min.

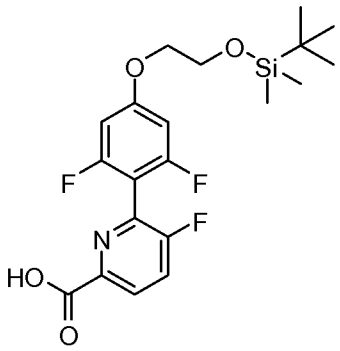
Synthesis of methyl 6-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinate



To a solution of methyl 6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinate (1.0 equiv.) and potassium carbonate (4.0 equiv.) in DMF (0.4 M) was added (2-bromoethoxy)(tert-butyl)dimethylsilane (2 equiv.). After stirring for 72 hours at rt the heterogeneous solution was diluted with water, extracted with EtOAc, dried over $MgSO_4$,

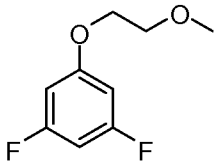
filtered, concentrated and purified by ISCO SiO_2 chromatography to yield methyl 6-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinate in 74% yield. LC/MS = 442.1 (M+H), R_t = 1.22 min.

Synthesis of 6-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinic acid



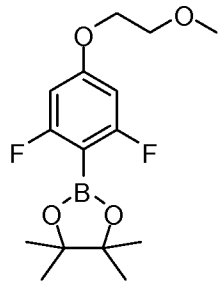
Method 2 was followed using methyl 6-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinate to give 6-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-2,6-difluorophenyl)-5-fluoropicolinic acid in 94% yield. LC/MS = 428.1 (M+H), R_t = 1.13 min.

Synthesis of 1,3-difluoro-5-(2-methoxyethoxy)benzene



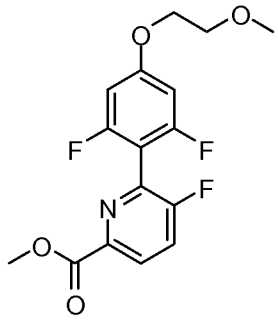
To a solution of 3,5-difluorophenol (1.0 equiv.), 2-methoxyethanol (3.0 equiv.) and triphenylphosphine (3.0 equiv) in THF (0.1 M) was added DIAD (3.0 equiv.). After stirring at rt for 18 hours, the volatiles were removed *in vacuo* and the residue was purified by SiO_2 chromatography to yield 1,3-difluoro-5-(2-methoxyethoxy)benzene in 95% yield. ^1H NMR (400 MHz, <cdcl3>) δ ppm 6.41-6.47 m (3 H), 4.08 (t, 2H), 3.74 (t, 2H), 3.45 (s, 3 H).

Synthesis of 2-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



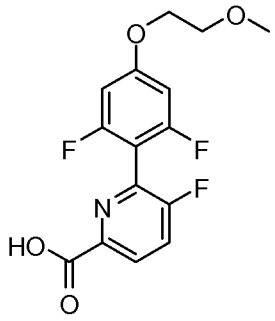
To a solution of 1,3-difluoro-5-(2-methoxyethoxy)benzene (1.0eq) in dry THF (0.2M) under an atmosphere of N_2 at -78°C was added n-butyllithium (1eq, 1.6M in hexanes) slowly keeping the internal temperature below -65°C. The reaction was stirred for 1 hr at -78°C, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.1 eq). The reaction was allowed to warm to room temperature. Upon completion, the reaction was quenched with $NaHCO_{3\,(sat.)}$ and extracted with EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to yield 2-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^1H NMR (400 MHz, <cdcl3>) δ ppm 6.42 (d, 2 H), 4.10 (m, 2H), 3.74 (m, 2H), 3.44 (s, 3 H), 1.37 (s, 12 H).

Synthesis of methyl 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinate



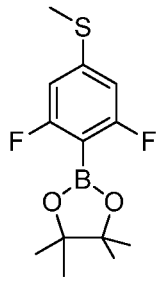
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 2-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.75 equiv.) at 80 °C for 1 hour to give methyl 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinate in 95% yield. LC/MS = 341.9 (M+H), R_t = 0.89 min.

Synthesis of 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinic acid



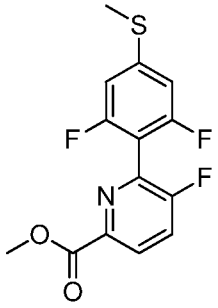
Method 2 was followed using methyl 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinic acid in 98% yield. LC/MS = 327.9 (M+H), R_t = 0.71 min.

Synthesis of 2-(2,6-difluoro-4-(methylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



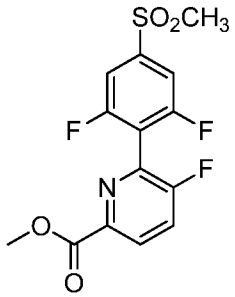
To a solution of (3,5-difluorophenyl)(methyl)sulfane (1.0eq) in dry THF (0.2M) under an atmosphere of N_2 at -78°C was added n-butyllithium (1eq, 1.6M in hexanes) slowly keeping the internal temperature below -65°C. The reaction was stirred for 2 hrs at -78°C, followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.15eq). The reaction was allowed to warm to room temperature. Upon completion, the reaction was quenched with $NaHCO_{3\,(sat.)}$ and extracted with EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to yield a 2-(2,6-difluoro-4-(methylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 91%. 1H NMR (400 MHz, <*cdcl3*>) δ ppm 6.71 (dd, 2 H), 2.48 (s, 3 H), 1.37 (s, 12 H).

Synthesis of methyl 6-(2,6-difluoro-4-(methylthio)phenyl)-5-fluoropicolinate



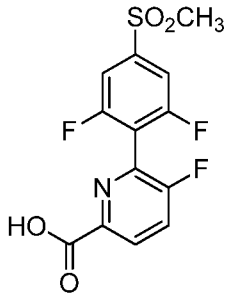
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 2-(2,6-difluoro-4-(methylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.75 equiv.) to give methyl 6-(2,6-difluoro-4-(methylthio)phenyl)-5-fluoropicolinate in 73% yield. LC/MS = 313.9 (M+H), Rt = 0.90 min.

Synthesis of methyl 6-(2,6-difluoro-4-(methylsulfonyl)phenyl)-5-fluoropicolinate



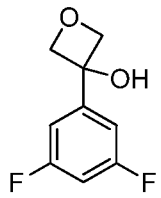
To a solution of methyl 6-(2,6-difluoro-4-(methylthio)phenyl)-5-fluoropicolinate (1.0 equiv) in CH_2Cl_2 (0.2 M) at 0 °C was added MCPBA (3.2 equiv.). After stirring for 40 minutes, the reaction was quenched with $Na_2S_2O_{3(aq.)}$, diluted with EtOAc, washed with $NaHCO_{3(sat.)}$, brine, dried over $MgSO_4$, filtered, concentrate, purified by SiO_2 chromatography to yield methyl 6-(2,6-difluoro-4-(methylsulfonyl)phenyl)-5-fluoropicolinate in 56 % yield. LC/MS = 345.9 (M+H), Rt = 0.69 min.

Synthesis of 6-(2,6-difluoro-4-(methylsulfonyl)phenyl)-5-fluoropicolinic acid



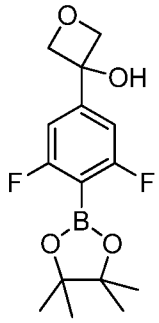
To a solution of methyl 6-(2,6-difluoro-4-(methylsulfonyl)phenyl)-5-fluoropicolinate (1.0eq) in THF (0.1M) was added LiOH (5.5eq, 2M) and allowed to stir at 37 °C for 2 hrs. The volatiles were removed *in vacuo*, and the residual aqueous was acidified with 2M HCl to pH 4. The precipitate was filtered and dried to yield 6-(2,6-difluoro-4-(methylsulfonyl)phenyl)-5-fluoropicolinic acid as a solid in 91% yield. LCMS (m/*z*): 331.8 (MH^+), R_t = 0.59 min.

Synthesis of 3-(3,5-difluorophenyl)oxetan-3-ol



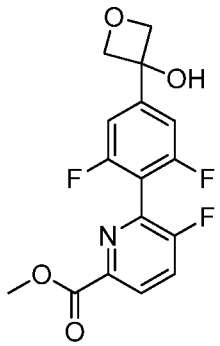
To a solution of 1-bromo-3,5-difluorobenzene in THF (0.27 M) under Ar was added Mg turnings (1.6 M). A reflux condenser was attached and the solution was submerged in a 90 °C oil bath and refluxed for two hours. The oxetan-3-one (1.0 equiv.) was added in THF via syringe. The solution was left stirring at rt under Ar overnight. The reaction solution was quenched by addition of $NH_4Cl_{(sat)}$ and the solution was extracted with EtOAc, washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography (0-100% EtOAc/n-heptanes gradient) to yield 3-(3,5-difluorophenyl)oxetan-3-ol in 56% yield. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.82 (d, J=7.63 Hz, 2 H), 4.91 (d, J=7.63 Hz, 2 H), 7.16 - 7.23 (m, 2 H).

Synthesis of 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-ol



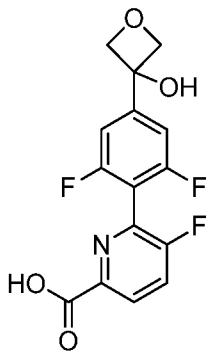
Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.5 equiv.), butyllithium (2.4 equiv.) and 3-(3,5-difluorophenyl)oxetan-3-ol (1.0 equiv.) to give 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-ol in 79% yield. 1H NMR (400 MHz, <cdcl3>) δ ppm1.34 - 1.42 (m, 12 H), 4.79 (d, *J*=7.63 Hz, 2 H), 4.90 (d, *J*=7.34 Hz, 2 H), 7.17 (d, *J*=8.22 Hz, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinate



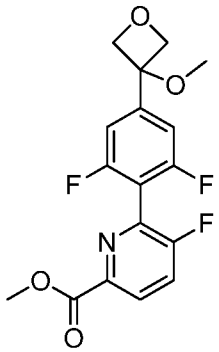
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 3-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-ol (1.4 equiv.) at 100 °C for 20 min in microwave to give methyl 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinate in 43% yield. LC/MS = 340.1 (MH^+), R_t = 0.69 min.

Synthesis of 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid



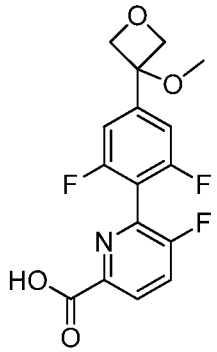
Method 2 was followed using methyl 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid in 99% yield. LC/MS = 325.9 (MH^+), R_t = 0.60 min.

Synthesis of methyl 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinate



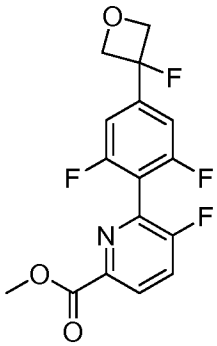
To a solution of methyl 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinate (1.0 equiv.) in DMF (0.34 M) at 0 °C was added NaH dispersion (1.4 equiv.). The solution was stirred in the ice bath for 1 hour, at which time MeI (1.5 equiv) was added. The solution was left stirring under Ar as the bath was allowed to warm up to rt and stirred at rt overnight.The solution was diluted with H_2O, and extracted with EtOAc. The organic was washed with H_2O, $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography (0-100 % EtOAc/n-heptanes) to yield methyl 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinate in 46% yield. LC/MS = 354.0 (MH^+), Rt = 0.82 min.

Synthesis of 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid



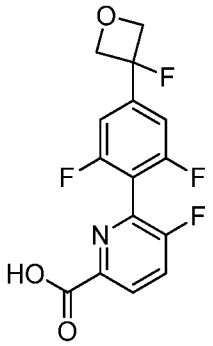
Method 2 was followed using methyl 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinic acid in 86% yield. LC/MS = 339.9 (MH^+), Rt = 0.71 min.

Synthesis of methyl 6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinate



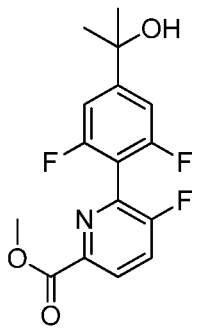
To a solution of methyl 6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinate (1.0 equiv.) in CH_2Cl_2 (0.04 M) at -78 °C under Ar was added methylDAST (1.7 equiv.). After addition, the solution was stirred under Ar at -78 °C for 10 minutes and then the bath was removed. The reaction was allowed to warm up to rt and quenched by addition of $NaHCO_3$(sat.). The solution was diluted with EtOAc, washed with $NaHCO_3$(sat.), NaCl(sat.), dried over $MgSO_4$, filtered, concentrated, purified by ISCO SiO_2 chromatography (24 gram column, 0-100 EtOAc/n-heptanes) to yield methyl 6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinate in 56% yield. LC/MS = 342.0 (MH+), R_t = 0.85 min.

Synthesis of 6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinic acid



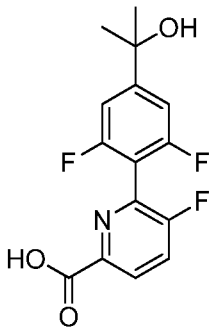
Method 2 was followed using methyl 6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinic acid in 99% yield. LC/MS = 327.9 (MH^+), R_t = 0.74 min.

Synthesis of methyl 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinate



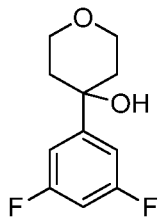
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and (2-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yloxy)triisopropylsilane (1.6 equiv.) at 100 °C for 30 min in the microwave to give methyl 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinate in 90% yield. LC/MS = 325.9 (MH^+), R_t = 0.81 min. 1H NMR (400 MHz, <cdcl3>) δ ppm 1.59 (s, 6 H), 4.00 (s, 3 H), 7.15 (d, J=9.00 Hz, 2 H), 7.62 - 7.68 (m, 1 H), 8.23 - 8.29 (m, 1 H).

Synthesis of 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinic acid



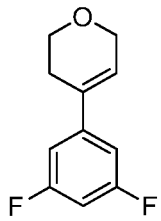
Method 2 was followed using methyl 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinic acid in 94% yield. LC/MS = 312.0 (MH^+), R_t = 0.69 min.

Synthesis of 4-(3,5-difluorophenyl)tetrahydro-2H-pyran-4-ol



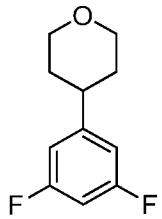
To a solution of 1-bromo-3,5-difluorobenzene (1.6 equiv.) in THF (0.26 M) under Ar was added Mg turnings (1.6 equiv.). A reflux condenser was attached and the solution was submerged in a 90 °C oil bath and refluxed for two hours. The dihydro-2H-pyran-4(3H)-one (1.0 equiv.) was added in THF via syringe. The solution was left stirring at rt under Ar for 5 hrs. The reaction solution was quenched by addition of $NH_4Cl_{(sat)}$ and the solution was extracted with EtOAc, washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography (0-100% EtOAc/n-heptanes gradient) to yield 4-(3,5-difluorophenyl)tetrahydro-2H-pyran-4-ol in 71% yield. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.59 - 1.68 (m, 3 H), 2.07 - 2.19 (m, 2 H), 3.87 - 3.93 (m, 4 H), 6.72 (tt, J=8.75, 2.20 Hz, 1 H), 6.97 - 7.06 (m, 2 H).

Synthesis of 4-(3,5-difluorophenyl)-3,6-dihydro-2H-pyran



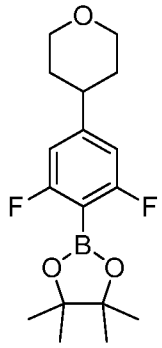
4-(3,5-difluorophenyl)tetrahydro-2H-pyran-4-ol (1.0 equiv.) was dissolved in DCM (0.2 M) and cooled to 0 °C. TEA (2.8 equiv.) was added to the solution, followed by MsCl (1.3 equiv.). The reaction was stirred at rt for 2hrs. The solution was cooled to 0°C and DBU (3.0 equiv.) was added. The reaction was stirred at rt for 18hrs. The solution was concentrated and the residue was purified by SiO_2 chromatography (0-100% EtOAc in Heptanes) to afford 4-(3,5-difluorophenyl)-3,6-dihydro-2H-pyran in 38% yield. ^{1}H NMR (400 MHz, <cdcl3>) δ ppm 2.42 - 2.49 (m, 2 H), 3.93 (t, J=5.48 Hz, 2 H), 4.32 (q, J=2.74 Hz, 2 H), 6.16 - 6.22 (m, 1 H), 6.70 (tt, J=8.80, 2.35 Hz, 1 H), 6.85 - 6.94 (m, 2 H).

Synthesis of 4-(3,5-difluorophenyl)tetrahydro-2H-pyran



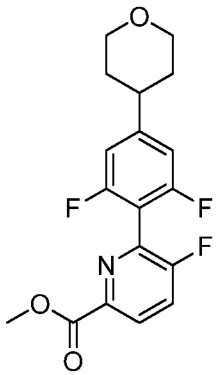
To a solution of 4-(3,5-difluorophenyl)-3,6-dihydro-2H-pyran (1.0 equiv.) in methanol (0.2 M) was added 10% Pd/C (0.05 equiv.). The reaction was placed under an atmosphere of hydrogen and stirred for 18 hours. Upon completion, the solution was filtered over a pad of Celite, the pad was washed with DCM, the filtrate was concentrated *in vacuo* to give 4-(3,5-difluorophenyl)tetrahydro-2H-pyran in 71% yield. ^{1}H NMR (400 MHz, <cdcl3>) δ ppm 1.76 (br. s., 4 H), 2.75 (br. s., 1 H), 3.50 (br. s., 2 H), 4.08 (d, *J*=9.78 Hz, 2 H), 6.56 - 6.94 (m, 3 H).

Synthesis of 2-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



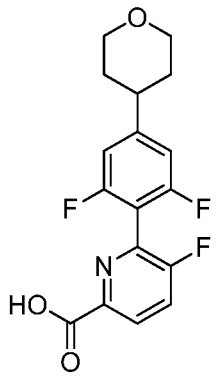
Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.2 equiv.), butyllithium (1.1 equiv.) and 4-(3,5-difluorophenyl)tetrahydro-2H-pyran (1.0 equiv.) to give 2-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 100% yield. ^{1}H NMR (400 MHz, <cdcl3>) δ ppm 1.16 - 1.19 (m, 12 H), 1.65 - 1.74 (m, 4 H), 2.60 - 2.75 (m, 1 H), 3.37 - 3.51 (m, 2 H), 4.01 (dt, *J*=11.54, 3.42 Hz, 2 H), 6.67 (d, *J*=8.22 Hz, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate



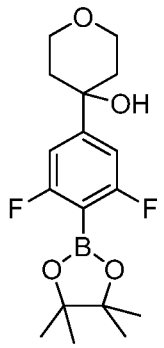
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 2-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.0 equiv.) at 100 °C for 20 min in microwave to give methyl 6-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate in 59% yield. LC/MS = 352.2 (MH^+), R_t = 0.92 min.

Synthesis of 6-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid



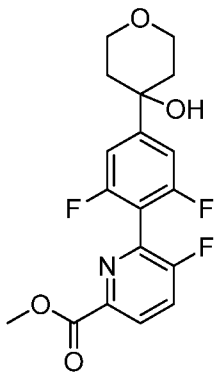
Method 2 was followed using methyl 6-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid in 71% yield. LC/MS = 338.1 (MH^+), R_t = 0.80 min.

Synthesis of 4-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydro-2H-pyran-4-ol



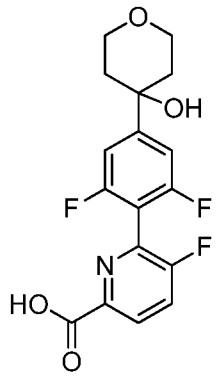
Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.5 equiv.), butyllithium (2.4 equiv.) and 4-(3,5-difluorophenyl)tetrahydro-2H-pyran-4-ol (1.0 equiv.) to give 4-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydro-2H-pyran-4-ol in 97% yield. ^1H NMR (400 MHz, <cdcl3>) δ ppm 1.32 - 1.42 (m, 12 H), 1.56 - 1.65 (m, 2 H), 2.11 (d, J=3.13 Hz, 2 H), 3.86 - 3.92 (m, 4 H), 6.99 (d, J=9.00 Hz, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate



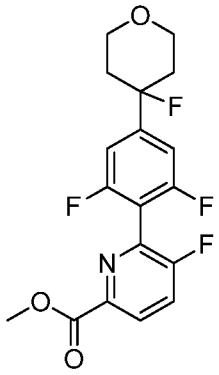
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 4-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydro-2H-pyran-4-ol (1.8 equiv.) at 100 °C for 20 min in microwave to give methyl 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate. LC/MS = 368.0 (MH^+), R_t = 0.75 min.

Synthesis of 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid



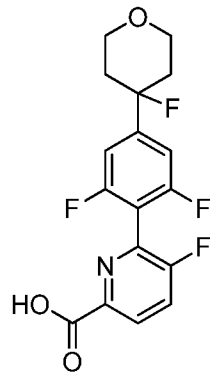
Method 2 was followed using methyl 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid in 69% yield. LC/MS = 354.0 (MH^+), R_t = 0.64 min.

Synthesis of methyl 6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate



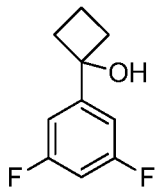
To a solution of methyl 6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate (1.0 equiv.) in CH_2Cl_2 (0.04 M) at -78 °C under Ar was added methylDAST (2.0 equiv.). After addition, the solution was stirred under Ar at -78 °C for 10 minutes and then the bath was removed. The reaction was allowed to warm up to rt and quenched by addition of $NaHCO_{3(sat.)}$. The solution was diluted with EtOAc, washed with $NaHCO_{3(sat.)}$, $NaCl_{(sat.)}$, dried over MgSO4, filtered, concentrated, purified by ISCO SiO_2 chromatography (0-100 EtOAc/n-heptanes) to yield methyl 6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate in 100% yield. LC/MS = 370.0 (MH^+), R_t = 0.94 min.

Synthesis of 6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid



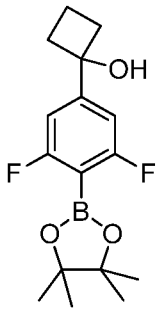
Method 2 was followed using methyl 6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinic acid in 95% yield. LC/MS = 355.9 (MH^+), R_t = 0.81 min.

Synthesis of 1-(3,5-difluorophenyl)cyclobutanol



To a solution of 1-bromo-3,5-difluorobenzene (1.0 equiv.) in THF (0.26 M) under Ar was added Mg turnings (1.6 equiv.). A reflux condenser was attached and the solution was submerged in a 90 °C oil bath and refluxed for two hours. The cyclobutanone (1.0 equiv.) was added in THF via syringe. The solution was left stirring at rt under Ar for 5 hrs. The reaction solution was quenched by addition of $NH_4Cl_{(sat)}$ and the solution was extracted with EtOAc, washed with $NaCl_{(sat.)}$, dried over $MgSO_4$, filtered, concentrated and purified by ISCO SiO_2 chromatography (0-100% EtOAc/n-heptanes gradient) to yield 1-(3,5-difluorophenyl)cyclobutanol in 54% yield. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.69 - 1.83 (m, 1 H), 2.03 - 2.13 (m, 1 H), 2.31 - 2.43 (m, 2 H), 2.45 - 2.56 (m, 2 H), 6.71 (tt, *J*=8.80, 2.35 Hz, 1 H), 6.98 - 7.07 (m, 2 H).

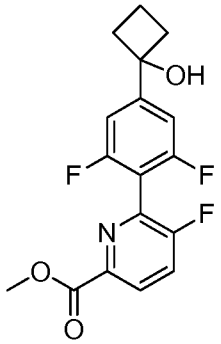
Synthesis of 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanol



Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.5 equiv.), butyllithium (2.4 equiv.) and 1-(3,5-

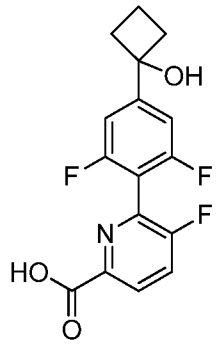
difluorophenyl)cyclobutanol (1.0 equiv.) to give 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanol in 100% yield. ^{1}H NMR (400 MHz, <cdcl3>) δ ppm 1.23 - 1.25 (m, 12 H), 1.69 - 1.82 (m, 1 H), 2.05 - 2.12 (m, 1 H), 2.37 (br. s., 2 H), 2.47 (br. s., 2 H), 7.00 (d, *J*=8.80 Hz, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinate



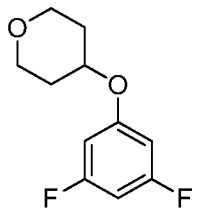
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 1-(3,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclobutanol (1.6 equiv.) at 100 °C for 30 min in microwave to give methyl 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinate in 71% yield. LC/MS = 338.0 (MH^+), R_t = 0.85 min.

Synthesis of 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinic acid



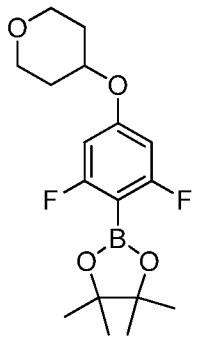
Method 2 was followed using methyl 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinic acid in 90% yield. LC/MS = 323.9 (MH+), R_t = 0.74 min.

Synthesis of 4-(3,5-difluorophenoxy)tetrahydro-2H-pyran



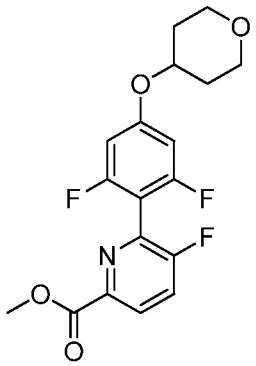
To a solution of 3,5-difluorophenol (1.0 equiv.), tetrahydro-2H-pyran-4-ol (1.2 equiv.), and triphenylphosphine (2.0 equiv.) in THF (0.33 M) at 0 °C was added DIAD (2.0 equiv.) dropwise. The reaction mixture was stirred at rt overnight. The mixture was concentrated and purified by flash chromatography over silica gel (heptanes:ethyl acetate gradient) to give 4-(3,5-difluorophenoxy)tetrahydro-2H-pyran in 90 % yield. 1H NMR (400 MHz, <cdcl3>) δ ppm 1.72 - 1.84 (m, 2 H), 1.96 - 2.09 (m, 2 H), 3.59 (ddd, *J*=11.64, 8.31, 3.52 Hz, 2 H), 3.90 - 4.04 (m, 2 H), 4.44 (tt, *J*=7.78, 3.77 Hz, 1 H), 6.32 - 6.53 (m, 3 H).

Synthesis of 2-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



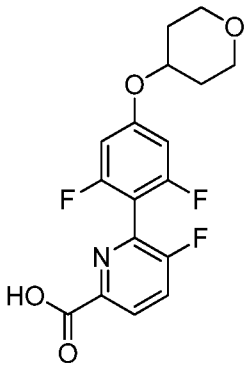
Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 equiv.), butyllithium (1.3 equiv.) and 4-(3,5-difluorophenoxy)tetrahydro-2H-pyran (1.0 equiv.) to give 2-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 33% yield. 1H NMR (400 MHz, <cdcl3>) δ ppm 1.21 - 1.34 (m, 12 H), 1.78 (dtd, J=12.72, 8.31, 8.31, 3.91 Hz, 2 H), 1.93 - 2.09 (m, 2 H), 3.59 (ddd, J=11.64, 8.31, 3.13 Hz, 2 H), 3.89 - 4.01 (m, 2 H), 4.48 (tt, J=7.78, 3.77 Hz, 1 H), 6.40 (d, J=9.39 Hz, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinate



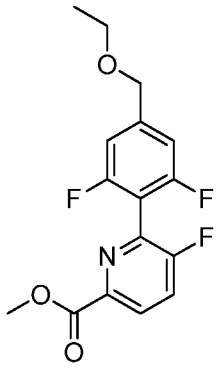
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.0 equiv.) and 2-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 equiv.) at 100 °C for 30 min in microwave to give methyl 6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinate in 77 % yield. LC/MS = 368.0 (MH+), Rt = 0.95 min.

Synthesis of 6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinic acid



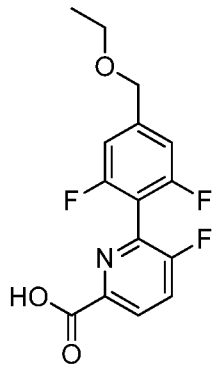
Method 2 was followed using methyl 6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinic acid in 100% yield. LC/MS = 353.9 (MH+), R_t = 0.82 min.

Synthesis of methyl 6-(4-(ethoxymethyl)-2,6-difluorophenyl)-5-fluoropicolinate



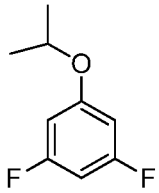
To a solution of methyl 6-(2,6-difluoro-4-(hydroxymethyl)phenyl)-5-fluoropicolinate (1.0 equiv.) in DMF (0.20 M) at 0 °C was added sodium hydride (1.2 equiv.) and the reaction was stirred at 0 °C for 2 min. Ethyl iodide (1.2 equiv.) was added and the reaction was allowed to warm to room temperature. After 1h, additional 1.0 equiv. of NaH was added and stirred for 15 mi. Reaction was quenched by the addition of sat. Ammonium chloride. The aqueous was acidified with conc HCl to pH3 and extracted with ethyl acetate three times. The organics were combined, dried with $MgSO_4$, filtered and concentrated. The crude mixture was used as is. LC/MS = 326.0 (MH^+), R_t = 0.94 min.

Synthesis of 6-(4-(ethoxymethyl)-2,6-difluorophenyl)-5-fluoropicolinic acid



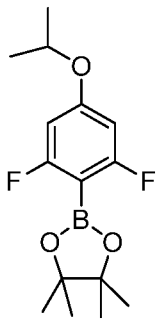
Method 2 was followed using methyl 6-(4-(ethoxymethyl)-2,6-difluorophenyl)-5-fluoropicolinate to give 6-(4-(ethoxymethyl)-2,6-difluorophenyl)-5-fluoropicolinic acid. LC/MS = 311.9 (MH^+), R_t = 0.82 min.

Synthesis of 1,3-difluoro-5-isopropoxybenzene



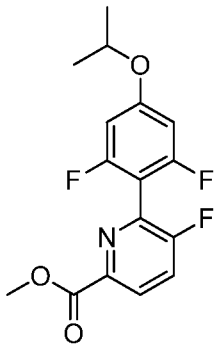
To a solution of 3,5-difluorophenol (1.0 equiv.) in DMF (0.26 M) was added potassium carbonate (2.2 equiv.) followed by 2-iodopropane (1.1 equiv.) and the reaction was stirred overnight at room temperature. The reaction was poured into a separatory funnel and diluted with a 3:1 (v/v) solution of EtOAc:heptanes. The organic phase was washed with water, then sat'd $NaHCO_3$. The remaining organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo to provide 1,3-difluoro-5-isopropoxybenzene in 88% yield. 1H NMR (400 MHz, <cdcl3>) δ ppm 1.33 (d, J=6.26 Hz, 6 H), 4.48 (dt, J=11.93, 6.16 Hz, 1 H), 6.31 - 6.47 (m, 3 H).

Synthesis of 2-(2,6-difluoro-4-isopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



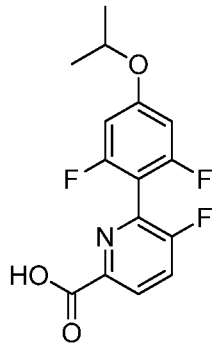
Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.2 equiv.), butyllithium (1.2 equiv.) and 1,3-difluoro-5-isopropoxybenzene (1.0 equiv.) to give 2-(2,6-difluoro-4-isopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 99% yield. 1H NMR (400 MHz, <cdcl3>) δ ppm 1.24 (s, 12 H), 1.31 - 1.33 (m, 6 H), 4.43 - 4.56 (m, 1 H), 6.31 - 6.44 (m, 2 H).

Synthesis of methyl 6-(2,6-difluoro-4-isopropoxyphenyl)-5-fluoropicolinate



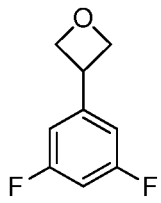
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (0.8 equiv.) and 2-(2,6-difluoro-4-isopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv.) at 70 °C for 1 hour to give methyl 6-(2,6-difluoro-4-isopropoxyphenyl)-5-fluoropicolinate. LC/MS = 325.9 (MH+), Rt = 1.04 min.

Synthesis of 6-(2,6-difluoro-4-isopropoxyphenyl)-5-fluoropicolinic acid



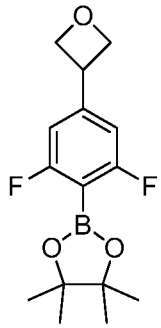
Method 2 was followed using methyl 6-(2,6-difluoro-4-isopropoxyphenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-isopropoxyphenyl)-5-fluoropicolinic acid in 35% yield. LC/MS = 311.9 (MH+), Rt = 0.92 min.

Synthesis of 3-(3,5-difluorophenyl)oxetane



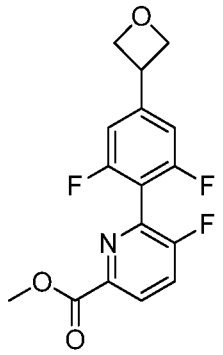
3,5-difluorophenylboronic acid (2.0 equiv.), (1R,2R)-2-aminocyclohexanol (0.06 equiv.), NaHMDS (2.0 equiv.), and nickel(II) iodide (0.06 equiv.) were dissolved in 2-propanol (0.35 M). The mixture was degassed with N_2, stirred at rt for 10min and then a solution of 3-iodooxetane (1.0 equiv.) in 2-Propanol (0.70 M) was added. The mixture was sealed and heated at 80°C in the microwave for 20 minutes. The mixture was filtered through celite, eluting with EtOH and concentrated. The crude residue was purified by ISCO SiO_2 chromatography eluting with 0-100% EtOAc in Heptanes to afford 3-(3,5-difluorophenyl)oxetane in 63% yield. 1H NMR (400 MHz, <cdcl3>) δ 6.88 - 6.96 (m, 2H), 6.72 (tt, J = 2.20, 8.95 Hz, 1H), 5.08 (dd, J = 6.26, 8.22 Hz, 2H), 4.71 (t, J = 6.26 Hz, 2H), 4.14 - 4.24 (m, 1H).

Synthesis of 2-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



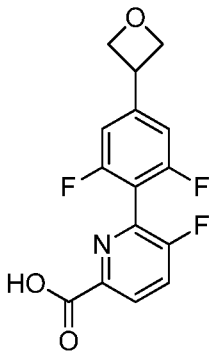
Method 3 was followed using 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 equiv.), butyllithium (1.1 equiv.) and 3-(3,5-difluorophenyl)oxetane (1.0 equiv.) to give 2-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 8% yield. 1H NMR (400 MHz, <cdcl3>) δ ppm 6.90 (d, *J* = 8.22 Hz, 2H), 5.07 (dd, *J* = 6.06, 8.41 Hz, 2H), 4.70 (t, *J* = 6.26 Hz, 2H), 4.13 - 4.23 (m, 1H), 1.39 (s, 12H).

Synthesis of methyl 6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinate



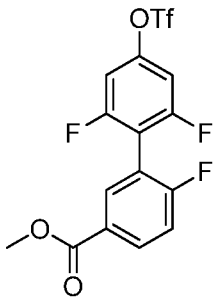
Method 1 was followed using methyl 6-bromo-5-fluoropicolinate (1.2 equiv.) and 2-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv.) at 80 °C for 15 min in microwave to give methyl 6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinate in 47% yield. LC/MS = 324.0 (MH+), Rt = 0.75 min.

Synthesis of 6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinic acid



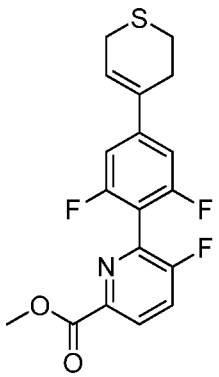
Method 2 was followed using methyl 6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinate to give 6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinic acid in 71% yield. LC/MS = 309.9 (MH+), Rt = 0.69 min.

Synthesis of methyl 2',6,6'-trifluoro-4'-(trifluoromethylsulfonyloxy)biphenyl-3-carboxylate



To a solution of methyl 2',6,6'-trifluoro-4'-hydroxybiphenyl-3-carboxylate (1.0 equiv.) in DCM (0.35 M) at 0 °C was added pyridine (1.5 equiv.) and allowed to stir for 5 mins, followed by the addition of TriflicAnhydride (1.1 equiv.). The reaction was allowed to stir warming to RT. The reaction was quenched with $NaHCO_{3(sat)}$, extracted in DCM and the organics were washed wtih water and brine. The organics were dried over Na_2SO_4, filtered, and concentrated to yield methyl 2',6,6'-trifluoro-4'-(trifluoromethylsulfonyloxy)biphenyl-3-carboxylate in 81% yield.

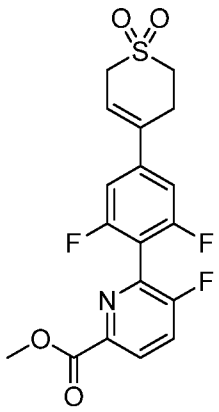
Synthesis of methyl 6-(4-(3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinate



To a degassed solution of methyl 6-(2,6-difluoro-4-(trifluoromethylsulfonyloxy)phenyl)-5-fluoropicolinate (1.0 equiv.) and 3,6-dihydro-2H-thiopyran-4-ylboronic acid (1.5 equiv.) in DME/2M Na_2CO_3 (3/1, 0.10 M) was added $PdCl_2(dppf).CH_2Cl_2$ adduct (0.10 equiv.). The reaction was heated to 90 °C in an oil bath for 15 min. The reaction mixture was partitioned with water and EtOAc; the organics were dried over $MgSO_4$, filtered, and concentrated. The crude was purified via ISCO. Pure fractions were combined and concentrated to yield methyl 6-(4-(3,6-dihydro-2H-

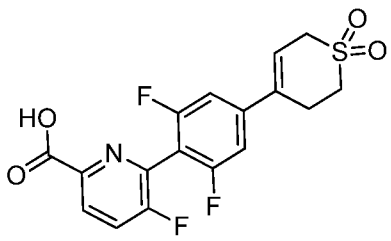
thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinate in 60% yield. LC/MS = 366.1 (M+H), Rt = 1.00 min.

Synthesis of methyl 6-(4-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinate



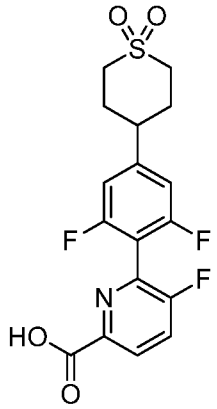
To a solution of methyl 6-(4-(3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinate (1.0 equiv.) in DCM (0.10 M) at rt was added oxone (6.0 equiv.) in one portion. The resulting mixture was stirred at RT overnight, and then refluxed at 40 °C for 4 hrs. 10.0 equiv. of oxone were added and the reaction was allowed to stir at 40°C over the weekend. The reaction mixture was then diluted with DCM and washed with water the aqueous layer was then separated and extracted with DCM. The combined organic were then dried over $MgSO_4$ and concentrated in vacuo to yield methyl 6-(4-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinate in 100% yield. LC/MS = 398.0 (M+H), Rt = 0.76 min.

Synthesis of 6-(4-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinic acid



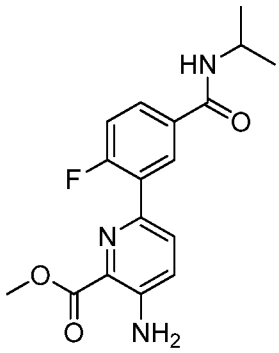
Method 2 was followed using methyl 6-(4-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinate to give 6-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinic acid in 74% yield. LC/MS = 384.0 (M+H), Rt = 0.64 min.

Synthesis of 6-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinic acid



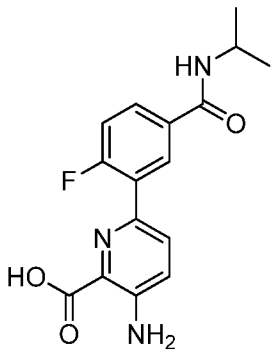
To a degassed solution of 6-(4-(1,1-dioxido-3,6-dihydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinic acid (1.0 equiv.) in EtOH (0.10 M) was added Pd/C (0.1 equiv.). The mixture was stirred at rt under H_2 for 16 hrs. Add Pd/C (0.1 equiv.) and the reaction was stirred for additional 16 hrs. The reaction was taken up and filtered through a syringe filter. The combined organics were concentrated to yield 6-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2,6-difluorophenyl)-5-fluoropicolinic acid in 100% yield. LC/MS = 386.0 (M+H), Rt = 0.64 min.

Synthesis of methyl 3-amino-6-(2-fluoro-5-isopropylcabamoyl)phenyl)-picolinate



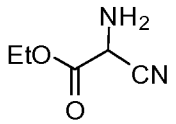
A solution of methyl 3-amino-6-bromopicolinate (1.0 equiv.), N-isopropyl 3-borono-4-fluorobenzamide (1.1 equiv.), and Pd(dppf)Cl_2-DCM (0.15 equiv.) in DME/2M Na_2CO_3 (3:1), at a concentration of 0.5 M, was stirred at 120°C for 1.5 hours. The reaction was filtered and washed with EtOAc. The organic was partitioned with H_2O (25mL), washed with $NaCl_{(sat.)}$ (25mL), dried over $MgSO_4$, and the volatiles were removed *in vacuo*. The residue was diluted in EtOAc and passed through a silica gel plug and the volatiles were removed *in vacuo* yielding methyl 3-amino-6-(2-fluoro-5-isopropylcabamoyl)-phenyl)picolinate (60%). LCMS (*m/z*): 332.2 (MH^+); LC R_t = 2.9 min.

Synthesis of 3-amino-6-(2-fluoro-5-isopropylcabamoyl)phenyl)picolinic acid



To a solution of methyl 3-amino-6-(2-fluoro-5-isopropylcabamoyl)phenyl)picolinate (1.0 equiv) in THF (0.5M), was added 1M LiOH (4.0 equiv). After stirring for 4 hours at 60°C, 1 N HCl (4.0 equiv.) was added and the THF was removed *in vacuo*. The resulting solid was filtered and rinsed with cold H_2O (3 x 20mL) to yield 3-amino-6-(2-fluoro-5-isopropylcabamoyl)phenyl)picolinic acid (98%). LCMS (*m/z*): 318.1 (MH^+); LC R_t = 2.4 min.

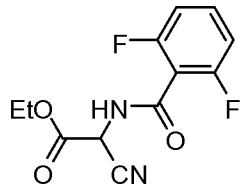
Synthesis of ethyl 2-amino-2-cyanoacetate



To a solution of ethyl 2-cyano-2-(hydroxyimino)acetate(1eq) in ethanol (1.4 M) was added PtO_2 (0.05 eq) and the solution was put under an H_2 atmosphere (4 bar) in a steel bomb and was stirred overnight. The reaction was filtered through a pad of celite, rinsing

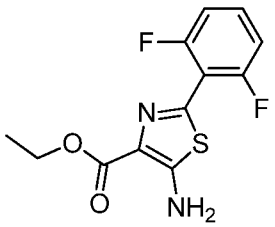
with CH_2Cl_2 and upon removal of voltiles *in vacuo* ethyl 2-amino-2-cyanoacetate was obtained in 89% yield. LC/MS (*m/z*): 129.0 (MH^+), R_t: 0.25 min.

Synthesis of ethyl 2-cyano-2-(2,6-difluorobenzamido)acetate



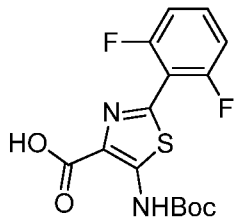
To a solution of ethyl 2-amino-2-cyanoacetate (1 eq) in 6 mL of dichloromethane was added pyridine (1.5 eq) and 2,6-difluorobenzoyl chloride (1 eq) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The mixture was diluted with ethyl acetate, washed with brine, then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1:1) to give the titled compound (84%). LC/MS (*m/z*): 269.1 (MH^+), R_t: 0.69 min.

Synthesis of ethyl 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylate



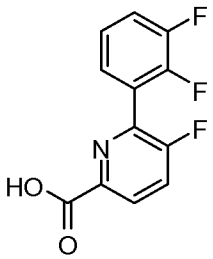
To a solution of the ethyl 2-cyano-2-(2,6-difluorobenzamido)acetate (1 eq) in pyridine (0.1 M) was added Lawesson reagent (1.5 eq.). The mixture was stirred at reflux under Ar for 18 hours. Solvents were removed under reduced pressure. The crude residue was purified by flash chromatography (EtOAc : hexanes= 1 : 1) to give the ethyl 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylate in 25% yield. LC/MS (*m/z*): 284.9 (MH^+), R_t: 0.76 min.

Synthesis of 5-((tert-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid



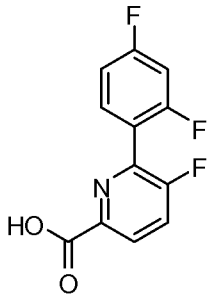
To a solution of the ethyl 5-amino-2-(2,6-difluorophenyl)thiazole-4-carboxylate (1 eq) in CH_2Cl_2 (0.1 M) was added Boc_2O (1.2 eq.) and DMAP (0.05 eq.). Upon stirring for 1 hour the volatiles were removed *in vacuo*, THF (0.1 M) and 2.0 M $LiOH_{(aq.)}$ (5 equiv) were added and the solution was stirred at 55 °C for 2 days. The volatiles were removed *in vacuo* and the remaining aqueous solution was adjusted to pH 5 by addition of 2M HCl. The resulting solid was filtered, rinsed with H_2O and pumped on to yield 5-((tert-butoxycarbonyl)amino)-2-(2,6-difluorophenyl)thiazole-4-carboxylic acid
25% yield. LC/MS (*m/z*): 357.1 (MH^+), R_t: 0.97 min.

Synthesis of 6-(2,3-difluorophenyl)-5-fluoropicolinic acid



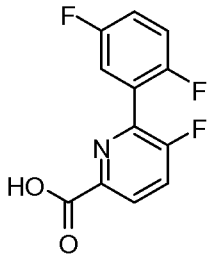
To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in DME and 2M Na_2CO_3 (3:1, 0.25 M) was added 2,3-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) in a microwave vial. The vial was heated in the microwave at 120 °C for 30 minutes. The mixture was diluted with ethyl acetate and 1N NaOH was added. The organic phase was separated and extracted three more times with 1N NaOH and once with 6N NaOH. The combined aqueous phases were filtered and acidified to pH 1 by the addition of concentrated HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 6-(2,3-difluorophenyl)-5-fluoropicolinic acid in 78%. LC/MS = 254.1 (M+H), Rt = 0.75 min.

Synthesis of 6-(2,4-difluorophenyl)-5-fluoropicolinic acid



To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in DME and 2M Na_2CO_3 (3:1, 0.25 M) was added 2,4-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) in a microwave vial. The vial was heated in the microwave at 120 °C for 30 minutes. The mixture was diluted with ethyl acetate and 1N NaOH was added. The organic phase was separated and extracted three more times with 1N NaOH and once with 6N NaOH. The combined aqueous phases were filtered and acidified to pH 1 by the addition of concentrated HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 6-(2,4-difluorophenyl)-5-fluoropicolinic acid in 79% yield. LC/MS = 254.1 (M+H), Rt = 0.75 min.

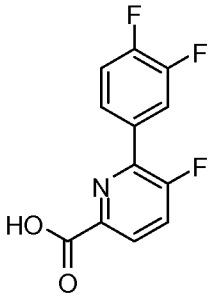
Synthesis of 6-(2,5-difluorophenyl)-5-fluoropicolinic acid



To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in DME and 2M Na_2CO_3 (3:1, 0.25 M) was added 2,5-difluorophenylboronic acid acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) in a microwave vial. The vial was heated in the microwave at 120 °C for 30 minutes. The mixture was diluted with ethyl acetate and 1N NaOH was added. The organic phase was separated and extracted three more times with 1N NaOH and once with 6N NaOH. The combined aqueous phases were filtered and acidified to pH 1 by the addition of concentrated HCl and extracted with ethyl acetate.

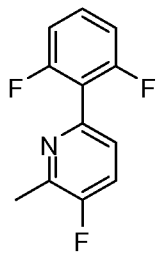
The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 6-(2,5-difluorophenyl)-5-fluoropicolinic acid in 80% yield. LC/MS = 254.1 (M+H), Rt = 0.74 min.

Synthesis of 6-(3,4-difluorophenyl)-5-fluoropicolinic acid



To a solution of 6-bromo-5-fluoropicolinic acid (1.0 equiv.) in DME and 2M Na_2CO_3 (3:1, 0.25 M) was added 3,4-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) in a microwave vial. The vial was heated in the microwave at 120 °C for 30 minutes. The mixture was diluted with ethyl acetate and 1N NaOH was added. The organic phase was separated and extracted three more times with 1N NaOH and once with 6N NaOH. The combined aqueous phases were filtered and acidified to pH 1 by the addition of concentrated HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 6-(3,4-difluorophenyl)-5-fluoropicolinic acid in 70% yield. LC/MS = 254.1 (M+H), Rt = 0.81 min.

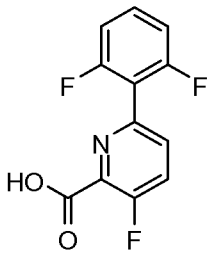
Synthesis of 6-(2,6-difluorophenyl)-3-fluoro-2-methylpyridine



To a solution of 6-bromo-3-fluoro-2-methylpyridine (1.0 equiv.) in ethanol and toluene (1:1, 0.2 M) was added 2,6-difluorophenylboronic acid, DIEA (5 equiv.) and Pd(PPh_3)$_4$ (0.2 equiv.). The reaction was heated in the microwave at 120 °C for 30 min.

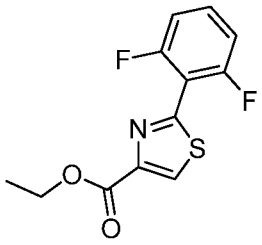
The solution was filtered and rinsed with ethyl acetate. The volatiles were removed *in vacuo and* the crude was purified via silica gel column chromatography eluting with ethyl acetate and hexanes (2.5-20% ethyl acetate). Upon concentration of the pure fractions, 6-(2,6-difluorophenyl)-3-fluoro-2-methylpyridine was isolated in 88% yield. LC/MS = 224.1 (M+H), Rt = 0.87 min.

Synthesis of 6-(2,6-difluorophenyl)-3-fluoropicolinic acid



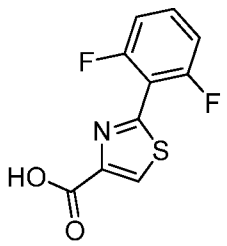
To a solution of 6-(2,6-difluorophenyl)-3-fluoro-2- (1.0 equiv.) in water (0.05 M) was added $KMnO_4$ (2.0 equiv.) and the reaction was heated to reflux overnight. Another 2.0 equiv. of $KMnO_4$ were added and stirred at reflux for another 8 hours. The solution was cooled to room temperature, filtered through Celite and washed with water. The filtrate was acidified with 6N HCl to pH =3, the white precipitate was filtered. The filtrate was further acidified to pH = 1 and filtered again. The filtrate was extracted with ethyl acetate until no more product in the aqueous layer. The organic phase was washed with brine and dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in ethyl acetate, washed with 1N NaOH, the aqueous layer was acidified to pH=1 and the white crystals were filtered. The combined products yielded 6-(2,6-difluorophenyl)-3-fluoropicolinic acid in 30% yield as a white solid. LC/MS = 254.1 (M+H), Rt = 0.70 min.

Synthesis of ethyl 2-(2,6-difluorophenyl)thiazole-4-carboxylate



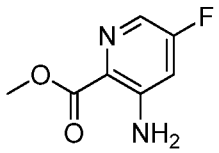
A solution of 2,6-difluorobenzothioamide (1.0 eq) and ethylbromopyruvate (1.0 eq.) in ethanol (1.0 M) was heated in the microwave at 130 °C for 30 minutes. Upon removal of volatiles in vacuo, ethyl acetate was added and the solution was washed with $Na_2CO_{3(sat.)}$, with $NaCl_{(sat.)}$, was dried over $MgSO_4$, filtered and concentrated yielding ethyl 2-(2,6-difluorophenyl)thiazole-4-carboxylate (84%). LCMS (*m/z*): 270.1 (MH^+); LC R_t = 3.79 min.

Synthesis of 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid



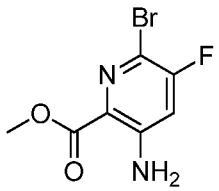
To a solution of ethyl 2-(2,6-difluorophenyl)thiazole-4-carboxylate (1.0 eq.) in 2:1 THF/MeOH (0.17 M) was added 1.0 M LiOH (2.0 eq.). After standing for 16 hours, 1.0 M HCl (2.0 eq.) was added and the THF/MeOH was removed in vacuo. The resulting solid was filtered, rinsed with H_2O and dried, yielding 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (88%) as a crusty solid. LCMS (*m/z*): 251.1 (MH^+); LC R_t = 2.68 min.

Synthesis of Methyl 3-amino-5-fluoropicolinate



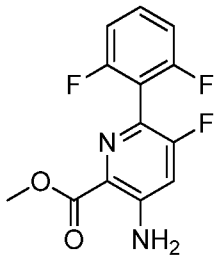
To a steel bomb reactor, 2-bromo-5-fluoropyridin-3-amine (1.0 equiv.), triethylamine (1.6 equiv.), Pd(BINAP)Cl_2 (0.0015 equiv.) and anhydrous methanol (0.4 M solution) were added. After degassed by nitrogen stream for 15 min, the steel bomb reactor was closed and filled with CO gas up to 60 psi. The reactor was then heated to 100 ^{o}C. After 3 h, more Pd catalyst (0.0015 equiv.) was added and the reaction mixture was re-heated to the same temperature for 3 h. After cooling down to room temperature, a brown precipitate was filtered off and the filtrate was extracted with EtOAc, which was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. After removing volatile materials, the crude yellow product was obtained and used for the next step without further purification (40%). LCMS (*m/z*): 271.2 (MH^+); LC R_t = 3.56 min.

Synthesis of Methyl 3-amino-6-bromo-5-fluoropicolinate



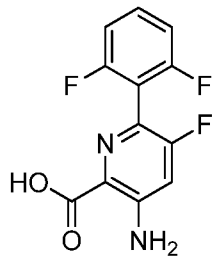
To a solution of methyl 3-amino-5-fluoropicolinate (1.0 equiv.) in acetonitrile (0.3 M solution) was added NBS (1.1 equiv.) for 2 minutes at room temperature. After quenched with water, the reaction mixture was extracted with EtOAc. The crude product was purified by silica column chromatography (20% to 50% EtOAc in hexanes) to give methyl 3-amino-6-bromo-5-fluoropicolinate (41%). LCMS (*m/z*): 249.1 (MH^+); LC R_t = 2.80 min.

Synthesis of methyl 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinate



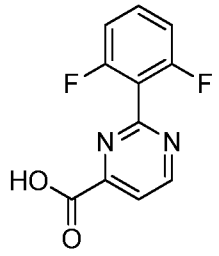
Method 1 was followed using methyl 3-amino-6-bromo-5-fluoropicolinate (1.0 equiv.) and 2,6-difluorophenylboronic acid (1.3 equiv.) and $Pd(dppf)Cl_2$-DCM (0.05 equiv.) to give 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinate in 94% yield. LCMS (*m/z*): 283.0 (MH^+), R_t = 0.76 min.

Synthesis of 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinic acid



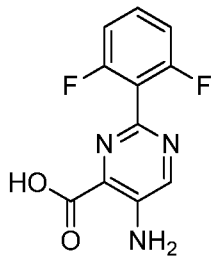
Method 2 was followed using 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinate (1.0 equiv.) and LiOH (1.0 equiv.) to give 3-amino-6-(2,6-difluorophenyl)-5-fluoropicolinic acid in 79% yield. LCMS (*m/z*): 269.0 (MH^+), R_t = 0.79 min.

Synthesis of 2-(2,6-difluorophenyl)pyrimidine-4-carboxylic acid



To a solution of 2-chloropyrimidine-4-carboxylic acid (1.0 equiv.) in DME and 2M Na_2CO_3 (3:1, 0.25 M) was added 2,6-difluorophenylboronic acid (1.3 equiv.) and Pd(dppf)Cl_2-DCM (0.05 equiv.) in a microwave vial. The vial was heated in the microwave at 120 °C for 30 minutes. The mixture was diluted with ethyl acetate and 1N NaOH was added. The organic phase was separated and extracted three more times with 1N NaOH and once with 6N NaOH. The combined aqueous phases were filtered and acidified to pH 1 by the addition of concentrated HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 2-(2,6-difluorophenyl)pyrimidine-4-carboxylic acid in 81%. LCMS (*m/z*): 237.0 (MH^+), R_t = 0.54 min.

Synthesis of 5-amino-2-(2,6-difluorophenyl)pyrimidine-4-carboxylic acid

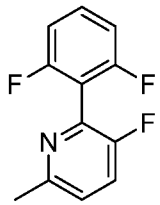


A 2.68 M NaOEt in EtOH solution (3 eq) was added to an ice-bath cooled mixture of 2, 6-difluorobenzimidamide hydrochloride (2 eq) in EtOH (0.1 M). The resulting mixture was allowed to warm to rt and stirred under N_2 for 30 min. To the reaction mixture was added drop wise a solution of mucobromic acid (1 eq) in EtOH and the reaction was heated in a 50 °C oil bath for 2.5 hr. After cooling to rt the reaction mixture was concentrated *in vacuo*. H_2O and 1.0 N NaOH were added and the aqueous mixture was washed with EtOAc. The aqueous phase was acidified to pH = 4 with 1.0 N HCl then extracted with EtOAc. Combined organic extracts were washed once with brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 5-bromo-2-(2, 6-difluorophenyl)pyrimidine-4-carboxylic acid. The crude product was used for the next step without further purification. LC/MS (*m/z*): 316.9 (MH^+). LC: R_t: 2.426 min.

$CuSO_4$ (0.1 eq) was added to a mixture of 5-bromo-2-(2,6-difluorophenyl)pyrimidine-4-carboxylic acid (1 eq) and 28% aqueous ammonium hydroxide solution in a microwave reaction vessel. The reaction mixture was heated in a

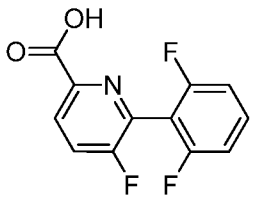
microwave reactor at 110 °C for 25 min. The reaction vessel was cooled in dry ice for 30 min then unsealed and concentrated *in vacuo*. To the resulting solids was added 1.0 N HCl and the mixture was extracted with EtOAc. Combined organic extracts were washed once with brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 5-amino-2-(2,6-difluorophenyl)pyrimidine-4-carboxylic acid. The crude product was used for the next step without further purification. LCMS (*m/z*): 252.0 (MH^+), R_t=2.0 min.

Synthesis of 2-(2,6-difluorophenyl)-3-fluoro-6-methylpyridine



To a solution of 2-bromo-3-fluoro-6-methylpyridine (1.0 equiv.) in THF and Water (10:1, 0.2 M) was added 2,6-difluorophenylboronic acid (2.0 equiv.) and potassium fluoride (3.3 equiv.). The reaction was degassed for 10 minutes, then $Pd_2(dba)_3$ (0.05 equiv.) was added, followed by tri-t-butylphosphine (0.1 equiv.). The reaction was stirred to 60 °C for 1 hour at which point, all starting material was consumed as indicated by LC/MS. The reaction was allowed to cool to room temperature, partitioned with ethyl acetate and water, the organic phase was dried with sodium sulfate, filtered, and concentrated. The crude material was diluted in EtOH to 0.1 M, and 0.5 equiv. of $NaBH_4$ was added to reduce the dba. The reaction was stirred for one hour at room temperature, then quenched with water and concentrated under vacuo to remove the ethanol. The product was extracted in ether, washed with brine, the organics were dried over sodium sulfate, filtered, and concentrated. The crude material was loaded on silica gel and purified via column chromatography (ISCO) eluting with hexanes and ethyl acetate (0%-10% ethyl acetate). The pure fractions were combined, and concentrated to yield 2-(2,6-difluorophenyl)-3-fluoro-6-methylpyridine as a light yellow oil in 86% yield. LC/MS = 224.0 (M+H), R_t = 0.84 min.

Synthesis of 6-(2,6-difluorophenyl)-5-fluoropicolinic acid



To a solution of 2-(2,6-difluorophenyl)-3-fluoro-6-methylpyridine (1.0 equiv.) in water (0.05 M) was added $KMnO_4$ (2.0 equiv.) and the reaction was heated to reflux overnight. Another 2.0 equiv. of $KMnO_4$ were added and stirred at reflux for another 8 hours. The solution was cooled to room temperature, filtered through Celite and washed with water. The filtrate was acidified with 6N HCl to pH =3, the white precipitate was filtered. The filtrate was further acidified to pH = 1 and filtered again. The filtrate was extracted with ethyl acetate until no more product was in the aqueous layer. The organic phase was washed with brine and dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in ethyl acetate, washed with 1N NaOH, the aqueous layer was acidified to pH=1 and the white crystals were filtered. The combined products yielded 6-(2,6-difluorophenyl)-5-fluoropicolinic acid in 32% yield as a white solid. LC/MS = 254.0 (M+H), R_t = 0.71 min.

Method 4

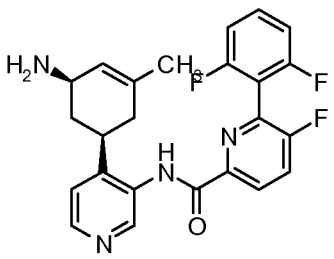
A homogeneous solution of 1 eq each of amine, carboxylic acid, HOAT and EDC in DMF, at a concentration of 0.5 M, was left standing for 24 hours at which time water and ethyl acetate were added. The organic phase was dried with sodium sulfate and purified via silica gel column chromatography eluting with ethyl acetate and hexanes to give the desired protected amide product. Alternatively the crude reaction mixture was directly purified by HPLC. Upon lyophilization, the TFA salt of the protected amide product was obtained. Alternatively, the HPLC fractions could be added to EtOAc and solid Na_2CO_3, separated and washed with $NaCl_{(sat.)}$. Upon drying over $MgSO_4$, filtering and removing the volatiles *in vacuo*, the protected amide product was obtained as a free base. Alternatively, the crude reaction mixture was used for the deprotection step without further purification.

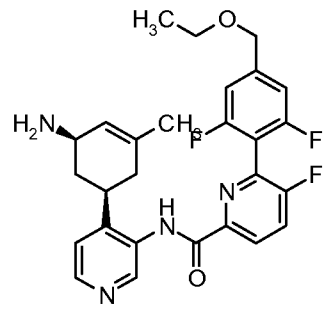
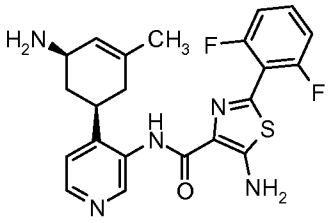
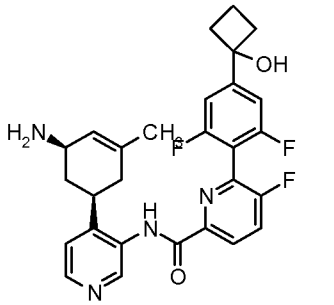
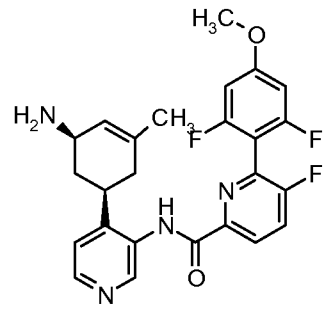
If an N-Boc protected amine was present, it was removed by treating with excess 4M HCl/ dioxane for 14 hours or by treating with 25% TFA/CH_2Cl_2 for 2 hours. Upon removal of the volatiles *in vacuo*, the material was purified by RP HPLC yielding after lyophilization the amide product as the TFA salt. Alternatively, the HPLC fractions could be added to EtOAc and solid Na_2CO_3, separated and washed with $NaCl_{(sat.)}$. Upon drying over $MgSO_4$, filtering and removing the volatiles *in vacuo* the free base was obtained. Upon dissolving in MeCN/H_2O, adding 1 eq. of 1 N HCl and lyophilizing, the HCl salt of the amide product was obtained.

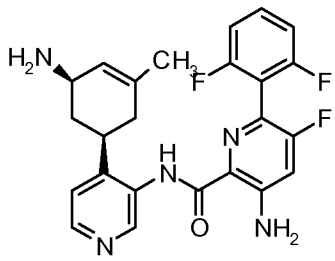
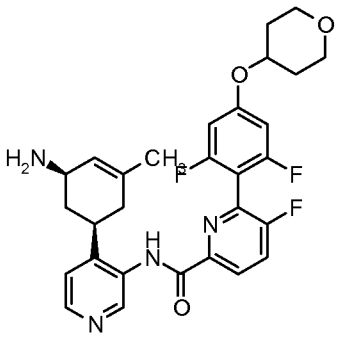
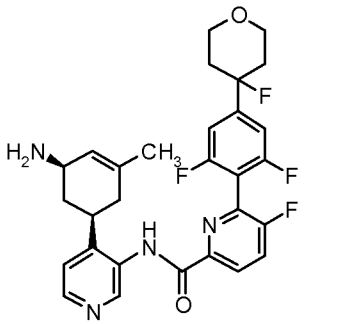
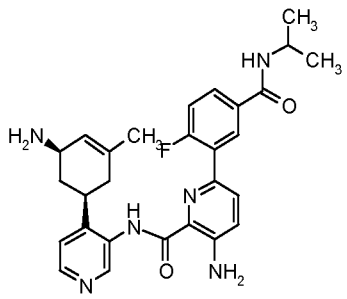
If a TBDMS ether was present, it was deprotected prior to Boc removal by treating with 6N HCl, THF, methanol (1:2:1) at room temperature for 12 h. After removal of volatiles *in vacuo*, the Boc amino group was deprotected as described above. Alternatively, the TBDMS ether and Boc group could be both deprotected with 6N HCl, THF, methanol (1:2:1) if left at rt for 24 hours, or heated at 60 °C for 3 hours.

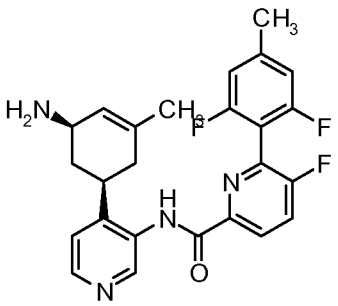
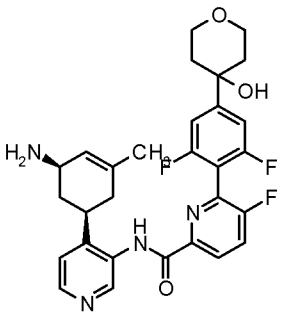
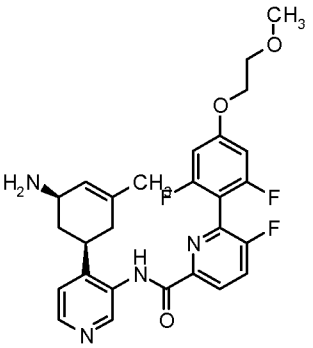
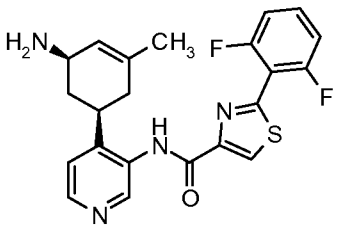
Following the procedures described herein, the following compounds were prepared:

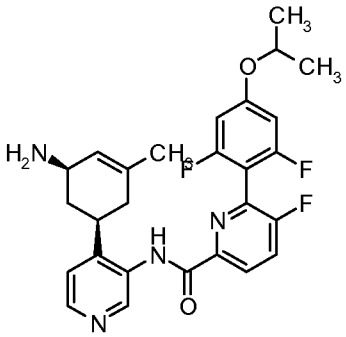
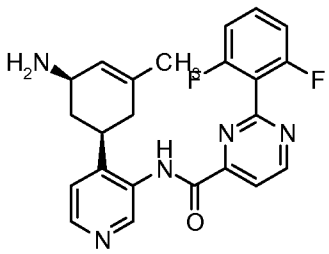
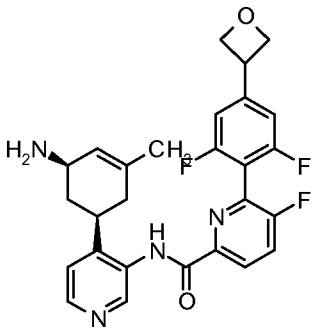
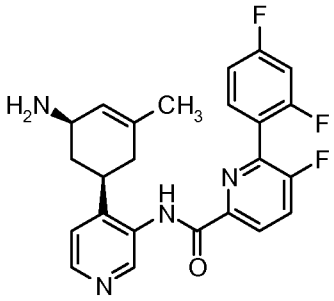
TABLE 1

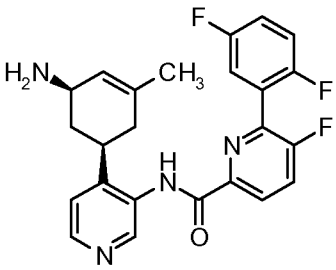
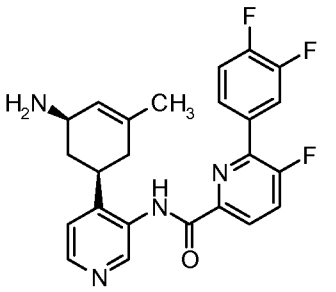
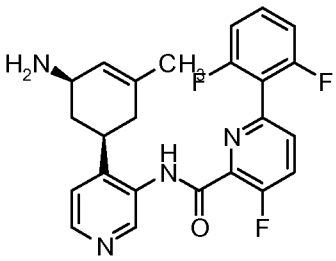
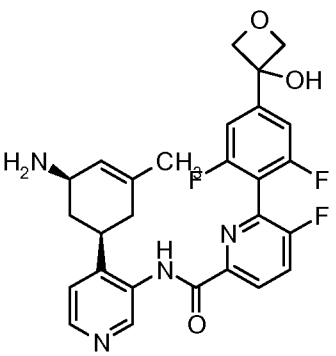
Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
1		439.2	0.59	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-enyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide

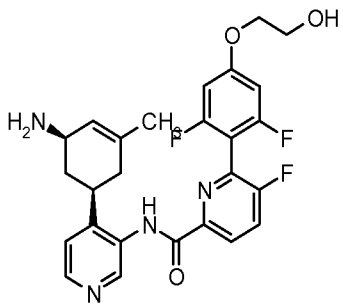
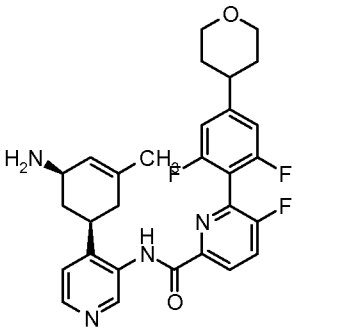
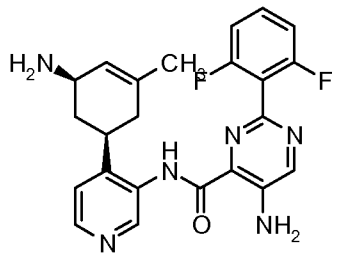
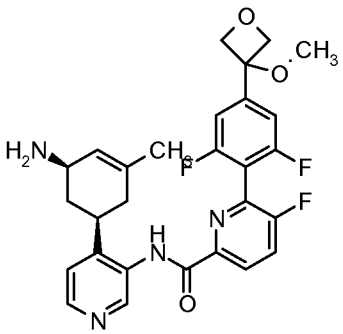
Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
2		497.3	0.67	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(4-(ethoxymethyl)-2,6-difluorophenyl)-5-fluoropicolinamide
3		442.2	0.58	5-amino-N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide
4		509.3	0.63	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide
5		469.3	0.64	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide

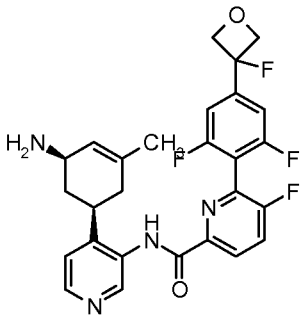
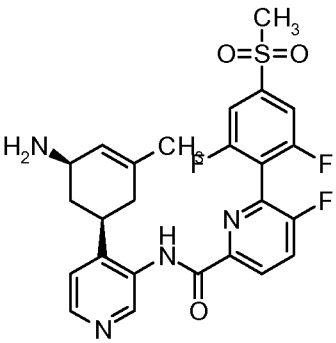
Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
6		454.3	0.62	3-amino-N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide
7		539.3	0.66	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide
8		541.3	0.68	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide
9		503.4	0.58	3-amino-N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2-fluoro-5-(isopropylcarbamoyl)phenyl)picolinamide

Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
10		453.3	0.63	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinamide
11		539.4	0.56	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide
12		513.3	0.63	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide
13		427.3	0.56	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide

Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
14		497.3	0.71	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-isopropoxyphenyl)-5-fluoropicolinamide
15		422.3	0.50	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)pyrimidine-4-carboxamide
16		495.3	0.59	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(oxetan-3-yl)phenyl)-5-fluoropicolinamide
17		439.3	0.61	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,4-difluorophenyl)-5-fluoropicolinamide

Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
18		439.3	0.60	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,5-difluorophenyl)-5-fluoropicolinamide
19		439.3	0.61	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(3,4-difluorophenyl)-5-fluoropicolinamide
20		439.3	0.56	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluorophenyl)-3-fluoropicolinamide
21		511.2	0.56	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinamide

Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
22		499.1	0.58	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide
23		523.2	0.66	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(tetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide
24		437.1	0.51	5-amino-N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-2-(2,6-difluorophenyl)pyrimidine-4-carboxamide
25		525.2	0.62	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide

Ex#	Structure	LC/MS (M+H)	LC/MS ($R_t$min)	Chemical Name
26		513.1	0.63	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinamide
27		517.1	0.56	N-(4-((1R,5R)-5-amino-3-methylcyclohex-3-en-1-yl)pyridin-3-yl)-6-(2,6-difluoro-4-(methylsulfonyl)phenyl)-5-fluoropicolinamide

In addition to LC/MS and LC characterization, representative compounds were analyzed by ^{1}H-NMR. The following data in Table 2 are typical spectra of the compounds of the invention.

TABLE 2

Ex#	NMR data
1	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.46 (s, 1H), 8.65 (d, J=4.0, 1H), 8.49 (d, J=4.0, 1H), 8.33 (dd, J=8.0, 4.0, 1H), 8.20 (dd, J=8.0, 8.0, 1H), 7.90-7.98 (m, 1H), 7.67-7.74 (m, 1H), 7.43 (d, J=4.0, 1H), 7.32 (dd, J=8.0, 8.0, 2H), 5.36 (s, 1H), 3.10-3.16 (m, 1H), 2.04-2.14 (m, 3H), 1.66 (s, 3H), 1.58-1.67 (m, 1H)

Ex#	NMR data
2	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 1.09 - 1.26 (m, 3 H) 1.49 - 1.73 (m, 4 H) 1.90 - 2.20 (m, 3 H) 3.37 - 3.60 (m, 2 H) 3.66 - 3.89 (m, 1 H) 4.42 -4.70 (m, 2 H) 5.36 (br. s., 1 H) 7.16 - 7.32 (m, 2 H) 7.46 (d, J=5.09 Hz, 1 H) 7.81 - 8.09 (m, 3 H) 8.10 - 8.21 (m, 1 H) 8.24 - 8.35 (m, 1 H) 8.50 (d,J=5.09 Hz, 1 H) 8.68 (s, 1 H) 10.30 - 10.51 (m, 1 H)
3	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 1.55 - 1.73 (m, 3 H) 2.01 - 2.25 (m, 2 H) 3.11 - 3.36 (m, 1 H) 3.84 (br. s., 1 H) 5.39 (br. s., 1 H) 7.25 (t, J=8.61 Hz, 1 H) 7.47 (d, J=5.09 Hz, 1 H) 7.50 - 7.74 (m, 2 H) 7.99 (br. s., 2 H) 8.46 (d, J=5.09 Hz, 1 H) 8.70 - 8.89 (m, 1 H) 9.36 - 9.64 (m, 1 H)
4	^{1}H NMR 400 MHz in CD_3OD: δ 1.72 (s, 3 H) 1.75 - 1.93 (m, 2 H) 2.04 - 2.38 (m, 5 H) 2.39 - 2.61 (m, 4 H) 3.95 (br. s., 1 H) 5.43 (br. s., 1 H) 7.33 (d, J=9.49 Hz, 2 H) 7.61 (d, J=5.43 Hz, 1 H) 8.02 (t, J=8.73 Hz, 1 H) 8.40 (dd, J=8.66, 3.91 Hz, 1 H) 8.51 (d, J=5.38 Hz, 1 H) 9.02 (s, 1 H)
5	^{1}H NMR 400 MHz in CD_3OD: δ 1.72 (s, 3 H) 1.78 - 1.91 (m, 1 H) 2.14 - 2.39 (m, 3 H) 3.34 - 3.42 (m, 1 H) 3.90 (s, 4 H) 5.44 (br. s., 1 H) 6.78 (d, J=10.17 Hz, 2 H) 7.71 (d, J=5.87 Hz, 1 H) 7.98 (s, 1 H) 8.32 - 8.41 (m, 1 H) 8.51 - 8.60 (m, 1 H) 9.14 (s, 1 H)
6	^{1}H NMR 400 MHz in CD_3OD: δ 1.64 (s, 3 H) 1.82 - 1.95 (m, 1 H) 2.09 - 2.25 (m, 1 H) 2.27 - 2.40 (m, 2 H) 3.35 - 3.42 (m, 1 H) 3.84 - 3.99 (m, 1 H) 5.42 (br. s., 1 H) 7.05 - 7.20 (m, 3 H) 7.47 - 7.60 (m, 1 H) 7.72 - 7.87 (m, 1 H) 8.43 - 8.61 (m, 1 H) 9.39 - 9.54 (m, 1 H)
7	^{1}H NMR 400 MHz in CD_3OD: δ 1.69 - 1.85 (m, 6 H) 2.03 - 2.13 (m, 2 H) 2.14 - 2.39 (m, 3 H) 3.63 (ddd, J=11.74, 8.78, 3.01 Hz, 2 H) 3.88 - 4.02 (m, 3 H) 4.65 - 4.75 (m, 1 H) 5.43 (br. s., 1 H) 6.82 (d, J=10.08 Hz, 2 H) 7.60 (d, J=5.43 Hz, 1 H) 7.98 (t, J=8.73 Hz, 1 H) 8.36 (dd, J=8.61, 3.91 Hz, 1 H) 8.51 (d, J=5.38 Hz, 1 H) 8.97 (s, 1 H)

Ex#	NMR data
8	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 1.47 - 1.74 (m, 4 H) 1.77 - 1.95 (m, 3 H) 1.97 - 2.41 (m, 4 H) 3.02 - 3.33 (m, 1 H) 3.53 - 4.07 (m, 4 H) 5.35 (br. s., 1 H) 7.31 - 7.50 (m, 3 H) 7.95 (d, J=3.13 Hz, 2 H) 8.12 - 8.25 (m, 1 H) 8.32 (dd, J=8.61, 3.91 Hz, 1 H) 8.50 (d, J=5.48 Hz, 1 H) 8.61 - 8.72 (m, 1 H) 10.47 (s, 1 H)
9	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 1.14 (d, J=6.65 Hz, 6 H) 1.47 - 1.78 (m, 4 H) 2.14 (d, J=11.35 Hz, 3 H) 3.20 (d, J=3.52 Hz, 1 H) 3.79 (br. s., 1 H) 4.07 (d, J=7.04 Hz, 1 H) 5.30 (br. s., 1 H) 7.28 - 7.41 (m, 2 H) 7.46 (d, J=5.48 Hz, 1 H) 7.78 (dd, J=8.80, 1.76 Hz, 1 H) 7.83 - 8.02 (m, 4 H) 8.31 (d, J=7.43 Hz, 1 H) 8.38 (dd, J=7.63, 2.15 Hz, 1 H) 8.49 (d, J=5.09 Hz, 1 H) 8.89 (s, 1 H) 10.41 (s, 1 H)
10	^{1}H NMR 400 MHz in CD_3OD: δ 8.96 (s, 1H), 8.49 (d, J=4.0, 1H), 8.36 (dd, J=8.0, 4.0, 1H), 7.99 (t, J=8.0, 1H), 7.57 (d, J=4.0, 1H), 7.02 (d, J=12.0, 2H), 5.42 (br.s., 1H), 3.93 (br.s., 1H), 2.47 (s, 3H), 2.21-2.32 (m, 3H), 1.78-1.82 (m, 1H), 1.72 (s, 3H).
11	^{1}H NMR 400 MHz in CD_3OD: δ 8.99 (s, 1H), 8.48 (d, J=4.0, 1H), 8.38 (dd, J=8.0, 4.0, 1H), 8.0 (t, J=8.0, 1H), 7.52 (d, J=4.0, 1H), 7.33 (d, J=12.0, 2H), 5.42 (br.s., 1H), 3.85-3.98 (m, 5H), 2.12-2.34 (m, 5H), 1.78-1.82 (m, 1H), 1.72 (s, 3H), 1.66-1.70 (m, 2H).
12	^{1}H NMR 400 MHz in CD_3OD: δ 8.96 (s, 1H), 8.49 (d, J=4.0, 1H), 8.35 (dd, J=8.0, 4.0, 1H), 7.98 (t, J=8.0, 1H), 7.55 (d, J=4.0, 1H), 6.80 (d, J=12.0, 2H), 5.43 (br.s., 1H), 4.22 (t, J=4.0, 2H), 3.94 (br.s., 1H), 3.78 (t, J=4.0, 2H), 3.44 (s, 2H), 2.17-2.34 (m, 3H), 1.78-1.82 (m, 1H), 1.73 (s, 3H).
13	^{1}H NMR 400 MHz in CD_3OD: δ 8.93 (s, 1H), 8.64 (s, 1H), 8.54 (d, J=4.0, 1H), 7.59-7.65 (m, 2H), 7.21-7.25 (m, 2H), 5.46 (br.s., 1H), 4.00 (br.s., 1H), 3.36-3.43 (m, 1H), 2.23-2.40 (m, 3H), 1.81 (s, 3H), 1.79-1.82 (m, 1H).

Ex#	NMR data
14	^{1}H NMR 400 MHz in DMSO$_{d6}$: δ 10.43 (s, 1H), 8.68 (s, 1H), 8.50 (d, J=8.0, 1H), 8.28 (dd, J=12.0, 4.0, 1H), 8.15 (t, J=8.0, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.43 (d, J=4.0, 1H), 6.94 (d, J=12.0, 2H), 5.37 (s, 1H), 4.78 (septet, J=4.0, 1H), 3.75-3.85 (broad s, 1H), 3.10-3.20 (m, 1H), 2.04-2.18 (m, 3H), 1.66 (s, 3H), 1.60-1.68 (m, 1H), 1.31 (d, J=4.0, 6H).
15	^{1}H NMR 400 MHz in DMSO$_{d6}$: δ 10.70 (s, 1H), 9.32 (d, J=4.0, 1H), 8.62 (s, 1H), 8.51 (d, J=4.0, 1H), 8.16 (d, J=4.0, 1H), 7.92 (d, broad base, J=4.0, 2H), 7.64-7.72 (m, 1H), 7.43 (d, J=4.0, 1H), 7.32 (t, J=8.0, 2H), 5.37 (s, 1H), 3.79 (broad s, 1H), 3.10-3.20 (m, 1H), 2.04-2.18 (m, 3H), 1.69 (s, 3H), 1.60-1.68 (m, 1H).
16	^{1}H NMR 400 MHz in DMSO$_{d6}$: δ 10.47 (s, 1H), 8.67 (s, 1H), 8.50 (d, J=4.0, 1H), 8.32 (dd, J=8.0, 4.0, 1H), 8.20 (t, J=8.0, 1H), 7.95 (d, broad base, J=4.0, 2H), 7.44 (d, J=4.0, 1H), 7.41 (d, J=8.0, 2H), 5.37 (s, 1H), 4.98 (t, J=8.0, 2H), 4.68 (t, J=8.0, 2H), 4.40 (quintet, J=8.0, 1H), 3.80 (broad s, 1H), 3.13-3.19 (m, 1H), 2.04-2.18 (m, 3H), 1.66 (s, 3H), 1.60-1.69 (m, 1H).
17	^{1}H NMR 400 MHz in DMSO$_{d6}$: δ 10.47 (s, 1H), 8.72 (s, 1H), 8.51 (d, J=8.0, 1H), 8.26 (dd, J=8.0, 4.0, 1H), 8.13 (t, J=8.0, 1H), 7.92-7.98 (m, 3H), 7.48 (dt, J=8.0, 2.0, 1H), 7.44 (d, J=4.0, 1H), 7.32 (dt, J=8.0, 2.0, 1H), 5.37 (s, 1H), 3.82 (broad s, 1H), 3.17-3.23 (m, 1H), 2.04-2.18 (m, 3H), 1.65 (s, 3H), 1.62-1.71 (m, 1H).
18	^{1}H NMR 400 MHz in DMSO$_{d6}$: δ 10.49 (s, 1H), 8.69 (s, 1H), 8.51 (d, J=4.0, 1H), 8.28 (dd, J=8.0, 4.0, 1H), 8.14 (t, J=8.0, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.77-7.81 (m, 1H), 7.48-7.52 (m, 2H), 7.44 (d,J=4.0, 1H), 5.37 (s, 1H), 3.79 (broad s, 1H), 3.17-3.23 (m, 1H), 2.04-2.18 (m, 3H), 1.64 (s, 3H), 1.62-1.71 (m, 1H).
19	^{1}H NMR 400 MHz in DMSO$_{d6}$: δ 10.57 (s, 1H), 8.71 (s, 1H), 8.54 (d, J=4.0, 1H), 8.39-8.44 (m, 1H), 8.19 (dd, J=8.0, 4.0, 1H), 8.11 (t, J=8.0, 1H), 8.0-8.06 (m, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.59-7.66 (m, 1H), 7.47 (d,J=4.0, 1H), 5.36 (s, 1H), 3.88 (broad s, 1H), 3.21-3.28 (m, 1H), 2.07-2.23 (m, 3H), 1.64 (s, 3H), 1.65-1.73 (m, 1H).

Ex#	NMR data
20	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.45 (s, 1H), 8.70 (s, 1H) ,8.50 (d, J=4.0, 1H), 8.12 (t, J=8.0, 1H), 7.94-8.00 (m, 3H), 7.61 (quintet, J=8.0, 1H), 7.44 (d, J=4.0, 1H), 7.28 (t, J=8.0, 2H), 5.38 (s, 1H), 3.80 (broad s, 1H), 3.21-3.28 (m, 1H), 2.04-2.21 (m, 3H), 1.67 (s, 3H), 1.62-1.71 (m, 1H).
21	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.46 (s, 1H), 8.66 (s, 1H), 8.50 (d, J=4.0, 1H), 8.33 (dd, J=8.0, 4.0, 1H), 8.21 (t, J=8.0, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.53 (d, J=8.0, 2H), 7.43 (d, J=4.0, 1H), 6.76 (bs, 1H), 5.37 (s, 1H), 4.84 (d, J=8.0, 2H), 4.73 (d, J=8.0, 2H), 3.81 (broad s, 1H), 3.13-3.20 (m, 1H), 2.04-2.19 (m, 3H), 1.66 (s, 3H), 1.60-1.69 (m, 1H).
22	^{1}H NMR in $DMSO_{d6}$: δ 10.43 (s, 1H), 8.67 (s, 1H), 8.50 (d, J=4.0, 1H), 8.28 (dd, J=8.0, 4.0, 1H), 8.16 (t, J=8.0, 1H), 7.93 (d, broad base, J=4.0, 2H), 7.42 (d, J=8.0, 2H), 6.97 (d, J=12.0, 1H), 5.37 (s, 1H), 4.13 (t, J=4.0, 2H), 3.81 (bs, 1H), 3.75 (t, J=4.0, 2H), 3.13-3.20 (m, 1H), 2.04-2.19 (m, 3H), 1.67 (s, 3H), 1.60-1.69 (m, 1H
23	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.46 (s, 1H), 8.65 (s, 1H), 8.50 (d, J=4.0, 1H), 8.31 (dd, J=8.0, 4.0, 1H), 8.18 (t, J=8.0, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.42 (d, J=4.0, 1H), 7.27 (d, J=8.0, 2H), 5.37 (s, 1H), 3.95-4.03 (m, 2H), 3.71 (bs, 1H), 3.42-3.49 (m, 2H), 3.11-3.16 (m, 1H), 2.92-2.97 (m, 1H), 2.04-2.19 (m, 3H), 1.72-1.78 (m, 4H), 1.67 (s, 3H), 1.60-1.69 (m, 1H).
24	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.40 (s, 1H), 8.75 (s, 1H), 8.67 (s, 1H), 8.48 (d, J=8.0, 1H), 7.92 (bs, 2H), 7.53-7.59 (m, 1H), 7.42 (d, J=4.0, 1H), 7.21 (7, J=8.0, 2H), 7.15-7.24 (m, 2H), 5.38 (s, 1H), 3.79 (bs, 1H), 3.11-3.16 (m, 1H), 2.04-2.19 (m, 3H), 1.72-1.78 (m, 4H), 1.66 (s, 3H), 1.60-1.69 (m, 1H).
25	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.47 (s, 1H), 8.66 (s, 1H), 8.50 (d, J=4.0, 1H), 8.34 (dd, J=8.0, 4.0, 1H), 8.22 (t, J=8.0, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.57 (d, J=8.0, 2H), 7.43 (d, J=4.0, 1H), 5.36 (s, 1H), 4.82 (dd, J=12.0, 4.0, 4H), 3.80 (broad s, 1H), 3.15 (s, 3H), 3.13-3.20 (m, 1H), 2.04-2.19 (m, 3H), 1.66 (s, 3H), 1.60-1.69 (m, 1H).

Ex#	NMR data
26	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.47 (s, 1H), 8.64 (s, 1H), 8.50 (d, J=4.0, 1H), 8.34 (dd, J=8.0, 4.0, 1H), 8.22 (t, J=8.0, 1H), 7.94 (d, broad base, J=4.0, 2H), 7.58 (d, J=8.0, 2H), 7.42 (d, J=4.0, 1H), 5.36 (s, 1H), 4.95-5.04 (m, 4H), 3.71 (broad s, 1H), 3.13-3.20 (m, 1H), 2.04-2.19 (m, 3H), 1.65 (s, 3H), 1.60-1.68 (m, 1H).
27	^{1}H NMR 400 MHz in $DMSO_{d6}$: δ 10.48 (s, 1H), 8.62 (s, 1H), 8.50 (d, J=4.0, 1H), 8.38 (dd, J=8.0, 4.0, 1H), 8.27 (t, J=8.0, 1H), 7.97 (d, J=4.0, 2H), 7.91 (d, broad base, J=4.0, 2H), 7.41 (d, J=8.0, 1H), 5.36 (s, 1H), 3.79 (broad s, 1H), 3.55 (s, 3H), 3.13-3.21 (m, 1H), 2.04-2.19 (m, 3H), 1.66 (s, 3H), 1.59-1.68 (m, 1H).

Pim1, Pim2, Pim3 AlphaScreen Assays

Pim 1, Pim 2 & Pim 3 AlphaScreen assays using high ATP (11 - 125X ATP Km) were used to determine the biochemical activity of the inhibitors. The activity of Pim 1, Pim 2, & Pim 3 is measured using a homogeneous bead based system quantifying the amount of phosphorylated peptide substrate resulting from kinase-catalyzed phosphoryl transfer to a peptide substrate. Compounds to be tested are dissolved in 100% DMSO and directly distributed to a white 384-well plate at 0.25 µl per well. To start the reaction, 5 µl of 100 nM Bad peptide (Biotin-AGAGRSRHSSYPAGT–OH (SEQ ID NO:1)) and ATP (concentrations described below) in assay buffer (50 mM Hepes, pH=7.5, 5 mM $MgCl_2$, 0.05% BSA, 0.01% Tween-20, 1 mM DTT) is added to each well. This is followed by the addition of 5 µl/well of Pim 1, Pim 2 or Pim 3 kinase in assay buffer (concentrations described below). Final assay concentrations (described below) are in 2.5% DMSO. The reactions are performed for ~2 hours, then stopped by the addition of 10 µl of 0.75 µg/ml anti-phospho Ser/Thr antibody (Cell Signaling), 10 µg/ml Protein A AlphaScreen beads (Perkin Elmer), and 10 µg/ml streptavidin coated AlphaScreen beads in stop/detection buffer (50 mM EDTA, 95 mM Tris, pH=7.5, 0.01% Tween-20). The stopped reactions are incubated overnight in the dark. The phosphorylated peptide is detected via an oxygen anion initiated chemiluminescence/fluorescence cascade using the Envision plate reader (Perkin Elmer).

AlphaScreen Assay Conditions				
Enzyme source	Enzyme conc. (nM)	b-BAD peptide conc. (nM)	ATP conc. (uM)	ATP Km (app) (uM)
Pim 1 (INV)	0.0025	50	2800	246
Pim 2 (INV)	0.01	50	500	4
Pim 3 (NVS)	0.005	50	2500	50

Compounds of the foregoing examples were tested by the Pim 1, Pim 2 & Pim 3 AlphaScreen assays and found to exhibit an IC_{50} values as shown in Table 3 below. IC_{50}, the half maximal inhibitory concentration, represents the concentration of test compound that is required for 50% inhibition of its target *in vitro*.

Cell Proliferation Assay

KMS11 (human myeloma cell line), were cultured in IMDM supplemented with 10% FBS, sodium pyruvate and antibiotics. Cells were plated in the same medium at a density of 2000 cells per well into 96 well tissue culture plates, with outside wells vacant, on the day of assay.

Test compounds supplied in DMSO were diluted into DMSO at 500 times the desired final concentrations before dilution into culture media to 2 times final concentrations. Equal volumes of 2x compounds were added to the cells in 96 well plates and incubated at 37 °C for 3 days.

After 3 days plates were equilibrated to room temperature and equal volume of CellTiter-Glow Reagent (Promega) was added to the culture wells. The plates were agitated briefly and luminescent signal was measured with luminometer. The percent inhibition of the signal seen in cells treated with DMSO alone vs. cells treated with control compound was calculated and used to determine EC_{50} values (i.e., the concentration of a test compound that is required to obtain 50% of the maximum effect in the cells) for tested compounds, as shown in Table 3.

Using the procedures of the Pim1, Pim2, Pim3 AlphaScreen Assays the IC_{50} concentrations of compounds of the previous examples were determined as shown in the Table 3.

Using the procedures of Cell Proliferation Assay, the EC_{50} concentrations of compounds of the examples were determined in KMS11 cells as shown in Table 3.

TABLE 3

Ex#	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11 EC_{50} µM
1		0.00176		0.230
2	0.00003	0.00144	0.00238	0.024
3	0.00002	0.00065	0.00025	0.012
4	0.00002	0.00075	0.00114	0.021
5	0.00003	0.00189	0.00136	0.094
6	0.00002	0.00053	0.00040	0.011
7	0.00002	0.00188	0.00123	0.030
8	0.00002	0.00114	0.00225	0.071
9	0.00005	0.00089	0.00109	0.048

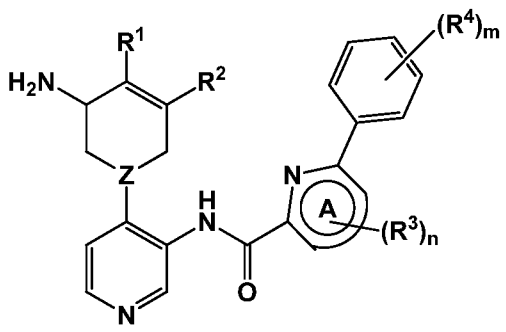
Ex#	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11 EC_{50} µM
10	0.00001	0.00108	0.00109	0.055
11	0.00002	0.00101	0.00186	0.026
12	0.00003	0.00329	0.00199	0.088
13	0.00028	0.01227	0.00392	0.361
14	0.00002	0.00098	0.00095	0.066
15	0.00119	0.05340	0.02883	0.454
16	0.00002	0.00143	0.00326	0.053
17	0.00033	0.04223	0.02344	0.719
18	0.00016	0.00654	0.00914	0.391
19	0.00437	0.17842	0.10604	2.462

Ex#	Pim1 IC_{50} µM	Pim2 IC_{50} µM	Pim3 IC_{50} µM	KMS11 EC_{50} µM
20	0.00069	0.01301	0.01387	0.364
21	0.00003	0.00095	0.00252	0.061
22	0.00002	0.00119	0.00066	0.030
23	0.00001	0.00046	0.00075	0.042
24	0.00010	0.00185	0.00212	0.037
25	0.00005	0.00250	0.00833	0.077
26	0.00004	0.00472	0.00707	0.090
27	0.00024	0.01684	0.05278	0.393

Compound structures in the tables marked as "Chiral" were prepared and tested in optically active form, having the absolute stereochemistry as shown; other compounds were prepared and tested in racemic form, and the depicted structure represents the relative stereochemistry at each chiral center.

CLAIMS

1. A compound of Formula (I):



(I)

wherein:

Z is CH or N;

Aromatic ring A is a pyridine, pyrimidine, pyrazine, or thiazole ring with N located as shown;

R^1 is H, Me, Et, $-CH_2OH$, or $-CH_2OMe$;

R^2 is C_{1-4} alkyl, CF_3, or phenyl optionally substituted with 1-2 groups selected from halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and CN;

R^3 is halo, Me, CF_3, or NH_2 independently at each occurrence; and

each R^4 is independently selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, $-S(O)_p-R^*$, C_{1-4} haloalkoxy, $-(CH_2)_{0-3}-OR^*$, $-O-(CH_2)_{1-3}-OR^*$, $COOR^*$, $C(O)R^*$, $-CONR^*_2$, $-(CR'_2)_{1-3}-OR'$ or $-(CR'_2)_{1-3}-OR'$, and an optionally substituted member selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl, wherein C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycloalkyl are each optionally substituted with up to two groups selected from halo, CN, NH_2, hydroxy, C_{1-4} haloalkyl, C_{1-4} alkoxy, and R*;

where each R' is independently H or Me

and each R* is independently H or a 4-7 membered cyclic ether, 4-6 membered cycloalkyl, or C_{1-6} alkyl, each of which is optionally substituted with up to three groups selected from halo, oxo, C_{1-4} alkyl, C_{1-4} alkoxy, OH, NH_2, COOH, COOMe, COOEt, OMe, OEt, and CN;

m is 1, 2 or 3;

n is 0, 1 or 2; and

p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^1 is H or Me.

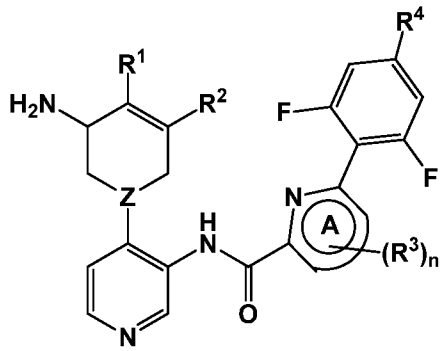
3. The compound of claim 1, wherein R^2 is Me or CF_3.

4. The compound of any of claims 1-3, wherein Z is CH.

5. The compound of any of claims 1-3, wherein Z is N.

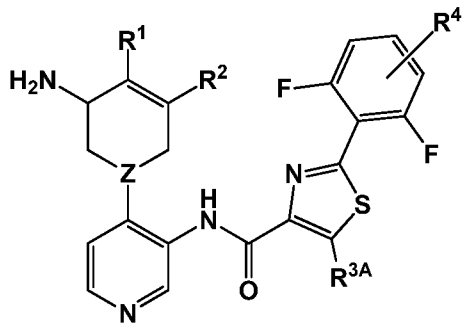
6. The compound of any of claims 1-3, wherein two R^4 groups each represent F.

7. The compound of any of claims 1-3, wherein the compound is of the formula:



.

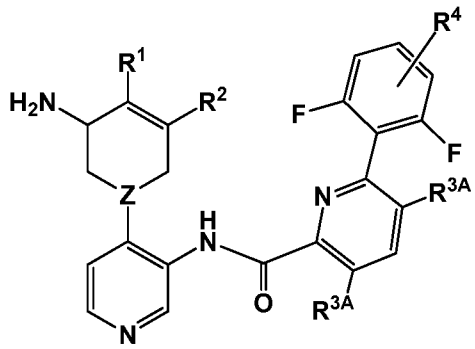
8. The compound of claim 7, wherein the compound is of the formula:



,

where R^{3A} is H, F or NH_2.

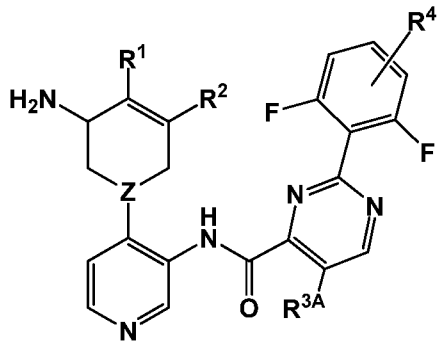
9. The compound of claim 7, wherein the compound is of the formula:



,

where each R^{3A} is independently H, F or NH_2.

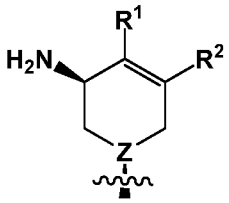
10. The compound of claim 7, which is of the formula:



,

where R^{3A} is H, F or NH_2.

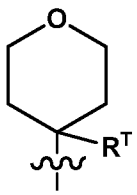
11. The compound of claim 1, wherein the unsaturated ring has the relative stereochemistry of this formula:



.

12. The compound of claim 11, wherein at least one R^3 or R^{3A} is F or NH_2.

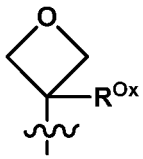
13. The compound of claim 1, wherein one R^4 is a tetrahydropyranyl group of the formula:



,

wherein R^T is H, OH, OMe, or F.

14. The compound of claim 1, wherein one R^4 is an oxetanyl group of the formula:



,

wherein R^{Ox} is H, OH, OMe, or F.

15. The compound of claim 1, wherein one R^4 is OMe, OEt, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, or OPr.

16. The compound of claim 1, wherein one R^4 is $-CH_3$, $-CH_2OMe$, 1-hydroxycyclobutyl, $-SO_2Me$, or $-CH_2OEt$.

17. The compound of claim 1, which is selected from the compounds in Table I.

18. A pharmaceutical composition comprising a compound of claim 1 and at least one pharmaceutically acceptable excipient.

19. The pharmaceutical composition of claim 18, further comprising a co-therapeutic agent.

20. The pharmaceutical composition of claim 19, wherein the co-therapeutic agent is selected from irinotecan, topotecan, gemcitabine, 5-fluorouracil, cytarabine, daunorubicin, PI3 Kinase inhibitors, mTOR inhibitors, DNA synthesis inhibitors, leucovorin, carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, and trastuzumab.

21. A method to treat a condition caused or exacerbated by excessive Pim kinase activity, which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

22. The method of claim 21, wherein the condition is a cancer.

23. The method of claim 21, wherein the cancer is selected from carcinoma of the lungs, pancreas, thyroid, ovary, bladder, breast, prostate, or colon, melanoma, myeloid leukemia, multiple myeloma, erythroleukemia, villous colon adenoma, and osteosarcoma; or the autoimmune disorder is selected from Crohn's disease, inflammatory bowel disease, rheumatoid arthritis, and chronic inflammatory diseases.

24. A compound according to claim 1 for use in therapy.

25. Use of a compound according to claim 1 for the preparation of a medicament.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/058034

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/14 C07D401/12 C07D417/12 A61K31/4427 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/026124 A1 (NOVARTIS AG [CH]; BURGER MATTHEW T [US]; HAN WOOSEOK [US]; LAN JIONG []) 11 March 2010 (2010-03-11) cited in the application See the compounds in tables 1-3 -----	1-25
A	WO 2009/109576 A1 (NOVARTIS AG [CH]; BURGER MATTHEW [US]; LAN JIONG [US]; LINDVALL MIKA []) 11 September 2009 (2009-09-11) See the examples -----	1-25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2014	23/01/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Menchaca, Roberto

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/058034

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