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(54) Title: COMPOUNDS AND COMPOSITIONS USEFUL FOR TREATING DISORDERS RELATED TO NTRK

(57) Abstract: This invention relates to inhibitors of NTRK comprising a pyrazolo[1,5-4]pyrimidine-3-carbonitrile structure. They are active against wild-type NTRK and its resistant mutants.

# COMPOUNDS AND COMPOSITIONS USEFUL FOR TREATING DISORDERS RELATED TO NTRK

## CLAIM OF PRIORITY

This application claims priority from U.S.S.N. 62/257,476 filed November 19, 2015, which is incorporated herein by reference in its entirety.

## BACKGROUND

Neurotrophic Tyrosine Receptor Kinase (NTRK) 1, 2 and 3 are receptor tyrosine kinases (RTKs) that activate multiple downstream pathways involved in cell proliferation and survival. Various genetic fusions, arising from aberrant chromosomal translocations of the genes coding for these RTKs, are implicated in the etiology of multiple cancers including high and low grade glioma, cholangiocarcinoma, papillary thyroid carcinoma, colon cancer and non-small cell lung cancer. A genomics analysis on the landscape of kinase fusions identified NTRK fusions in a wide array of additional cancer types including head and neck squamous cell carcinoma, pancreatic adenocarcinoma, sarcoma and melanoma, thereby providing further therapeutic rationale for deploying inhibitors of these kinases to treat multiple oncologic indications.

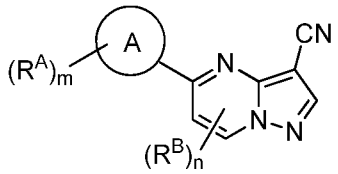
The identification of NTRK fusions as the underlying cause of certain cancers prompted the discovery and clinical development of several NTRK kinase inhibitors to treat tumors that harbor an NTRK fusion protein. Early clinical data support the viability of this approach in providing benefit to patients with specific human malignancies. Ultimately however, despite clear signs of clinical activity, most patients' cancers will become resistant to kinase inhibitor therapy leading to relapse and progression of the disease. When resistance occurs, the patient's treatment options are often very limited. There is thus a need for compounds that inhibit NTRK, as well as its resistant mutants.

## SUMMARY OF THE INVENTION

The present invention provides inhibitors of NTRK and NTRK mutants, *e.g.*, NTRK resistant mutants (as defined herein), for example, inhibitors of structural formula (I) and pharmaceutically acceptable salts and compositions thereof. The present invention further provides methods of using the compounds of the invention, and pharmaceutically acceptable salts and

compositions thereof, to inhibit the activity of NTRK or its mutants in a cell or patient. The present invention further provides methods for using the compounds of the invention, and pharmaceutically acceptable salts and compositions thereof, to treat a subject suffering from a condition mediated by aberrant NTRK activity, *e.g.*, cancer.

In one aspect, the invention features a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:




I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2;

provided that the compound is not (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of structural formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

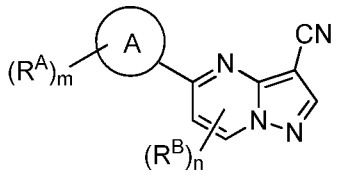
In another aspect, the present invention provides a method for inhibiting NTRK activity in a cell or in a patient. In some embodiments, said method comprises the step of contacting the cell or administering to the patient a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

In another aspect, the present invention provides a method for treating a subject suffering from a condition mediated by aberrant NTRK activity. In some embodiments, said method comprises administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

In another aspect, the present invention provides a method for treating a subject who has developed resistance to a cancer treatment. In some embodiments, said method comprises administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

## EMBODIMENTS OF THE INVENTION

In one aspect, the invention features a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:



I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

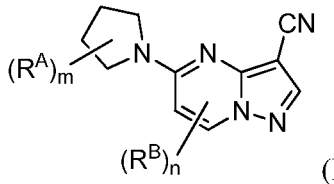
each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2;

provided that the compound is not (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

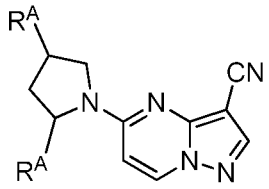
In some embodiments, the compound has Formula (Ia-1):



(Ia-1).

In some embodiments, at least one $R^A$ is halo.

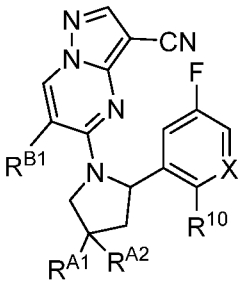
In other embodiments, the compound has Formula (Ib):



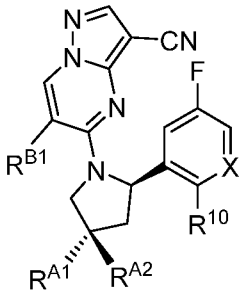
(Ib).

In some embodiments, one $R^A$ is halo and one $R^A$ is aryl or heteroaryl.

In some embodiments, the compound has Formula Ic:



(Ic), or Formula Ic-1:



(Ic-1), wherein:

X is N or C($R^9$);

$R^{A1}$ is fluoro or -CN;

$R^{A2}$ is fluoro or hydrogen;

$R^{B1}$ is hydrogen or fluoro;

$R^9$ is selected from hydrogen, halo, -CN, -$C_1$-$C_4$ alkyl, -C(O)N($R^{11}$)($R^{11}$), and -$S(O)_2$N($R^{11}$)($R^{11}$), wherein any alkyl portion of $R^9$ is optionally substituted with one or more substituents selected from -OH and -F;

$R^{10}$ is selected from hydrogen, halo, -O-($C_1$-$C_4$ alkyl) optionally substituted with one or more halo, and -C(O)N($R^{11}$)($R^{11}$); and

each $R^{11}$ is independently selected from hydrogen, and $C_1$-$C_4$ alkyl optionally substituted with one or more substituents selected from -OH and cyclopropyl.

In some embodiments of Formula Ic, $R^9$ is selected from hydrogen, fluoro, chloro, -CN, -$C(O)NH_2$, -$C(O)NHCH_3$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_2CH_2OH$, -$C(OH)(CH_3)_2$, -$S(O)_2NH_2$, and N-(cyclopropylmethyl)carbamyl.

In some embodiments of Formula Ic, $R^{10}$ is selected from hydrogen, fluoro, chloro, -$OCH_3$, -$OCF_3$ and -$C(O)NH_2$.

In another aspect, the invention features a method for inhibiting NTRK activity in a cell or in a patient comprising the step of contacting the cell or administering to the patient a compound described herein (*e.g.*, a compound in Table 1) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

In another aspect, the invention features a method for treating a subject suffering from a condition mediated by aberrant NTRK activity, comprising administering to the subject a therapeutically effective amount of a compound described herein (*e.g.*, a compound in Table 1) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

In another aspect, the present invention features a method for treating a subject who has developed resistance to a cancer treatment, comprising administering to the subject a therapeutically effective amount of a compound described herein (*e.g.*, a compound in Table 1) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

Definitions

As used herein, the terms a "patient," "subject," "individual," and "host" refer to either a human or a non-human animal suffering from or suspected of suffering from a disease or disorder associated with aberrant NTRK expression (*i.e.*, increased NTRK activity caused by signaling through NTRK) or biological activity.

"Treat" and "treating" such a disease or disorder refers to ameliorating at least one symptom of the disease or disorder. These terms, when used in connection with a condition such as a cancer, refer to one or more of: impeding growth of the cancer, causing the cancer to shrink by weight or volume, extending the expected survival time of the patient, inhibiting tumor growth, reducing tumor mass, reducing size or number of metastatic lesions, inhibiting the development of new metastatic lesions, prolonging survival, prolonging progression- free survival, prolonging time to progression, and/or enhancing quality of life.

The term "preventing" when used in relation to a condition or disease such as cancer, refers to a reduction in the frequency of, or delay in the onset of, symptoms of the condition or disease. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount.

The term "therapeutic effect" refers to a beneficial local or systemic effect in animals, particularly mammals, and more particularly humans, caused by administration of a compound or composition of the invention. The phrase "therapeutically-effective amount" means that amount of a compound or composition of the invention that is effective to treat a disease or condition caused by over expression of NTRK or aberrant NTRK biological activity at a reasonable benefit/risk ratio. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of skill in the art.

As used herein, "developing resistance" means that when a drug is first administered to the patient, the patient's symptoms improve, whether measured by decrease in tumor volume, a

decrease in the number of new lesions, or some other means that a physician uses to judge disease progression; however, those symptoms stop improving, or even worsen at some point. At that time, the patient is said to have developed resistance to the drug.

"Aliphatic group" means a straight-chain, branched-chain, or cyclic hydrocarbon group and includes saturated and unsaturated groups, such as an alkyl group, an alkenyl group, and an alkynyl group.

"Alkylene" refers to a divalent radical of an alkyl group, *e.g.*, $-CH_2-$, $-CH_2CH_2-$, and $CH_2CH_2CH_2-$.

"Alkenyl" means an aliphatic group containing at least one double bond.

"Alkoxyl" or "alkoxy" means an alkyl group having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. The term "haloalkoxy" refers to an alkoxy in which one or more hydrogen atoms are replaced by halo, and includes alkoxy moieties in which all hydrogens have been replaced by halo (*e.g.*, perfluoroalkoxy).

"Alkyl" refers to a monovalent radical of a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as $C_1$-$C_{12}$ alkyl, $C_1$-$C_{10}$ alkyl, and $C_1$-$C_6$ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

"Alkenylene" refers to an alkenyl group having two connecting points. For example, "ethenylene" represents the group -CH=CH-. Alkenylene groups can also be in an unsubstituted form or substituted form with one or more substituents.

"Alkynyl" refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and characterized in having one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, and 3-hexynyl. One of the triple bond carbons may optionally be the point of attachment of the alkynyl substituent.

"Alkynylene" refers to an alkynyl having two connecting points. For example, "ethynylene" represents the group -C≡C-. Alkynylene groups can also be in an unsubstituted form or substituted form with one or more substituents.

"Hydroxyalkylene" or "hydroxyalkyl" refers to an alkylene or alkyl moiety in which an alkylene or alkyl hydrogen atom is replaced by a hydroxyl group. Hydroxyalkylene or hydroxyalkyl includes groups in which more than one hydrogen atom has been replaced by a hydroxyl group.

"Aromatic ring system" is art-recognized and refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein at least one ring is aromatic.

"Aryl" refers to a monovalent radical of an aromatic ring system. Representative aryl groups include fully aromatic ring systems, such as phenyl, naphthyl, and anthracenyl, and ring systems where an aromatic carbon ring is fused to one or more non-aromatic carbon rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like.

"Arylalkyl" or "aralkyl" refers to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups.

"Aryloxy" refers to -O-(aryl), wherein the heteroaryl moiety is as defined herein.

"Halo" refers to a radical of any halogen, *e.g.*, -F, -Cl, -Br, or -I.

"Haloalkyl" and "haloalkoxyl" refers to alkyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

"Haloalkylene" refers to a divalent alkyl, *e.g.*, -$CH_2$-, -$CH_2CH_2$-, and -$CH_2CH_2CH_2$-, in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo.

"Heteroalkyl" refers to an optionally substituted alkyl, which has one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given, *e.g.* $C_1$-$C_6$ heteroalkyl which refers to the number of carbons in the chain, which in this example includes 1 to 6 carbon atoms. For example, a –$CH_2OCH_2CH_3$ radical is referred to as a "$C_3$" heteroalkyl. Connection to the rest of the molecule

may be through either a heteroatom or a carbon in the heteroalkyl chain. "Heteroalkylene" refers to a divalent optionally substituted alkyl, which has one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof.

"Carbocyclic ring system" refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein each ring is either completely saturated or contains one or more units of unsaturation, but where no ring is aromatic.

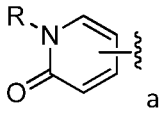
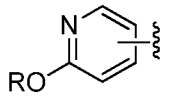
"Carbocyclyl" refers to a monovalent radical of a carbocyclic ring system. Representative carbocyclyl groups include cycloalkyl groups (*e.g.*, cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and the like), and cycloalkenyl groups (*e.g.*, cyclopentenyl, cyclohexenyl, cyclopentadienyl, and the like).

"Cycloalkyl" refers to a cyclic, bicyclic, tricyclic, or polycyclic non-aromatic hydrocarbon groups having 3 to 12 carbons. Any substitutable ring atom can be substituted (*e.g.*, by one or more substituents). The cycloalkyl groups can contain fused or spiro rings. Fused rings are rings that share a common carbon atom. Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclohexyl, methylcyclohexyl, adamantyl, and norbornyl.

"Cycloalkylalkyl" refers to a –(cycloalkyl)-alkyl radical where cycloalkyl and alkyl are as disclosed herein. The "cycloalkylalkyl" is bonded to the parent molecular structure through the cycloalkyl group.

"Heteroaromatic ring system" is art-recognized and refers to monocyclic, bicyclic or polycyclic ring system wherein at least one ring is both aromatic and comprises at least one heteroatom (*e.g.*, N, O or S); and wherein no other rings are heterocyclyl (as defined below). In certain instances, a ring which is aromatic and comprises a heteroatom contains 1, 2, 3, or 4 ring heteroatoms in such ring.

"Heteroaryl" refers to a monovalent radical of a heteroaromatic ring system. Representative heteroaryl groups include ring systems where (i) each ring comprises a heteroatom and is aromatic, *e.g.*, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrrolyl, furanyl, thiophenyl pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl; (ii) each ring is aromatic or carbocyclyl, at least one aromatic ring comprises a heteroatom and at least one other ring is a hydrocarbon ring or *e.g.*, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl,

phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, pyrido[2,3-b]-1,4-oxazin-3-(4H)-one, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl; and (iii) each ring is aromatic or carbocyclyl, and at least one aromatic ring shares a bridgehead heteroatom with another aromatic ring, *e.g.*, 4H-quinolizinyl. In some embodiments, heteroaryl can include  and  wherein R is H or $C_{1-6}$ alkyl.

"Heterocyclic ring system" refers to monocyclic, bicyclic and polycyclic ring systems where at least one ring is saturated or partially unsaturated (but not aromatic) and comprises at least one heteroatom. A heterocyclic ring system can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted.

"Heterocyclyl" refers to a monovalent radical of a heterocyclic ring system. Representative heterocyclyls include ring systems in which (i) every ring is non-aromatic and at least one ring comprises a heteroatom, *e.g.*, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl; (ii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is an aromatic carbon ring, *e.g.*, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl; and (iii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is aromatic and comprises a heteroatom, *e.g.*, 3,4-dihydro-1H-pyrano[4,3-c]pyridine, and 1,2,3,4-tetrahydro-2,6-naphthyridine.

"Heterocyclylalkyl" refers to an alkyl group substituted with a heterocyclyl group.

"Cyano" refers to a –CN radical.

"Nitro" refers to $–NO_2$.

"Hydroxy" or "hydroxyl" refers to –OH.

"Hydroxyalkyl" refers to a divalent alkyl, *e.g.*, $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$, in which one or more hydrogen atoms are replaced by a hydroxy, and includes alkyl moieties in which all hydrogens have been replaced by hydroxy.

"Substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted

with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned under this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

As used herein, the definition of each expression, *e.g.*, alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound, as well as enantiomeric mixtures thereof. The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below a composition contains 90% of one enantiomer, *e.g.*, the S enantiomer, and 10% of the other enantiomer, *i.e.*, the R enantiomer.

$$ee = (90\text{-}10)/100 = 80\%.$$

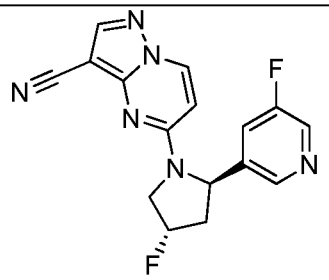
Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.

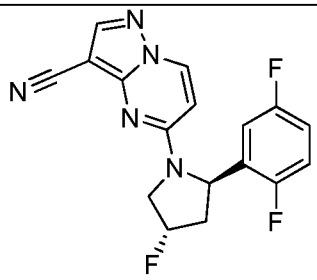
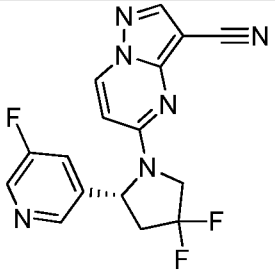
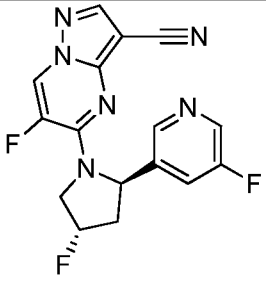
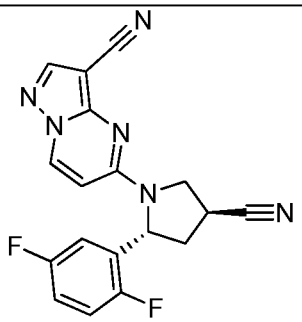
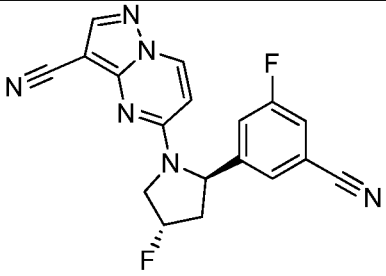
The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, *e.g.*, the S-enantiomer. In other words such compounds or compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer.

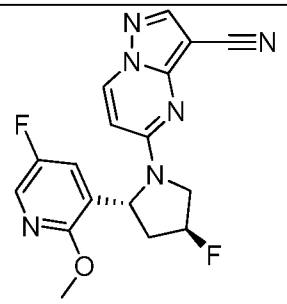
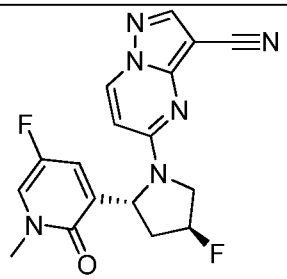
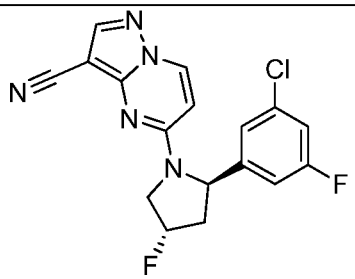
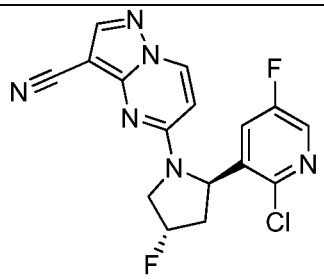
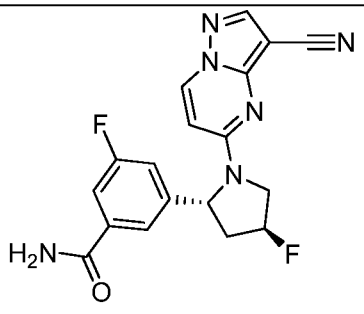
The compounds described herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example deuterium ($^{2}H$), tritium ($^{3}H$), carbon-13 ($^{13}C$), or carbon-14 ($^{14}C$). All isotopic variations of the compounds disclosed herein, whether radioactive or not, are intended to be encompassed within the scope of the present invention. In addition, all tautomeric forms of the compounds described herein are intended to be within the scope of the invention.

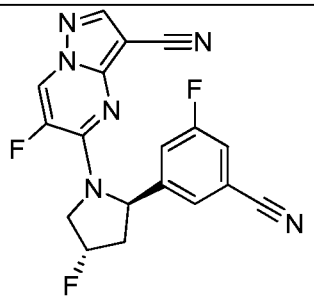
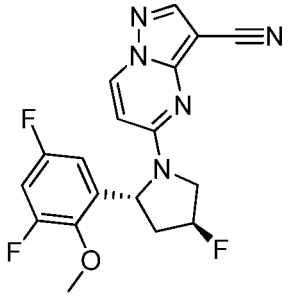
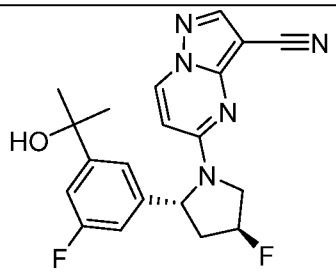
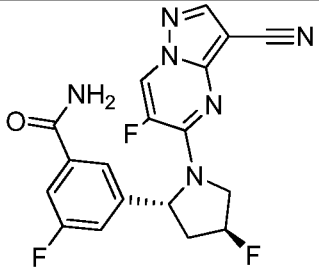
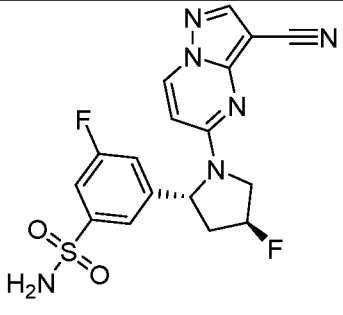
The compound can be useful as the free base or as a salt. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

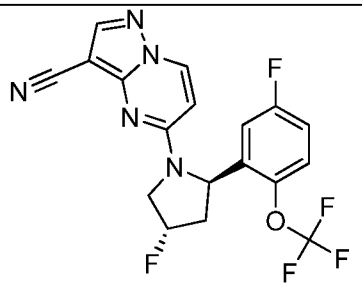
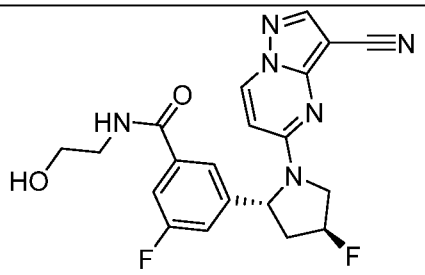
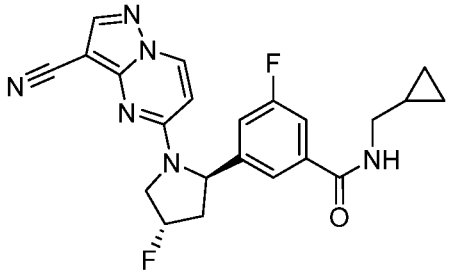
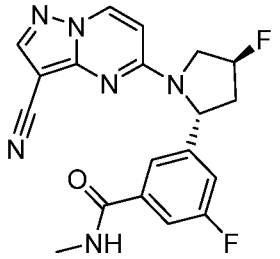
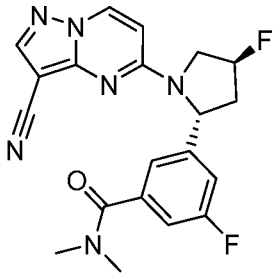
Table 1 below shows the structures of compounds described herein.

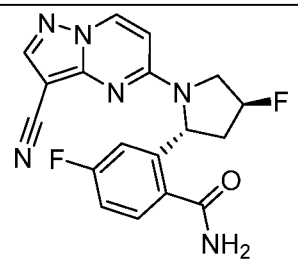
| Compound Number | Structure |
|---|---|
| 1 |  |

| | |
|---|---|
| **2** |  |
| **3** |  |
| **4** |  |
| **5** |  |
| **6** |  |

| | |
|---|---|
| **7** |  |
| **8** |  |
| **9** |  |
| **10** |  |
| **11** |  |

| | |
|---|---|
| **12** |  |
| **13** |  |
| **14** |  |
| **15** |  |
| **16** |  |

| | |
|---|---|
| **17** |  |
| **18** |  |
| **19** |  |
| **20** |  |
| **21** |  |

| | |
|---|---|
| 22 |  |

Pharmaceutically acceptable salts of these compounds are also contemplated for the uses described herein.

"Pharmaceutically acceptable salt" refers to any salt of a compound of the invention which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Pharmaceutically acceptable salts may be derived from a variety of organic and inorganic counter-ions well known in the art and include. Such salts include: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1 ,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; or (2) salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminum ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminum, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, N-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like. Pharmaceutically acceptable salts further include, by way of example only,

sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, besylate, acetate, maleate, oxalate and the like.

Pharmaceutical Compositions

Pharmaceutical compositions of the invention comprise one or more compounds of the invention and one or more physiologically or pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof. Each carrier must be "acceptable" in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The compositions of the invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions of the invention are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the 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 non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. 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. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tween, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by

topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration.

Dosages

Toxicity and therapeutic efficacy of compounds of the invention, including pharmaceutically acceptable salts and deuterated variants, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals. The $LD_{50}$ is the dose lethal to 50% of the population. The $ED_{50}$ is the dose therapeutically effective in 50% of the population. The dose ratio between toxic and therapeutic effects ($LD_{50}$/ $ED_{50}$) is the therapeutic index. Compounds that exhibit large therapeutic indexes are preferred. While compounds that exhibit toxic side effects may be used,

care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

Data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds may lie within a range of circulating concentrations that include the $ED_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the $IC_{50}$ (i.e., the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Treatment

NTRK fusions have been implicated in several types of cancers. These fusions harbor an intact NTRK kinase domain that is identical to the native or wild-type form of the receptor; therefore, as used herein, any NTRK protein (NTRK1, 2 or 3) with the same kinase domain as wild-type NTRK will be referred to as "wild-type NTRK." Mutations can occur in the NTRK kinase domain, leading to mutants that are resistant to kinase inhibitor therapy. These resistance mutations can be predicted using structural biology and computational analyses, as well as by examining codon sequences in which a sequence change gives rise to a codon for a different amino acid. Alternatively, resistance mutations for a given inhibitor can be identified experimentally by administration of that inhibitor (e.g., a known NTRK wild-type inhibitor) and exposing cells to a mutation-promoting agent, such as ENU (N-ethyl-N-nitrosourea). The cells are washed and then

plated with increasing concentrations (2-100X proliferation $IC_{50}$) of the compound of choice. The wells with cellular outgrowth are then collected after 3-4 weeks. In particular, a mutation at amino acid position 595 within the NTRK fusion (NTRK1 wt numbering), effecting a change from a glycine to an arginine residue (heretofore designated 'G595R') was identified via both methods. This mutation was subsequently demonstrated to confer significant resistance to two NTRK inhibitors that are being clinically evaluated (shown in the table below). As shown in the table, the compounds are active against the wild-type NTRK, but are markedly less active against the G595R mutant form of the NTRK fusion.

| Compound | NTRK wt Enzyme Assay $IC_{50}$ (nM) | NTRK wt Cellular $GI_{50}$ (nM) | NTRK G595R Cellular $GI_{50}$ (nM) |
|---|---|---|---|
| Entrectinib | 0.6 | 2 | 2700 |
| TSR-011 | 2.3 | 32 | 12000 |
| Crizotinib | 9.3 | 87 | 9000 |

The invention provides compounds that inhibit both wild-type NTRK and mutants thereof, including the G595R mutant. Furthermore, the inhibitors can be selective for wild-type NTRK, over other kinases, thus leading to reduced toxicities associated with inhibiting other kinases. Because of their activity against wild-type and mutant NTRK, the compounds described herein can be used to treat a patient with a condition associated with aberrant NTRK activity. They can also be used to treat various cancers. In some embodiments, the cancer is selected from non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, and spitzoid neoplasms.

The compounds can also be used to treat a patient who has developed resistance to a wild-type NTRK inhibitor, or a patient with a mutant form of NTRK, such as the G595R mutant. The method includes the step of administering a compound or composition of the invention that is active against the NTRK resistant mutant. By "active" is meant that a compound has an $IC_{50}$ of less than 1 μM, 500 nM, 250 nM, 100 nM, 75 nM, 50 nM, 25 nM, 10 nM, or 5 nM when measured in a biochemical assay, against at least one resistant mutant.

The compounds and compositions described herein can be administered alone or in combination with other compounds, including other NTRK-modulating compounds, or other therapeutic agents. In some embodiments, the compound or composition of the invention may be administered in combination with one or more compounds selected from Cabozantinib (COMETRIQ), Vandetanib (CALPRESA), Sorafenib (NEXAVAR), Sunitinib (SUTENT), Regorafenib (STAVARGA), Ponatinib (ICLUSIG), Bevacizumab (AVASTIN), Crizotinib (XALKORI), or Gefitinib (IRESSA). The compound or composition of the invention may be administered simultaneously or sequentially with the other therapeutic agent by the same or different routes of administration. The compound of the invention may be included in a single formulation with the other therapeutic agent or in separate formulations.

Synthesis

Compounds of the invention, including salts and N -oxides thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below. The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, (2006), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic

resonance (NMR) spectroscopy (*e.g.*, $^{1}H$ or $^{13}C$), infrared (IR) spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry (MS), or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).Analytical instruments and methods for compound characterization:

LC-MS: Unless otherwise indicated, all liquid chromatography-mass spectrometry (LC-MS) data (sample analyzed for purity and identity) were obtained with an Agilent model-1260 LC system using an Agilent model 6120 mass spectrometer utilizing ES-API ionization fitted with an Agilent Poroshel 120 (EC-C18, 2.7um particle size, 3.0 x 50mm dimensions) reverse-phase column at 22.4 degrees Celsius. The mobile phase consisted of a mixture of solvent 0.1% formic acid in water and 0.1% formic acid in acetonitrile. A constant gradient from 95% aqueous/5% organic to 5% aqueous/95% organic mobile phase over the course of 4 minutes was utilized. The flow rate was constant at 1mL/min.

Prep LC-MS: Preparative HPLC was performed on a Shimadzu Discovery VP® Preparative system fitted with a Luna 5u C18(2) 100A, AXIA packed, 250 x 21.2 mm reverse-phase column at 22.4 degrees Celsius. The mobile phase consisted of a mixture of solvent 0.1% formic acid in water and 0.1% formic acid in acetonitrile. A constant gradient from 95% aqueous/5% organic to 5% aqueous/95% organic mobile phase over the course of 25 minutes was utilized. The flow rate was constant at 20 mL/min. Reactions carried out in a microwave were done so in a Biotage Initiator microwave unit.

Chiral HPLC: Preparative HPLC to resolve chiral mixtures was performed on a Thar SFC Pre-80 instrument fitted with a Chiralpak AS-H column (5 mm, 3.0 cm id x 25 cm L). The mobile phases consisted of SFC $CO_2$ (A) and MeOH/0.1% $NH_4OH$ (B). A constant gradient from 67% to 33% (B) was maintained at a flow rate of 65 g/min, with a system back pressure of 100 bar. The separation progress was monitored by UV detection at a wavelength of 220 nm.

Silica gel chromatography: Silica gel chromatography was performed on either a Teledyne Isco CombiFlash® Rf unit or a Biotage® Isolera Four unit.

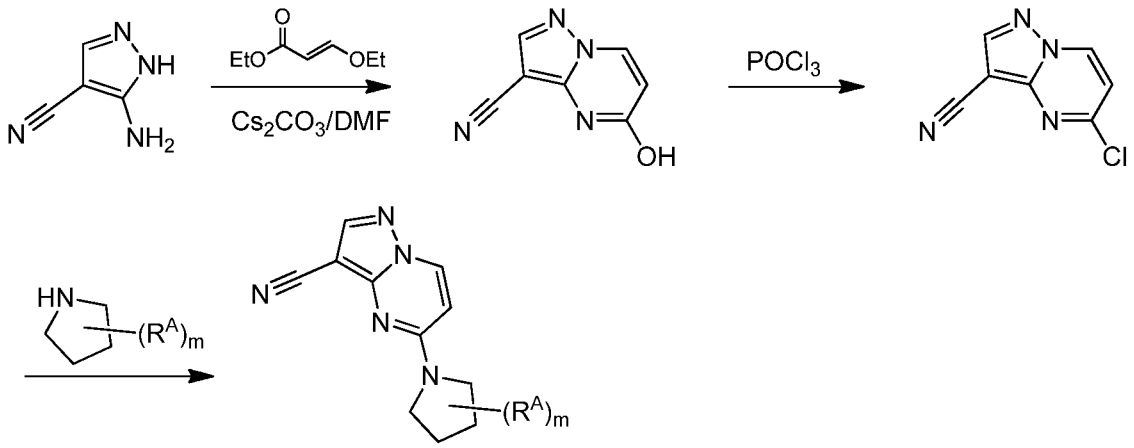
Proton NMR: Unless otherwise indicated, all $^{1}H$ NMR spectra were obtained with a Varian 400MHz Unity Inova 400 MHz NMR instrument (acquisition time = 3.5 seconds with a 1 second delay; 16 to 64 scans). Where characterized, all protons were reported in DMSO-$d_6$ solvent as parts-per million (ppm) with respect to residual DMSO (2.50 ppm).

## EXAMPLES

The following examples are intended to be illustrative, and are not meant in any way to be limiting.

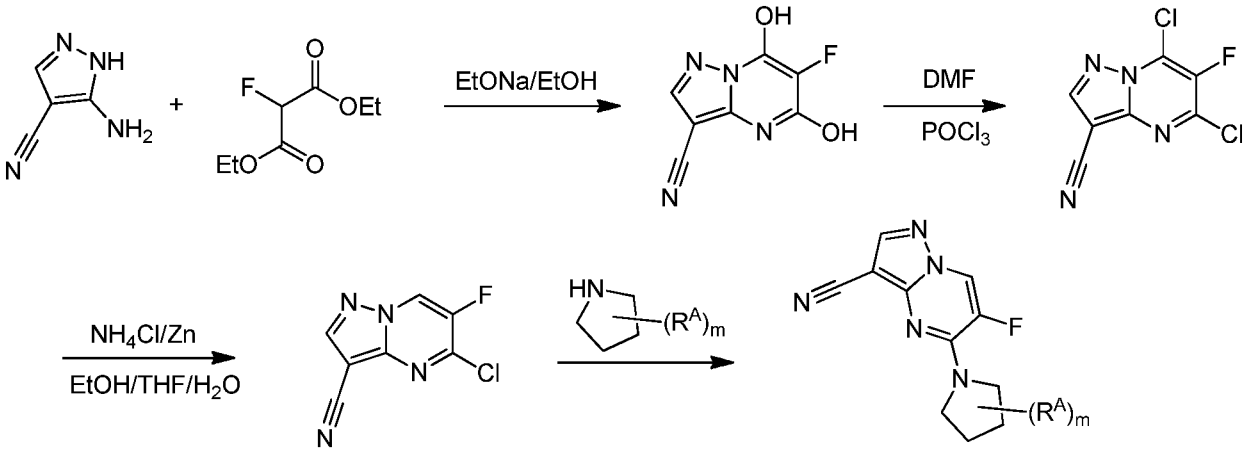
The below Schemes are meant to provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

Synthetic Protocol 1



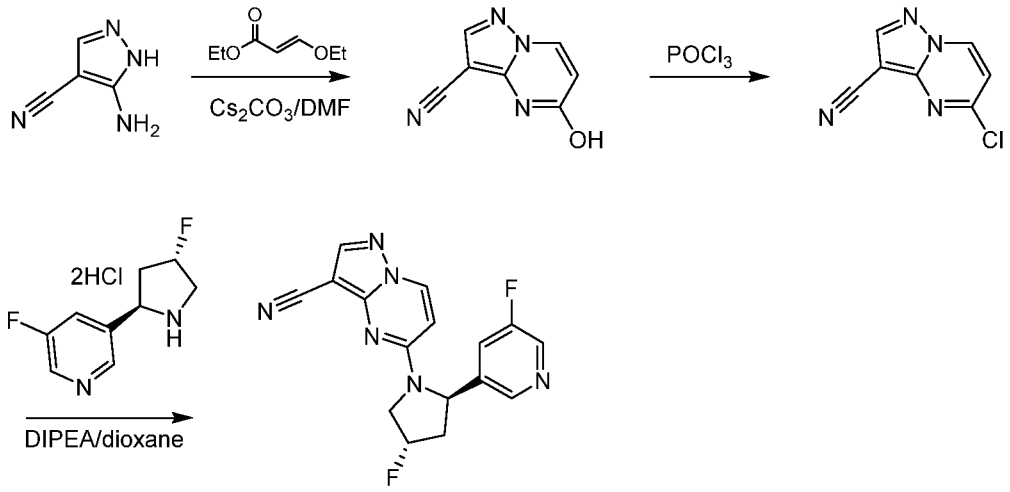

General synthetic protocol 1 involves formation of 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile via the cyclization of 5-amino-1H-pyrazole-4-carbonitrile and ethyl (E)-3-ethoxyacrylate or suitable equivalent, under thermal conditions in the presence of a base such as cesium carbonate. The hydroxyl group is converted to a leaving group such as chloride by reaction with phosphorous oxychloride. The chloro group is displaced by an amine in a solvent such as dioxane or n-butanol in the presence of a base such as DIPEA, or via Pd-catalyzed cross-coupling under, *e.g.*, Buchwald conditions, to give the desired products.

Synthetic Protocol 2

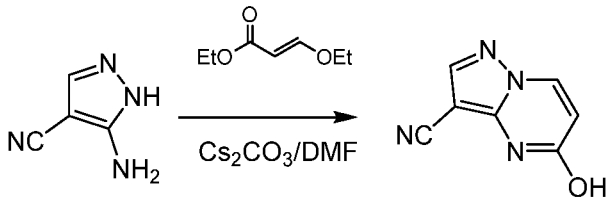



General synthetic protocol 2 involves formation of 6-fluoro-5,7-dihydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile via the cyclization of 5-amino-1H-pyrazole-4-carbonitrile and diethyl 2-fluoromalonate, or a suitable equivalent. The hydroxyl groups are converted to chlorides by reaction with phosphorous oxychloride. The 7-chloro group can be selectively reduced in the presence of the 5-chloro group in the presence of a reducting agent such as zinc. The remaining chloro group is displaced by an amine in a solvent such as dioxane or n-butanol in the presence of a base such as DIPEA, or via Pd-catalyzed cross-coupling under, *e.g.*, Buchwald conditions, to give the desired products.

**Example 1: 5-((2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 1)**

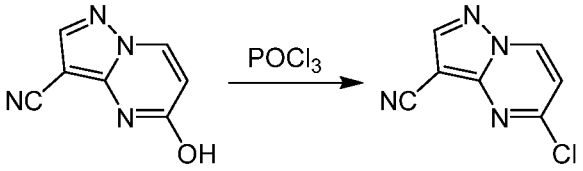


Step 1: Synthesis of 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile



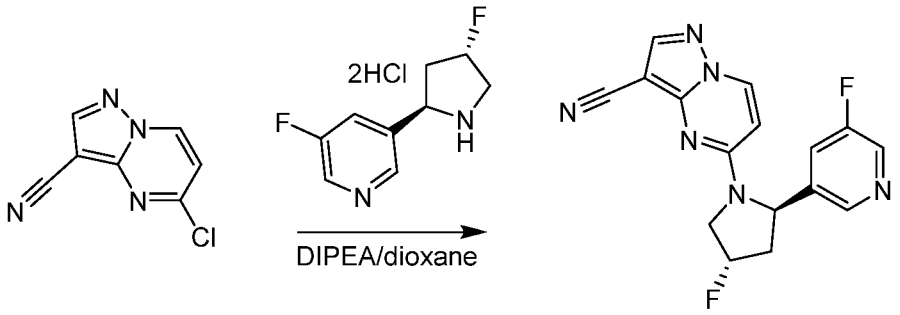

To a mixture of 5-amino-1H-pyrazole-4-carbonitrile (10.00 g, 92.51 mmol) in DMF (350.00 mL) was added ethyl (E)-3-ethoxyacrylate (13.34 g, 92.51 mmol) and $Cs_2CO_3$ (60.38 g, 185.02 mmol). The mixture was stirred at 100°C for 2 hrs. After LCMS showed the reaction was complete, the reaction mixture was cooled to 25°C, then added to water (300 mL), acidified by HCl (1 M) till pH = 4, then filtered. The filter cake was dried in vacuum to give 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile (10.00 g, yield: 67.51%) as a white solid.

Step 2: Synthesis of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile



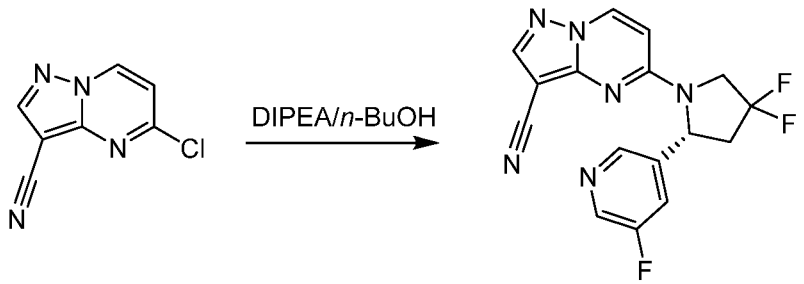

A mixture of 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile (10.00 g, 62.45 mmol) in $POCl_3$ (200.00 mL) was heated to 150°C for 4 hrs. After TLC (PE:EtOAc = 1:1) showed the reaction was complete, the mixture was concentrated to remove $POCl_3$, then dissolved in DCM (100 mL), concentrated and purified by column chromatography on silica gel (DCM) to give 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (6.00 g, yield: 53.80%) as a white solid.

Step 3: Synthesis of 5-((2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile



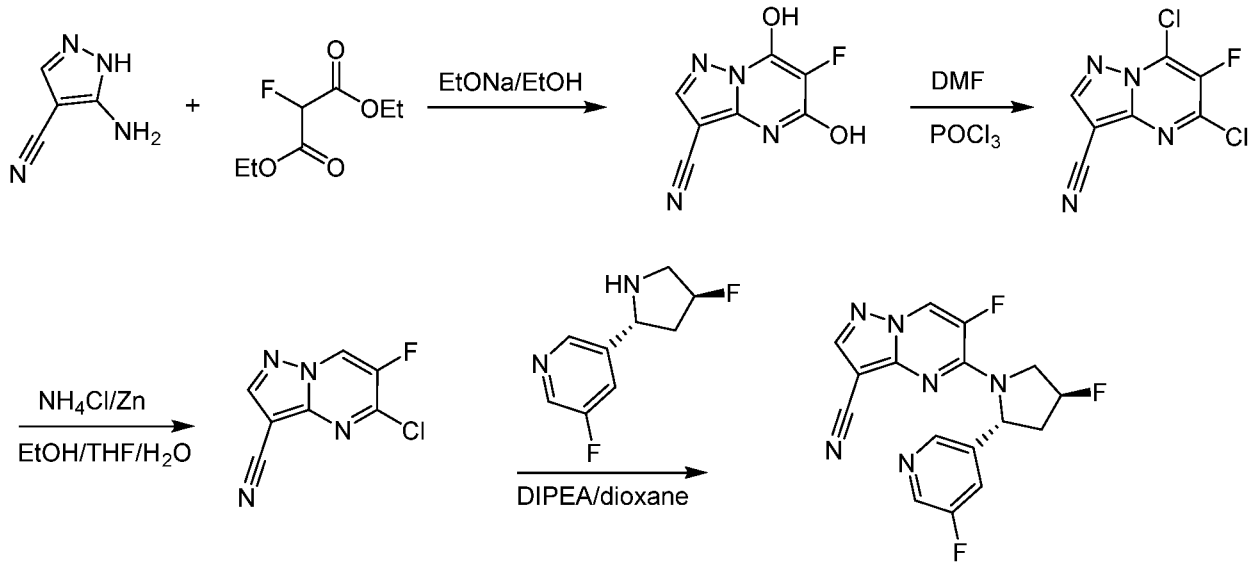

To a mixture of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (86.00 mg, 334.49 umol, 1.20 eq) and 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine HCl (49.78 mg, 278.74 umol, 1.00 eq) in dioxane (6.00 mL) was added DIPEA (108.07 mg, 836.23 umol, 3.00 eq) in one portion. The mixture was stirred at 130°C for 16 hrs. LCMS showed the reaction was complete. The reaction mixture was purified by acidic prep-HPLC to afford 5-((2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (90.60 mg, 163.43 umol, yield: 58.63%) as a yellow oil.

**Example 2: (R)-5-(4,4-difluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 3)**

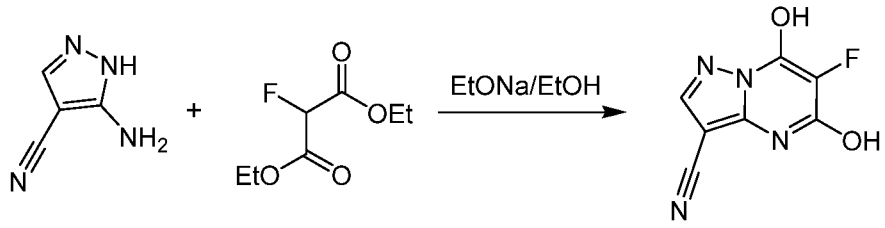



To a mixture of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (40.00 mg, 223.99 umol, 1.00 eq) and 3-[(2R)-4,4-difluoropyrrolidin-2-yl]-5-fluoro-pyridine (61.62 mg, 223.99 umol, 1.00 eq) in n-BuOH (2.00 mL) was added DIPEA (144.74 mg, 1.12 mmol, 5.00 eq). The resulting mixture was stirred at 100°C for 16 hrs. The mixture was concentrated and the crude product was purified by acidic prep-HPLC (TFA system). (R)-5-(4,4-difluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (48.70 mg, 85.09 umol, yield: 38%) was obtained as a brown solid.

**Example 3: 6-fluoro-5-((2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 4)**

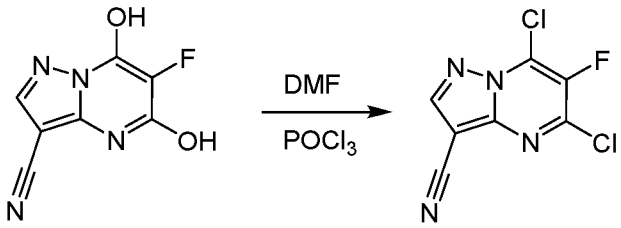



Step 1: 6-fluoro-5,7-dihydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile



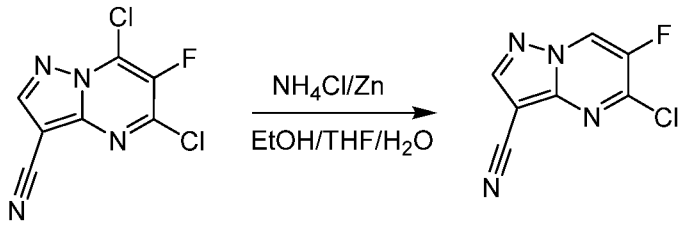

To the mixture of freshly prepared NaOEt (4.34 g, 63.83 mmol, 1.38 *eq*) in anhydrous EtOH (100.00 mL) was added 5-amino-1H-pyrazole-4-carbonitrile (5.00 g, 46.25 mmol, 1.00 *eq*) and diethyl 2-fluoromalonate (8.65 g, 48.56 mmol, 1.05 *eq*) at 20°C. The resulting mixture was heated to 120°C for 32 hrs. The mixture was concentrated to remove EtOH, and the resulting residue was dissolved in water (50 mL). The water layer was acidified by HCl (1 M) to pH = 2~3 and a white precipitate was generated. The solid was collected by filtration and dried *in vacuo* to give the crude 6-fluoro-5,7-dihydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile (4.00 g, yield: 44.54%) as a white solid. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 7.92 (s, 1H).

Step 2: 5,7-dichloro-6-fluoropyrazolo[1,5-a]pyrimidine-3-carbonitrile



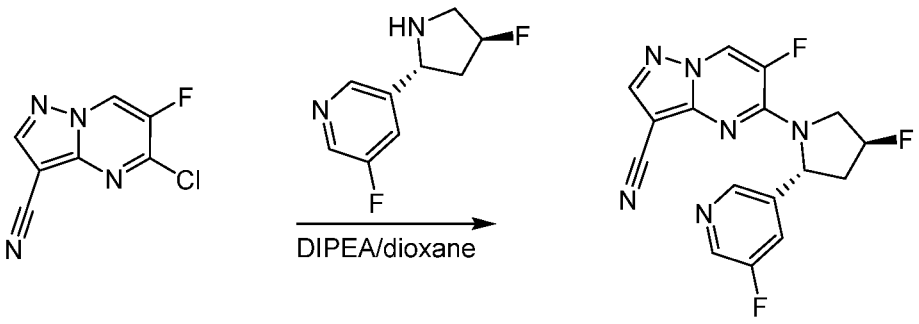

To a mixture of 6-fluoro-5,7-dihydroxypyrazolo[1,5-a]pyrimidine-3-carbonitrile (4.00 g, 20.61 mmol, 1.00 *eq*) in $POCl_3$ (80.00 mL) was added DMF (150.61 mg, 2.06 mmol, 158.53 uL, 0.10 *eq*), and the mixture was heated to 100°C for 16 hrs. The mixture was concentrated to give the crude product. The crude product was purified by flash column chromatography on silica gel (DCM) to give 5,7-dichloro-6-fluoropyrazolo[1,5-a]pyrimidine-3-carbonitrile (1.30 g, yield: 27.32%) as a yellow solid. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 8.48 (s, 1H).

Step 3: 5-chloro-6-fluoropyrazolo[1,5-a]pyrimidine-3-carbonitrile



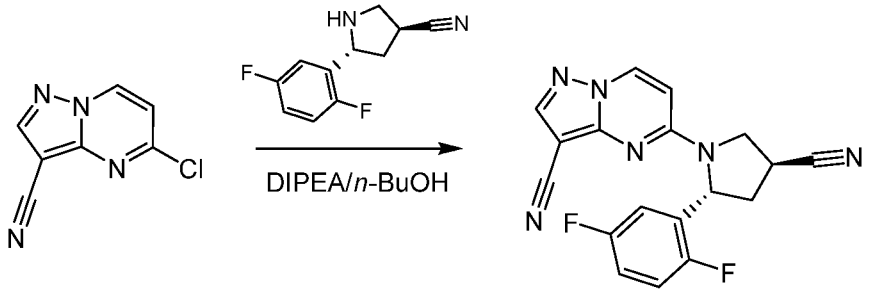

To a mixture of 5,7-dichloro-6-fluoropyrazolo[1,5-a]pyrimidine-3-carbonitrile (1.30 g, 5.63 mmol, 1.00 *eq*) in EtOH/THF/$H_2O$ (50.00 mL, V/V/V = 3/1/2) was added Zn powder (1.84 g, 28.14 mmol, 5.00 *eq*) and $NH_4Cl$ (1.20 g, 22.51 mmol, 786.96 uL, 4.00 *eq*). The mixture was stirred at 20°C for 0.1 hr. The mixture was concentrated to remove EtOH and THF. The mixture was extracted with EtOAc (10 mL*2), the organic layers were dried over $Na_2SO_4$, and concentrated to give 5-chloro-6-fluoropyrazolo[1,5-a]pyrimidine-3-carbonitrile (1.00 g, crude) as a yellow solid. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 8.75 (d, 1H, $J$ = 2.4 Hz), 8.40 (s, 1H).

Step 4: 6-fluoro-5-((2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile



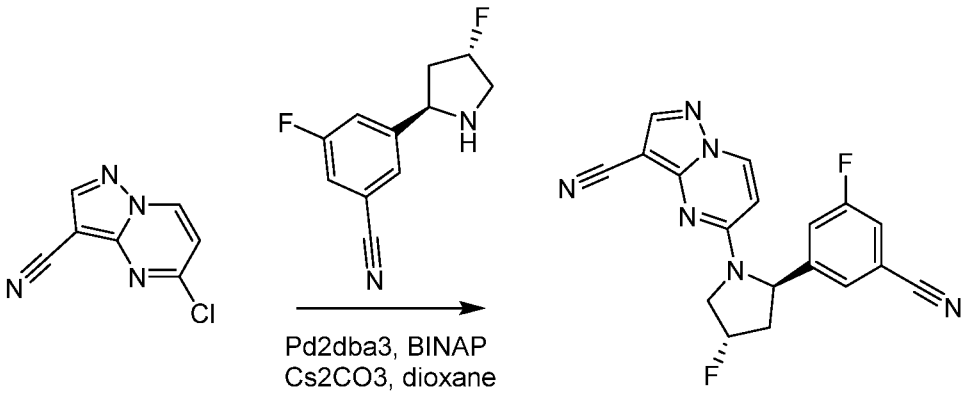

To a mixture of 5-chloro-6-fluoropyrazolo[1,5-a]pyrimidine-3-carbonitrile (200.50 mg, 1.02 mmol, 1.00 *eq*) in dioxane (5.00 mL) was added DIPEA (395.47 mg, 3.06 mmol, 3.00 *eq*) and 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine (187.87 mg, 1.02 mmol, 1.00 *eq*). The mixture was stirred at 100°C for 2 hrs. The mixture was concentrated to give the crude product. The crude product was purified by *prep*-HPLC (TFA system) to give 6-fluoro-5-((2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (163.30 mg, yield: 46.50%) as a yellow oil.

**Example 4: 5-((2R,4S)-4-cyano-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 5)**



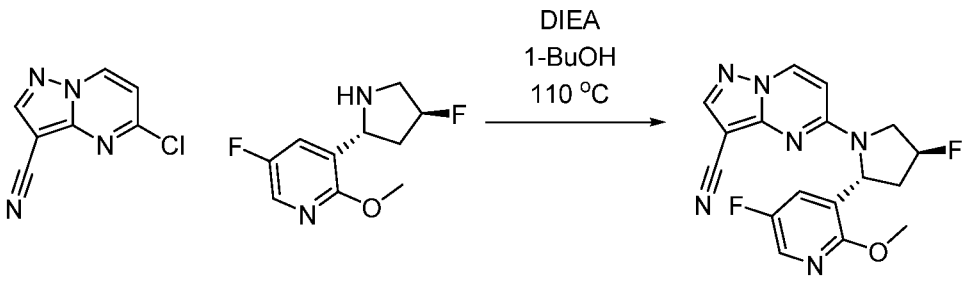

To a mixture of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (50.00 mg, 279.99 umol,) in n-BuOH (3.00 mL) was added DIPEA (72.37 mg, 559.98 umol) and (3S,5R)-5-(2,5-difluorophenyl)pyrrolidine-3-carbonitrile (58.30 mg, 279.99 umol). The mixture was stirred at 100°C for 16 hrs. LCMS showed the reaction was complete. The reaction mixture was concentrated to give the crude product. The crude product was purified by neutral prep-HPLC to give 5-((2R,4S)-4-cyano-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (10.60 mg, 30.26 umol, yield: 10.81%) as a white solid.

**Example 5: 5-((2R,4S)-2-(3-cyano-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 6)**




5-Chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (0.075 g, 0.420 mmol), 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzonitrile (0.096 g, 0.462 mmol) and Cs2CO3 (0.411 g, 1.260 mmol) were taken up in dioxane (2 ml). Pd2(dba)3 (0.038 g, 0.042 mmol) and BINAP (0.052 g, 0.084 mmol) were added and stirred at 110 °C for 4 hours. The solvent was removed *in vacuo*. The residue was purified via reverse phase chromatography (0-100% ACN/H2O) to give 5-((2R,4S)-2-(3-cyano-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (0.015 g, 0.043 mmol, 10.20 % yield) as a white foam.

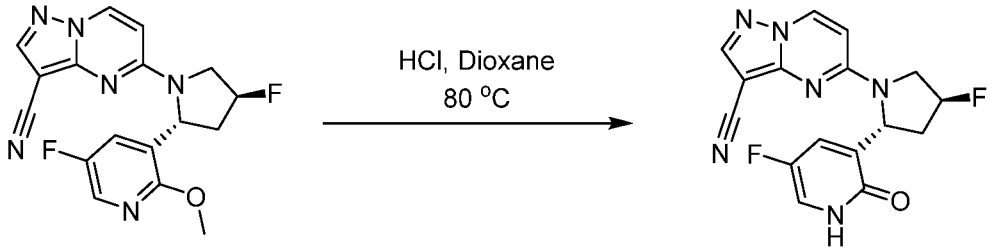
**Example 6: 5-((2R,4S)-4-fluoro-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 7)**




A mixture of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (88.5 mg, 0.50 mmol), 5-fluoro-3-((2R,4S)-4-fluoropyrrolidin-2-yl)-2-methoxypyridine hydrochloride (124 mg, 0.50 mmol) and DIEA (0.26 mL, 1.50 mmol) in n-butanol (2.5 mL) was heated in a microwave reactor at 110°C for 60 minutes. The mixture was concentrated to remove solvents and the residue was purified by

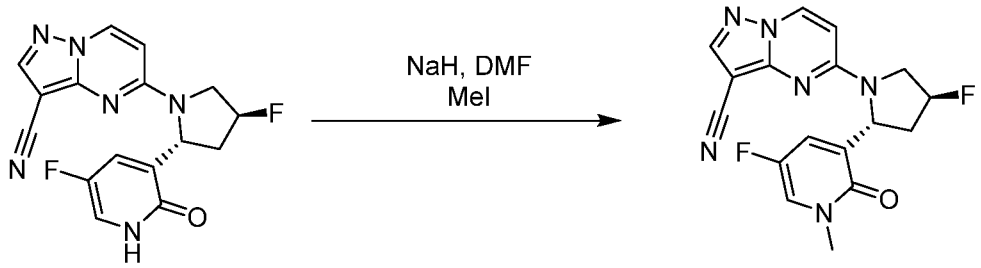
column chromatography on silica gel to give 5-((2R,4S)-4-fluoro-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile as a white solid (168 mg, yield: 95%).

**Example 7: 5-((2R,4S)-4-fluoro-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 8)**




Step 1: 5-((2R,4S)-4-fluoro-2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile

A mixture of 5-((2R,4S)-4-fluoro-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (110 mg, 0.31 mmol) and HCl in dioxane (4M, 0.4 mL, 1.50 mmol) in dioxane (1.2 mL) was heated at 85°C for 8 hours. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated to give the crude product which was carried over to the next step without further purification. To a solution of 5-((2R,4S)-4-fluoro-2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (100 mg, 0.29 mmol) in DMF (1.5 mL) at 0 °C was added NaH (60% dispersion, 14 mg, 0.35 mmol) and the solution was warmed at room temperature for 15 minutes. The reaction mixture was cooled again to 0 °C, added MeI (0.022 mL, 0.35 mmol) and warmed to room temperature overnight. LCMS showed that the starting material was consumed. The mixture was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with water (3x), dried over $Na_2SO_4$ and concentrated to give the crude product which was purified by column chromatography on silica gel to give 5-((2R,4S)-4-fluoro-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile as a white solid (86 mg, yield: 83%).

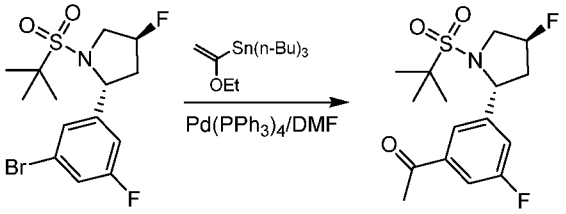



Step 2: Synthesis of 5-((2R,4S)-4-fluoro-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile

To a solution of 5-((2R,4S)-4-fluoro-2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (100 mg, 0.29 mmol) in DMF (1.5 mL) at 0 °C was added NaH (60% dispersion, 14 mg, 0.35 mmol) and the solution was warmed at room temperature for 15 minutes. The reaction mixture was cooled again to 0 °C, added MeI (0.022 mL, 0.35 mmol) and warmed to room temperature overnight. LCMS showed that the starting material was consumed. The mixture was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with water (3x), dried over $Na_2SO_4$ and concentrated to give the crude product which was purified by column chromatography on silica gel to give 5-((2R,4S)-4-fluoro-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile as a white solid (86 mg, yield: 83%).

**Example 8: 5-((2R,4S)-4-fluoro-2-(3-fluoro-5-(2-hydroxypropan-2-yl)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (Compound 14)**

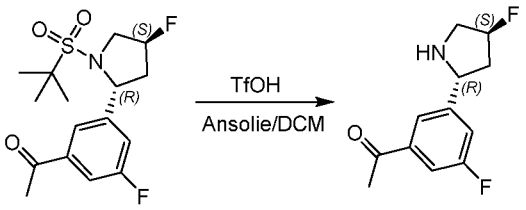
Step 1: 1-(3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5-fluorophenyl) ethan-1-one




To a mixture of (2R,4S)-2-(3-bromo-5-fluorophenyl)-1-(tert-butylsulfonyl)-4-fluoropyrrolidine (200.00 mg, 523.20 umol, 1.00 *eq*) in toluene (5.00 mL) was added $Pd(PPh_3)_4$ (60.46 mg, 52.32 umol, 0.10 *eq*) and tributyl(1-ethoxyvinyl)stannane (226.74 mg, 627.84 umol,

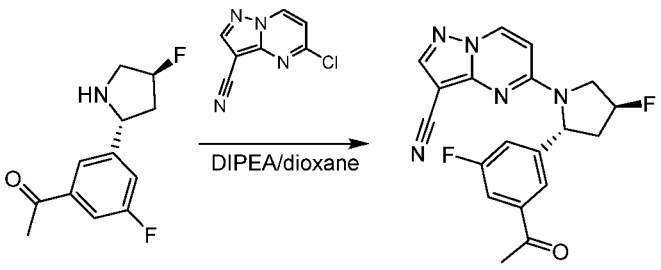
211.91 uL, 1.20 *eq*). The mixture was stirred at 110°C for 16 hrs under $N_2$. The mixture was concentrated to give the crude product. The crude product was purified by *prep*-TLC (PE:EtOAc = 3:1) to give 1-(3-((2R,4S)-1-(tert-butylsulfonyl)-4- fluoropyrrolidin-2-yl)-5-fluorophenyl)ethan-1-one (150.00 mg, 434.28 umol, yield: 83.00%) as a yellow oil.

Step 2: 1-(3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)phenyl)ethan-1-one




To a mixture of TfOH (195.53 mg, 1.30 mmol, 115.02 uL, 3.00 *eq*) in DCM (5.00 mL) was added anisole (70.44 mg, 651.42 umol, 70.44 uL, 1.50 *eq*) at -40°C. Then a solution of 1-(3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5-fluorophenyl)ethan-1-one (150.00 mg, 434.28 umol, 1.00 *eq*) in DCM (5.00 mL) was added to the above solution. After addition, the mixture was stirred at 25°C for 2 hrs. TLC (PE:EtOAc = 3:1) showed the reaction was complete. Saturated *aq*. $K_2CO_3$ (3 mL) was added to the mixture, which was then extracted with DCM (3 mL * 2). The organic layer was concentrated to give 1-(3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)phenyl)ethan-1-one (100.00 mg, crude) as a yellow oil.

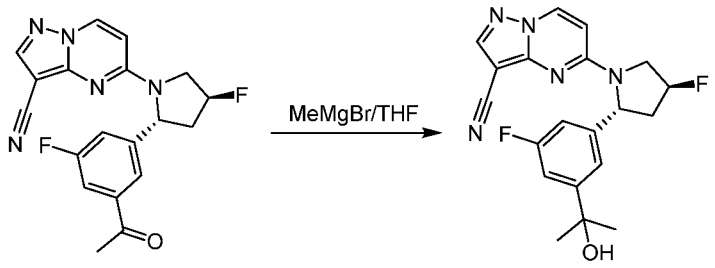
Step 3: 5-((2R,4S)-2-(3-acetyl-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo[1,5-a] pyrimidine-3-carbonitrile




To a mixture of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (80.00 mg, 447.98 umol, 1.00 *eq*) in dioxane (5.00 mL) was added DIPEA (173.69 mg, 1.34 mmol, 234.72 uL, 3.00 *eq*) and 1-(3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)phenyl)ethan-1-one (99.89 mg, 443.50 umol, 0.99

*eq*). The mixture was stirred at 100°C for 2 hrs. LCMS showed the reaction was complete. The mixture was concentrated to give the crude product. The crude product was purified by *prep*-TLC (PE:EtOAc = 1:1) to give 5-((2R,4S)-2-(3-acetyl-5-fluorophenyl)- 4-fluoropyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (100.00 mg, 272.22 umol, yield: 60.77%) as a yellow oil.

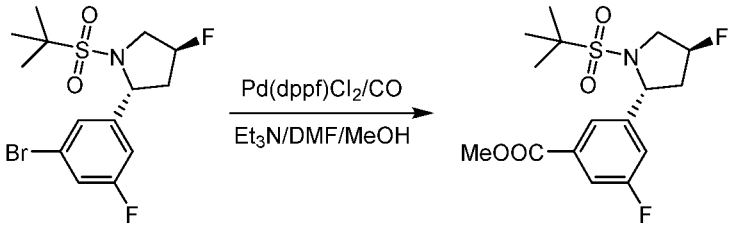
Step 4: 5-((2R,4S)-4-fluoro-2-(3-fluoro-5-(2-hydroxypropan-2-yl)phenyl)pyrrolidin- 1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile




To a mixture of 5-((2R,4S)-2-(3-acetyl-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo [1,5-a]pyrimidine-3-carbonitrile (50.00 mg, 136.11 umol, 1.00 *eq*) in THF (5.00 mL) was added dropwise MeMgBr (3 M, 136.11 uL, 3.00 *eq*) at -78°C. After addition, the mixture was stirred at 25°C for 16 hrs. HPLC showed the starting material was about 60% consumed. The mixture was added to MeOH (2 mL) and then concentrated to give the crude product. The crude product was purified by *prep*-HPLC (TFA) to give 5-((2R,4S)-4-fluoro- 2-(3-fluoro-5-(2-hydroxypropan-2-yl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (14.00 mg, 36.52 umol, yield: 26.83%) as a white solid. $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.35 (br.s, 1H), 8.11 (s, 1H), 7.28 (s, 1H), 7.10 (d, 1H, $J$ = 8.0 Hz), 6.91 (d, 1H, $J$ = 8.8 Hz), 6.17 (br.s, 1H), 5.42 (d, 1H, $J$ = 52.4 Hz), 5.23 (br.s, 1H), 4.16-4.08 (m, 1H), 2.91 (br.s, 1H), 2.31-2.17 (m, 1H), 1.47 (d, 6H, $J$ = 3.6 Hz). MS Calcd.: 383.4, MS Found: 384.1, 406.0 ($[M+1]^+$ and $[M+23]^+$).

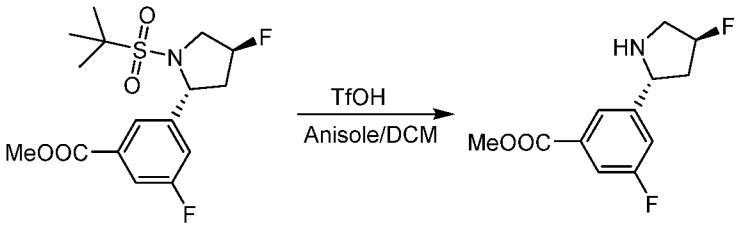
**Example 9: 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin- 2-yl)-5-fluoro-N-methylbenzamide (Compound 20)**

Step 1: Methyl 3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5-fluorobenzoate



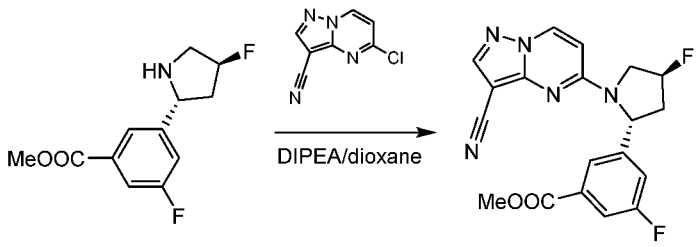

To a mixture of (2R,4S)-2-(3-bromo-5-fluorophenyl)-1-(tert-butylsulfonyl)- 4-fluoropyrrolidine (2.00 g, 5.23 mmol, 1.00 *eq*) in MeOH (10.00 mL) was added $Et_3N$ (1.59 g, 15.70 mmol, 3.00 *eq*), $Pd(dppf)Cl_2$ (191.41 mg, 261.60 umol, 0.05 *eq*). The mixture was stirred at 70°C for 16 hrs under CO (50 Psi). The mixture was filtered and the filtrate was concentrated to give the crude product. The crude product was purified by column chromatography on silica gel (PE:EtOAc = 15:1-8:1) to give methyl 3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5-fluorobenzoate (1.20 g, 3.32 mmol, yield: 63.46%) as a red solid.

Step 2: Methyl 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzoate



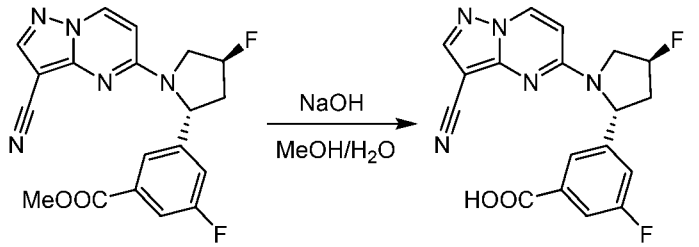

To a mixture of TfOH (1.37 g, 9.12 mmol, 3.00 *eq*) in DCM (50.00 mL) was added anisole (493.12 mg, 4.56 mmol, 1.50 *eq*) at -40°C. Then a solution of methyl 3-((2R,4S)-1- (tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5-fluorobenzoate (1.10 g, 3.04 mmol, 1.00 *eq*) in DCM (30.00 mL) was added dropwise to the mixture at -40°C over 0.1 hr. After addition, the mixture was warmed to 0°C and stirred at 0°C for 1 hr. The mixture was added to $K_2CO_3$ (*aq.* 10 mL) and stirred for 0.1 hr. The mixture was extracted with DCM (10 mL * 2). The organic layer was concentrated and then HCl/EtOAc (10 mL, 4 M) was added. The resulting mixture was stirred at 20°C for 0.5 hr and filtered. The filter cake was dried in vacuum to give methyl 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzoate (550.00 mg, crude, HCl) as a yellow solid.

Step 3: Methyl 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4- fluoropyrrolidin-2-yl)-5-fluorobenzoate



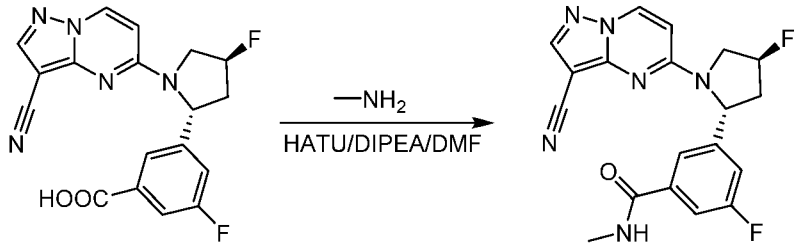

To a mixture of methyl 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzoate (400.00 mg, 2.24 mmol, 1.00 *eq*) in dioxane (50.00 mL) was added DIPEA (868.45 mg, 6.72 mmol, 3.00 *eq*) and 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (540.00 mg, 2.24 mmol, 1.00 *eq*). The mixture was stirred at 100°C for 16 hrs. The mixture was concentrated to give the crude product. The crude product was purified by column chromatography on silica gel (PE:EtOAc = 10:1-3:1) to give methyl 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)- 4-fluoropyrrolidin-2-yl)-5-fluorobenzoate (650.00 mg, 1.70 mmol, yield: 75.89%) as a yellow oil. $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.30-8.24 (m, 1H), 6.94-6.83 (m, 2H), 5.64 (t, 1H, $J$ = 9.2 Hz), 5.41 (d, 1H, $J$ = 52.0 Hz), 4.48-4.38 (m, 2H), 3.97 (s, 3H), 2.79-2.69 (m, 1H), 2.20-2.06 (m, 1H).

Step 4: 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2- yl)-5-fluorobenzoic acid




To a mixture of methyl 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2-yl)-5-fluorobenzoate (530.00 mg, 1.38 mmol, 1.00 *eq*) in MeOH/$H_2O$ (20.00 mL, v:v = 3:1) was added NaOH (110.40 mg, 2.76 mmol, 2.00 *eq*). The mixture was stirred at 20°C for 16 hrs. The mixture was concentrated to remove MeOH. To the water layer was added HCl (2 M) until the pH was below 7. The water layer was then extracted with EtOAc (3 mL * 3). The resulting organic layer was dried over $Na_2SO_4$ and concentrated to give 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin- 2-yl)-5- fluorobenzoic acid (400.00 mg, 1.08 mmol, yield: 78.48%) as a white solid.

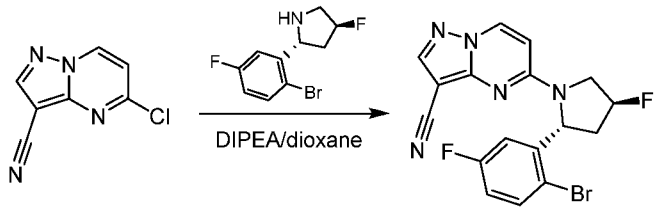
Step 5: 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2-yl)- 5-fluoro-N-methylbenzamide




To a mixture of 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4- fluoropyrrolidin-2-yl)-5-fluorobenzoic acid (80.00 mg, 216.61 umol, 1.00 *eq*) in DMF (2.00 mL) was added DIPEA (83.99 mg, 649.84 umol, 113.49 uL, 3.00 *eq*), HATU (98.84 mg, 259.94 umol, 1.20 *eq*) and methanamine (17.55 mg, 259.93 umol, 1.20 *eq*, HCl). The mixture was stirred at 20°C for 1 hr. LCMS showed the reaction was complete. The mixture was then concentrated to give the crude product. The crude product was purified by *prep*-HPLC (TFA) to give 3-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4- fluoropyrrolidin-2-yl)-5-fluoro-N-methylbenzamide (50.70 mg, 102.14 umol, yield: 47.15%, TFA) as a brown oil.

**Example 10: 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin- 2-yl)-4-fluorobenzamide (Compound 22)**

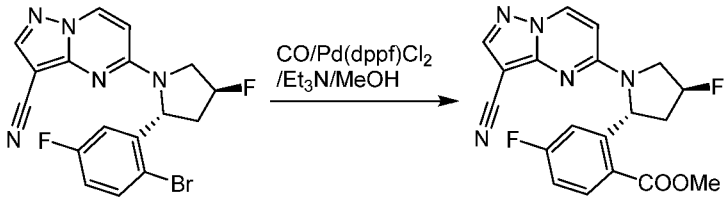
Step 1: 5-((2R,4S)-2-(2-bromo-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo [1,5-a]pyrimidine-3-carbonitrile




A mixture of 5-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (500.00 mg, 2.33 mmol, 1.00 *eq*, HCl), (2R,4S)-2-(2-bromo-5-fluoro-phenyl)-4-fluoro-pyrrolidine (694.17 mg, 2.33 mmol, 1.00 *eq*, HCl), DIPEA (751.26 mg, 5.81 mmol, 1.02 mL, 2.50 *eq*) in dioxane (8.00 mL) was stirred at 80°C for 16 hrs. TLC (PE:EtOAc = 3:1) showed the reaction was complete. To the mixture was

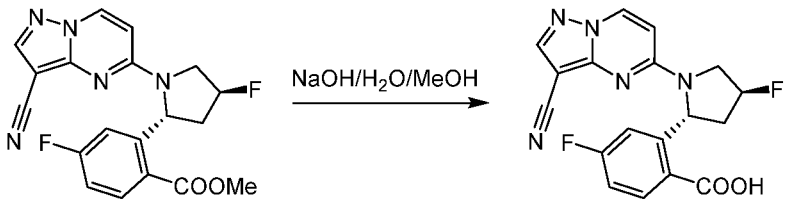
added $H_2O$ (10 mL), and then the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over $Na_2SO_4$, concentrated in vacuum to get 5-((2R,4S)-2-(2-bromo-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (1.00 g, crude) as a yellow oil.

Step 2: Methyl 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin -2-yl)-4-fluorobenzoate




A mixture of 5-((2R,4S)-2-(2-bromo-5-fluorophenyl)-4-fluoropyrrolidin-1-yl)pyrazolo[1,5-a] pyrimidine-3-carbonitrile (900.00 mg, 2.23 mmol, 1.00 *eq*), $Pd(dppf)Cl_2$ (326.34 mg, 446.00 umol, 0.20 *eq*), $Et_3N$ (676.96 mg, 6.69 mmol, 927.34 uL, 3.00 *eq*) in MeOH (10.00 mL) was degassed and purged with CO 3 times. Then the mixture was stirred at 70°C for 120 hrs under CO (50 psi) atmosphere. LCMS showed most of the starting material was consumed. The mixture was then filtered, and the filtrate was concentrated under vacuum to yield methyl 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin- 2-yl)-4-fluorobenzoate (700.00 mg, crude) as a yellow solid.

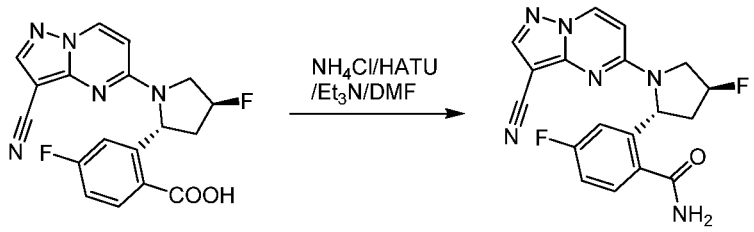
Step 3: 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2-yl)- 4-fluorobenzoic acid




A mixture of methyl 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2-yl)-4-fluorobenzoate (700.00 mg, 1.83 mmol, 1.00 *eq*), NaOH (146.08 mg, 3.65 mmol, 2.00 *eq*) in MeOH (5.00 mL) and $H_2O$ (5.00 mL) was stirred at 25°C for 16 hrs. LCMS

showed the reaction was complete. MeOH was removed under vacuum and then diluted HCl (1 M) was added to the mixture until pH = 6 causing a yellow precipitate to form. The precipitate was collected and dried under vacuum to yield 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2-yl)- 4-fluorobenzoic acid (280.00 mg, 758.15 umol, yield: 41.43%) as a yellow solid.

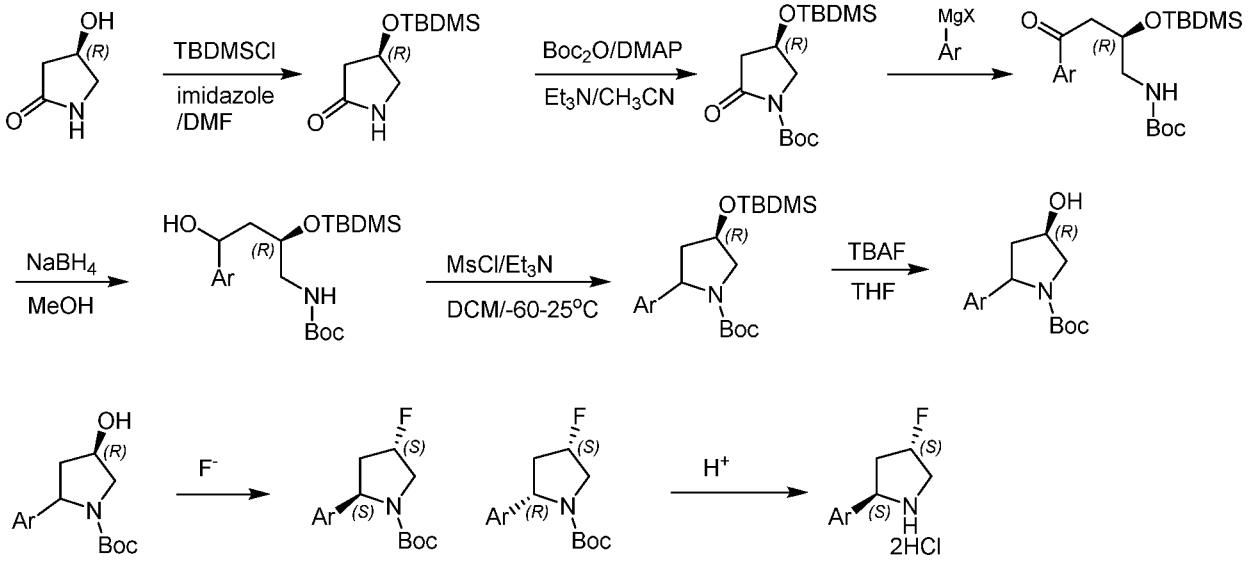
Step 4: 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin-2-yl)- 4-fluorobenzamide




A mixture of 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin-5-yl)-4-fluoropyrrolidin- 2-yl)-4-fluorobenzoic acid (100.00 mg, 270.77 umol, 1.00 *eq*), $NH_4Cl$ (43.45 mg, 812.31 umol, 28.40 uL, 3.00 *eq*), HATU (113.25 mg, 297.85 umol, 1.10 *eq*) and $Et_3N$ (82.20 mg, 812.31 umol, 112.60 uL, 3.00 *eq*) in DMF (2.00 mL) was stirred at 25°C for 16 hrs. LCMS showed the reaction was complete. The mixture was then concentrated under vacuum and purified by *prep*-HPLC (TFA) to produce 2-((2R,4S)-1-(3-cyanopyrazolo[1,5-a]pyrimidin- 5-yl)-4-fluoropyrrolidin-2-yl)-4-fluorobenzamide (26.70 mg, 72.49 umol, yield: 26.77%) as a yellow oil.

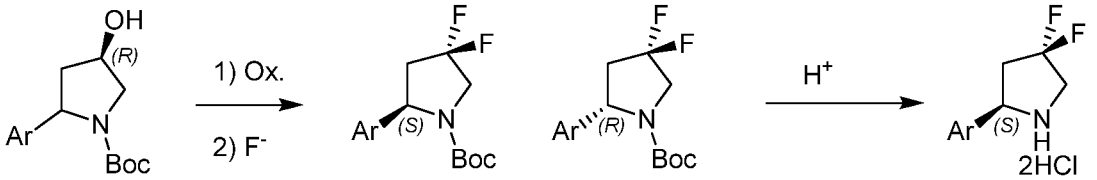
**Example 11: Synthesis of Intermediates**

4-fluoro-2-arylpyrrolidine



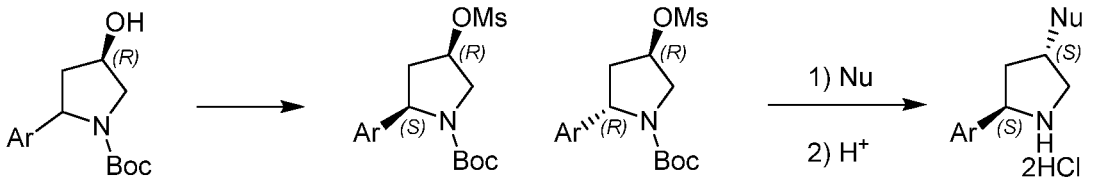

The general synthesis of 4-fluoro-2-arylpyrrolidine is shown above. (R)-4-Hydroxypyrrolidin-2-one is protected with a silyl group such as TBS while the lactam is protected with a suitable protecting group such as Boc. A nucleophilic Grignard reagent opens the lactam to give the di-protected 4-amino-3-hydroxy-1-phenylbutan-1-one. The ketone is reduced to the secondary alcohol with a reducing reagent such as sodium borohydride. Conversion of the alcohol to a leaving group, for example by forming the mesylate, leads to ring closure giving di-protected 4-fluoro-2-hydroxypyrrolidines. Alcohol deprotection with a fluoride source or acid followed by reaction with nucleophilic fluorine such as DAST or BAST gives the fluoro pyrrolidine, which can be deprotected under acid conditions, such as with TBAF, to provide the desired 4-fluoro-2-arylpyrrolidines.

(R)-4,4-Difluoro-2-phenylpyrrolidines

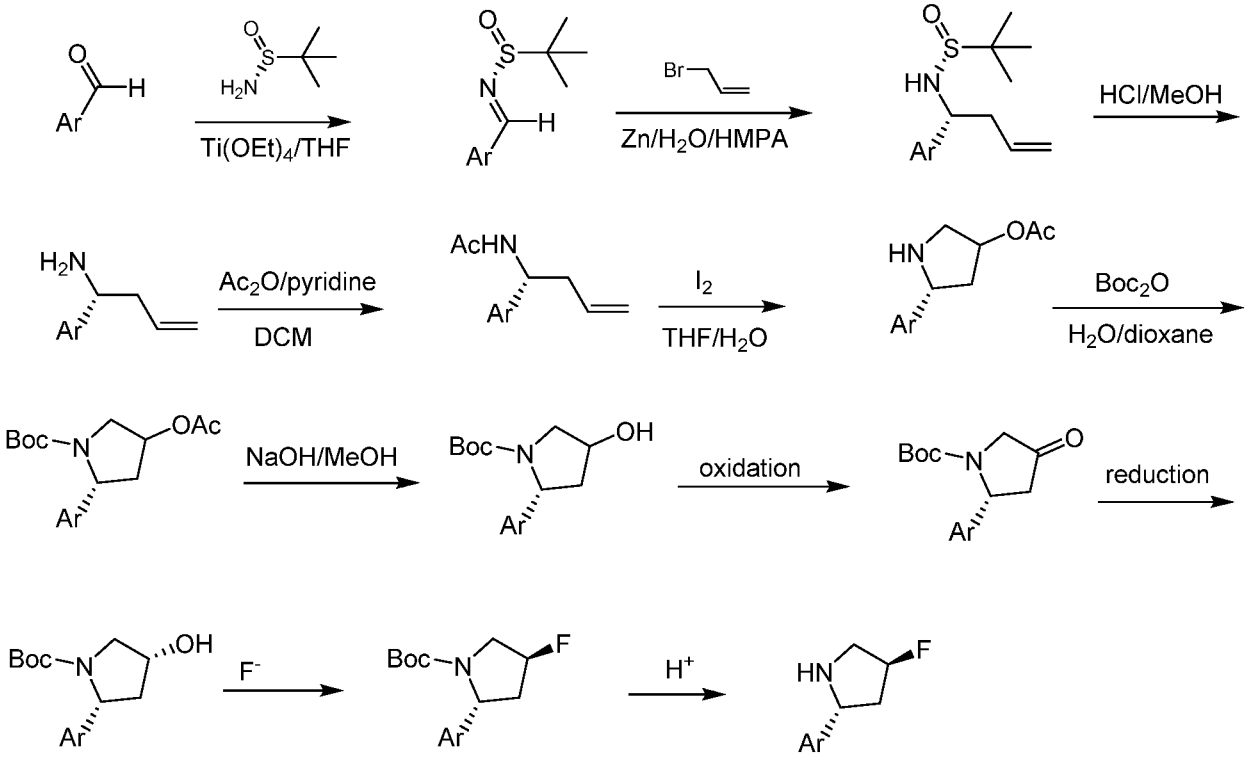



(R)-4,4-Difluoro-2-phenylpyrrolidines are prepared as shown above from tert-butyl (4R)-4-hydroxy-2-phenylpyrrolidine-1-carboxylate via oxidation of the secondary alcohol to a ketone with

an oxidating reagent, such as TEMPO or Dess-Martin periodinane, followed by fluorination with a reagent such as DAST. Acidic deprotection of the Boc group provides the desired aryl pyrrolidine.



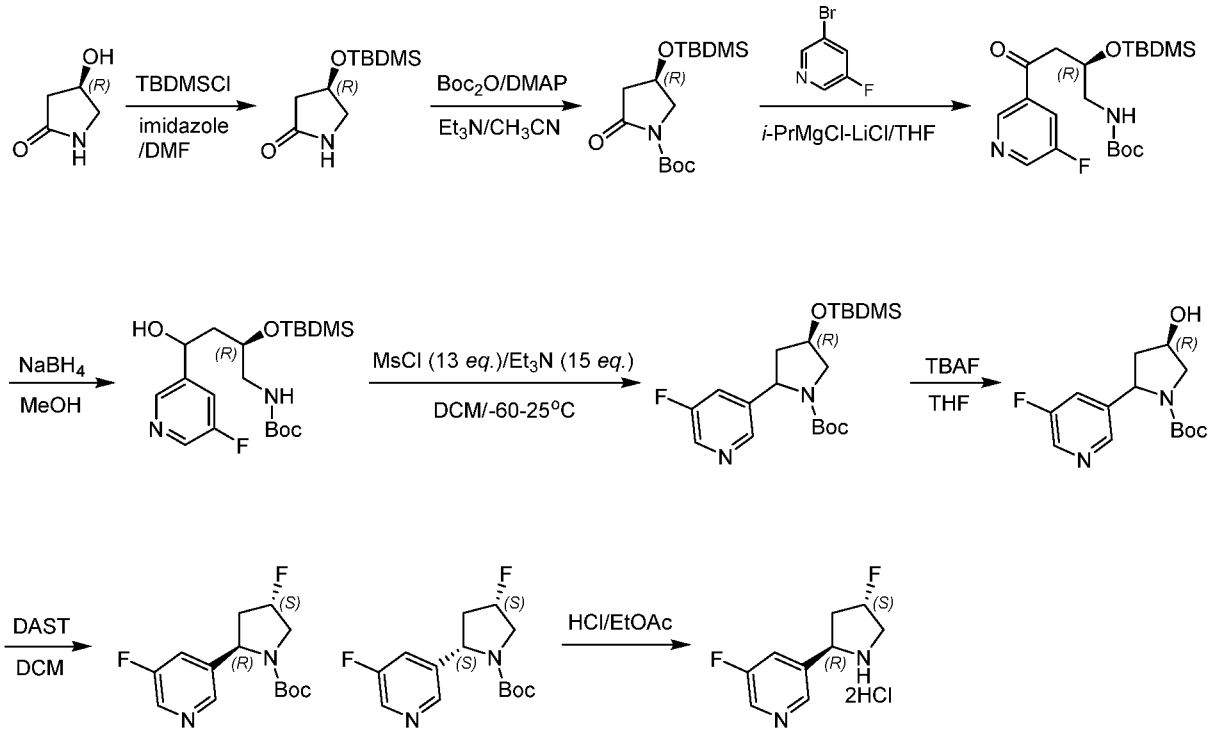

4-substituted 2-aryl pyrrolidines can also be obtained by nucleophilic displacement of the secondary mesylate which can arise from mesylation of tert-butyl (4R)-4-hydroxy-2-phenylpyrrolidine-1-carboxylate. Acidic deprotection of the Boc group provides the desired aryl pyrrolidines.



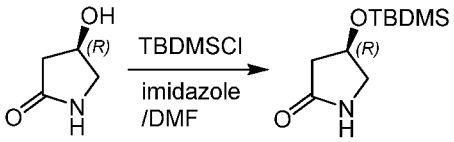

An additional method for preparing 4-fluoro-2-arylpyrrolidines involves formation of sulfinamides from benzaldehydes, which are stereoselectively reacted with allyl nucleophiles, such as allylzinc or allyl Grignard reagents. Conversion to the free amine under acidic conditions followed by acetylation and ring closure with iodine provides 2-aryl pyrrolidines. Protection of the

amine with a group such as Boc, deprotection of the acetate and oxidation with a reagent such as TEMPO or Dess-Martin periodinane provides the ketone which can be selectively reduced to the secondary alcohol with sodium borohydride. Fluorination followed by amine deprotection provides the desired aryl pyrrolidines.

3-Fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine



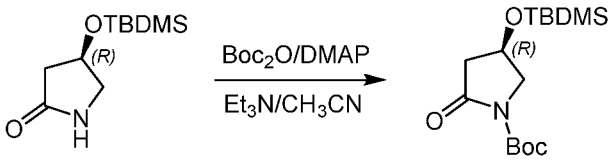

Step 1: (R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-one




To a mixture of (R)-4-hydroxypyrrolidin-2-one (9.0 g, 89.1 mmol) in DMF (50 mL) was added imidazole (9.09 g, 134 mmol) and TBDMSCl (14.1 g, 93.6 mmol) in one portion at 0°C. The reaction mixture was stirred at 25 °C for 3 hrs. TLC (DCM/MeOH = 10/1, $R_f$ = 0.8) showed the reaction was complete, then water (200 mL) was added and the resulting precipitate was collected by filtration and dried *in vacuo* to give (R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-one (15.5 g, yield: 80.7%) as a white solid. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 5.90 (br.s, 1H), 4.55-4.53 (m,

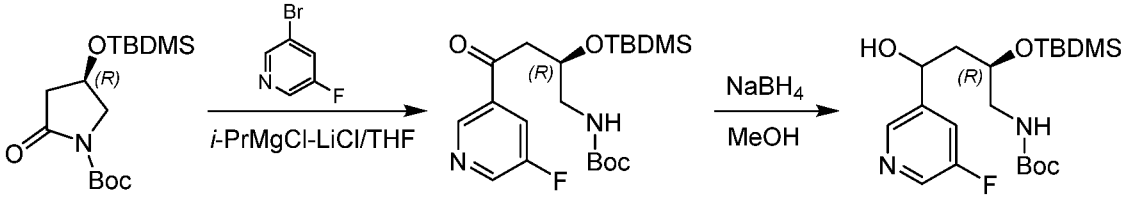
1H), 3.60-3.56 (m, 1H), 3.24-3.21 (m, 1H), 2.56-2.50 (m, 1H), 2.28-2.23 (m, 1H), 0.87-0.85 (m, 9H), 0.06-0.00 (m, 6H).

Step 2: tert-butyl (R)-4-((tert-butyldimethylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate




To the mixture of (R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-one (15.5 g, 72.0 mmol) in $CH_3CN$ (150 mL) was added $Et_3N$ (8.72 g, 86.4 mmol), DMAP (4.39 g, 36 mmol), and $Boc_2O$ (20.4 g, 93.7 mmol) in one portion at 0 °C. The reaction mixture was stirred at 25 °C for 10 hrs. TLC (PE/EtOAc = 3/1) showed the reaction was complete, then water (600 mL) was added, and the resulting precipitate was collected by filtration and dried *in vacuo* to give tert-butyl (R)-4-((tert-butyldimethylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate (19.2 g, yield: 84.6%) as a pink solid. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 4.33-4.30 (m, 1H), 3.81-3.77 (m, 1H), 3.56-3.54 (m, 1H), 2.67-2.61 (m, 1H), 2.41-2.37 (m, 1H), 1.46 (s, 9H), 0.80 (s, 9H), 0.00 (s, 6H).

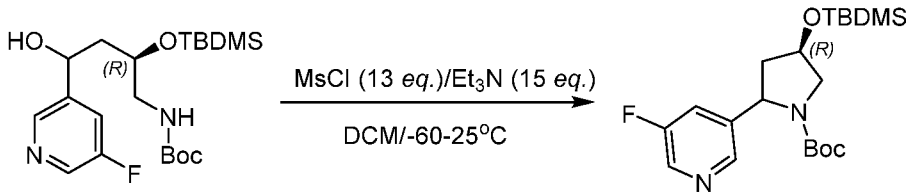
Step 3: tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-fluoropyridin-3-yl)-4-hydroxybutyl)carbamate




To the mixture of 3-bromo-5-fluoro-pyridine (3.35 g, 19.02 mmol, 1.20 *eq*) in THF (40.00 mL) was added *i*-PrMgCl-LiCl (1.3 M, 17.56 mL, 1.44 *eq*) dropwise at 0 °C over 30 minutes (exothermic). After addition, the temperature was raised to 25 °C over 1 hr and stirred at 25 °C for 30 mins. TLC (PE/EtOAc =10/1) showed a new spot was generated indicating that the Mg reagent was prepared successfully. Tert-butyl (R)-4-((tert-butyldimethylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate (5.00 g, 15.85 mmol, 1.00 *eq*) in THF (50 mL) was then added dropwise to the solution at -78°C over 30 mins. The mixture was allowed to warm to 25°C over 1 hr, then stirred at 25 °C

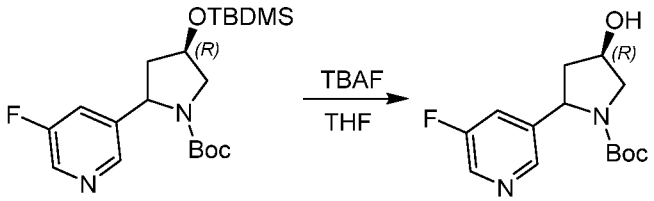
for 16 hrs. TLC (PE/EtOAc = 3/1) showed the starting material was consumed completely and the desired product, tert-butyl (R)-(2-((tert-butyldimethylsilyl)oxy)-4-(5-fluoropyridin-3-yl)-4-oxobutyl)carbamate, was detected. The reaction mixture was quenched by addition of MeOH (50 mL) at 0 °C. $NaBH_4$ (1.20 g, 31.70 mmol, 2.00 *eq*) was added at 0 °C, then the mixture was stirred at 25 °C for 4 hrs. TLC (PE/EtOAc = 2/1) and LCMS showed the reaction was complete. The combined reaction mixture (4 parallel reactions) was quenched by aqueous $NH_4Cl$ (400 mL) and extracted with EtOAc (600 mL*3). The combined organics were dried over $Na_2SO_4$ and concentrated *in vacuo*, and the residue was purified by HPLC to give tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-fluoropyridin-3-yl)-4-hydroxybutyl)carbamate (1.24 g, yield: 18.91%) as a yellow oil. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 8.26-8.22 (m, 2H), 7.37 (d, 1H, $J$ = 8.8 Hz), 4.95-4.88 (m, 2H), 4.69 (br.s, 1H), 4.00-3.98 (m, 2H), 3.23-3.10 (m, 2H), 1.73 (br.s, 2H), 1.32 (s, 9H), 0.80-0.79 (m, 9H), 0.00 (s, 6H).

Step 4: tert-butyl (4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate



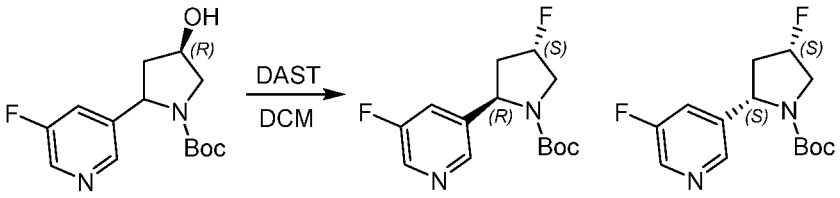

To a mixture of tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-fluoropyridin-3-yl)-4-hydroxybutyl)carbamate (8.70 g, 20.98 mmol, 1.00 *eq*) and $Et_3N$ (31.84 g, 314.70 mmol, 15.00 *eq*) in DCM (500.00 mL) was added dropwise MsCl (31.24 g, 272.74 mmol, 13.00 *eq*) at -60°C over 0.5 hr. The mixture was then stirred at -60 °C for 1 hr, and the reaction mixture was allowed to warm to 25 °C and stirred for 18 hrs. LCMS showed the starting material was consumed completely. The mixture was then washed with $H_2O$ (200 mL*3), and the aqueous phase was extracted with DCM (200 mL*4). The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo* to give crude product tert-butyl (4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (8.30 g, crude) as a black/ brown oil, which was used directly without purification.

Step 5: tert-butyl (4R)-2-(5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate




To the mixture of tert-butyl (4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (8.30 g, 20.93 mmol, 1.00 *eq*) in THF (250.00 mL) was added TBAF (9.43 g, 41.86 mmol, 2.00 *eq*) at 25°C. The mixture was stirred at 25 °C for 16 hrs. After TLC (PE/EtOAc = 1/1) showed the reaction was complete, the mixture was concentrated and the residue was dissolved in EtOAc (600 mL), washed with water (200 mL*5), dried over $Na_2SO_4$, and concentrated. The crude product was purified by HPLC to give tert-butyl (4R)-2-(5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (4.70 g, 16.65 mmol, yield: 79.54%) as a brown black oil. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 8.37-8.33 (m, 2H), 7.48 (br.s, 1H), 5.09-4.89 (m, 1H), 4.56-4.54 (m, 1H), 3.80-3.65 (m, 2H), 2.63-2.43 (m, 1H), 2.03-1.96 (m, 1H), 1.56-1.20 (m, 9H).

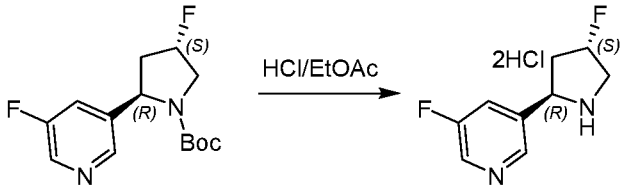
Step 6: tert-butyl (2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate




To a mixture of tert-butyl (4R)-2-(5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (4.70 g, 16.65 mmol, 1.00 *eq*) in DCM (150.00 mL) was added DAST dropwise (29.52 g, 183.15 mmol, 11.00 *eq*) at -78 °C over 0.5 hr. The reaction mixture was stirred at -78 °C for 2 hrs, then allowed to warm to 25 °C and stirred for 20 hrs. After TLC (PE/EtOAc = 0/1) showed the starting material was consumed completely, the mixture was cooled to 0 °C and quenched by saturated $NaHCO_3$ solution (100 mL) dropwise. The organic phase was separated and dried over $Na_2SO_4$, concentrated to give the residue, then purified by column chromatography on silica gel (PE:EtOAc from 10:1, 8:1 to 5:1, then 3:1) to give tert-butyl (2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (1.38 g, 4.85 mmol, yield: 29.15%, $R^f$ = 0.53) as a white solid and tert-butyl (2S,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (1.36 g, 4.78 mmol, yield:

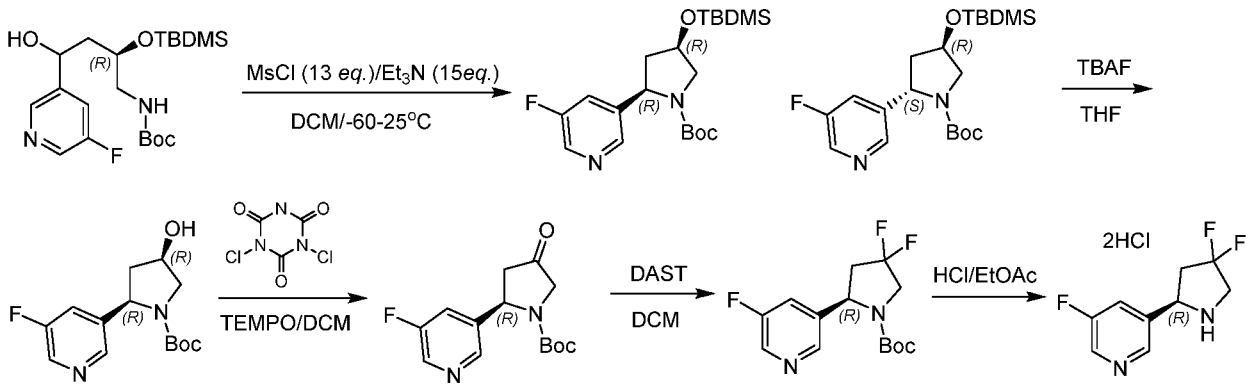
28.73%, $R_f = 0.43$) as a yellow oil. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 8.31-8.27 (m, 2H), 7.20-7.18 (m, 1H), 5.18 (d, 1H, $J = 51.6$ Hz), 4.97-4.88 (m, 1H), 4.04-4.00 (m, 1H), 3.64 (dd, 1H, $J =$ 38.8, 12.8 Hz), 2.67 (dd, 1H, $J = 15.6, 6.8$ Hz), 1.97-1.67 (m, 1H), 1.56-1.12 (m, 9H).

Step 7: 3-Fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine

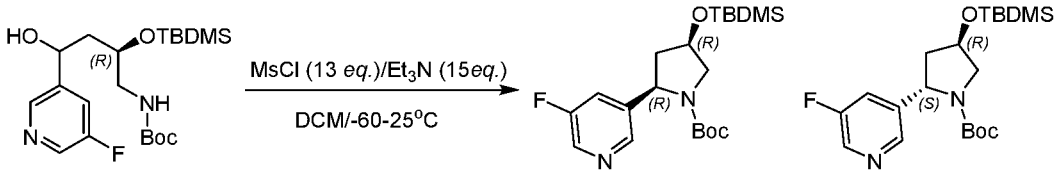



To a mixture of tert-butyl (2R,4S)-4-fluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (1.38 g, 4.85 mmol, 1.00 *eq*) in EtOAc (10 mL) was added dropwise HCl/EtOAc (40.00 mL, 4 M) at 0 °C. The mixture was allowed to warm to 25 °C and stirred 3 hrs. After TLC (PE:EtOAc =1:1) showed the reaction was complete, the solvent was evaporated to give 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine (1.25 g, 4.86 mmol, yield: 100.00%) as a brown solid. $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.84-8.81 (m, 2H), 8.31 (d, 1H, $J = 9.2$ Hz), 5.62 (dt, 1H, $J =$ 52.0, 2.4 Hz), 5.23-5.18 (m, 1H), 4.00-3.95 (m, 1H), 3.88-3.71 (m, 1H), 2.67 (td, 1H, $J = 16.0,6.0$ Hz), 1.69-1.59 (m, 1H).

(R)-3-(4,4-difluoropyrrolidin-2-yl)-5-fluoropyridine

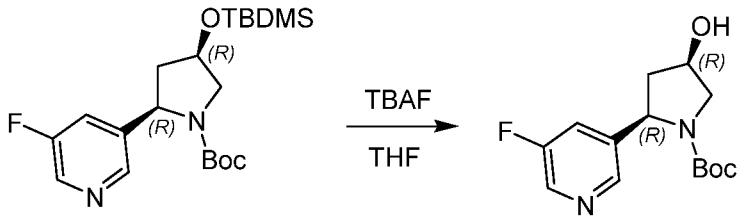



Step 1: tert-butyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate




To a mixture of tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-fluoropyridin-3-yl)-4-hydroxybutyl)carbamate (6.80 g, 16.40 mmol) and $Et_3N$ (24.89 g, 246.00 mmol) in DCM (500.00 mL) was added MsCl (24.42 g, 213.20 mmol) dropwise at -60°C over 30 minutes. The mixture was stirred at -60°C for 1 hr. The reaction mixture was allowed to warn to 25°C and stirred for an additional 18 hrs. The mixture was washed with $H_2O$ (200 mL*3). The aqueous phase was extracted with DCM (200 mL*4). The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc = 50/1, 20/1, 10/1) to afford tert-butyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (2.70 g, yield: 41.52%) and tert-butyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (2.40 g, yield: 36.89%) as brown oil. 1H-NMR (400 MHz, CDCl3) δ ppm 8.40 (br.s, 2H), 7.56-7.45 (m, 1H), 5.11-4.94 (m, 2H), 4.53 (br.s, 1H), 3.85-3.79 (m, 1H), 3.66-3.53 (m, 1H), 2.62-2.58 (m, 1H), 2.04-2.01 (m, 1H), 1.56 (s, 3H), 1.32 (s, 6H), 0.99-0.88 (m, 9H), 0.18-0.00 (m, 6H).

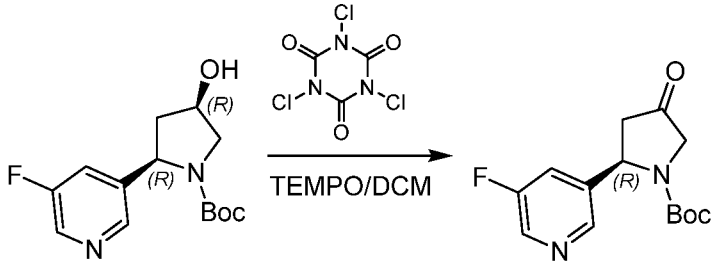
Step 2: tert-butyl (2R,4R)-2-(5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate




To a mixture of tert-butyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (2.40 g, 6.05 mmol) in THF (60.00 mL) was added TBAF (3.16 g, 12.10 mmol) in one portion at 25°C. The mixture was concentrated under reduced pressure at 50°C. The residue was added to water (20 mL). The aqueous phase was extracted with ethyl acetate (30 mL*3). The combined organic phase was washed with saturated brine (20 mL*2), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography

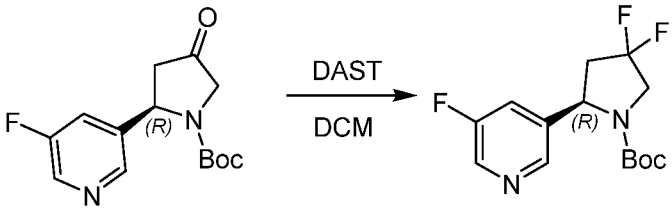
(PE:EtOAc = 20/1, 10/1,1/3) to afford tert-butyl (2R,4R)-2-(5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (1.30 g, yield: 76.11%) as a yellow solid. 1H-NMR (400 MHz, CDCl3) δ ppm 8.26 (d, 2H, J = 12.8 Hz), 7.39 (br.s, 1H), 4.95-4.81 (m, 1H), 4.48-4.47 (m, 1H), 3.73 (br.s, 1H), 3.56-3.53 (m, 1H), 2.55 (br.s, 1H), 1.97-1.98 (m, 1H), 1.65-1.16 (m, 9H).

Step 3: tert-butyl (R)-2-(5-fluoropyridin-3-yl)-4-oxopyrrolidine-1-carboxylate




To a mixture of tert-butyl (2R,4R)-2-(5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (1.30 g, 4.60 mmol) and trichloroisocyanuric acid (1.10 g, 4.60 mmol) was added TEMPO (72.41 mg, 460.49 umol) at -10°C. The mixture was stirred at -10°C for 15 min, then warmed to 25 °C and stirred for 1 hr. TLC (EtOAc) showed the reaction was complete. The organic phase was washed with $NaHCO_3$ (20 mL*2), dried over $Na_2SO_4$, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 50/1, 10/1) to afford tert-butyl (R)-2-(5-fluoropyridin-3-yl)-4-oxopyrrolidine-1-carboxylate (1.10 g, yield: 85.32%) as a brown oil.

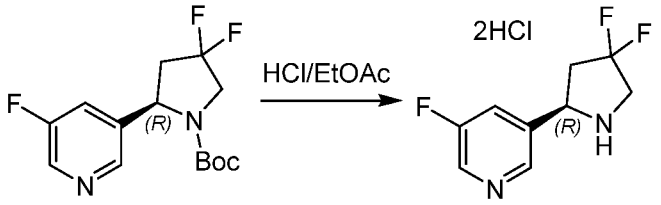
Step 4: tert-butyl (R)-4,4-difluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate




To a mixture of tert-butyl (R)-2-(5-fluoropyridin-3-yl)-4-oxopyrrolidine-1-carboxylate (1.00 g, 3.57 mmol) in DCM (100.00 mL) was added DAST (14.39 g, 89.25 mmol) dropwise at -70°C under $N_2$. The mixture was stirred at -70°C for 30 min. Then the mixture was stirred at 25°C for 16 hrs. The reaction mixture was quenched by saturated aq. $NaHCO_3$ slowly at 0°C and the aqueous

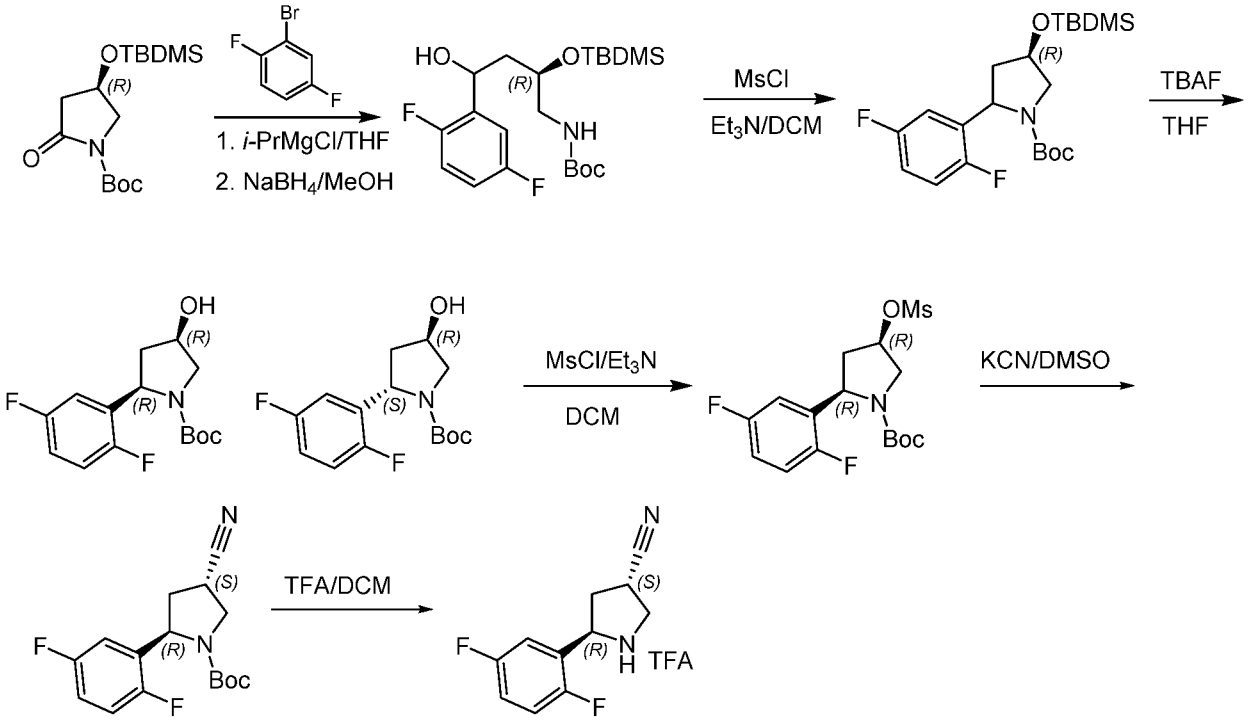
phase was extracted with DCM (50 mL*4). The combined organic phase was washed with saturated brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 100/1, 30/1) to afford tert-butyl (R)-4,4-difluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (1.00 g, yield: 92.66%) as a brown oil. 1H-NMR (400 MHz, CDCl3) δ ppm 8.40 (s, 1H), 8.34 (s, 1H), 7.30-7.21 (m, 1H), 5.06 (br.s, 1H), 4.14-3.85 (m, 2H), 2.91-2.84 (m, 1H), 2.39-2.32 (m, 1H), 1.43-1.14 (m, 9H).

Step 5: (R)-3-(4,4-difluoropyrrolidin-2-yl)-5-fluoropyridine

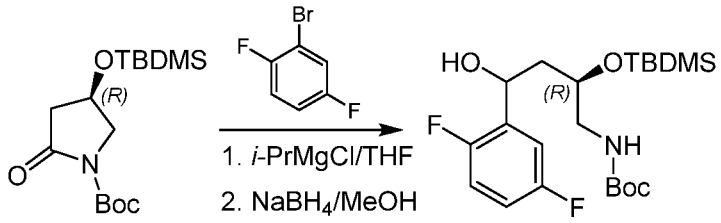



A mixture of tert-butyl (R)-4,4-difluoro-2-(5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (1.00 g, 3.31 mmol) in HCl/EtOAc (50.00 mL, 4 M) was stirred for 2 hrs at 25°C. The mixture was concentrated under reduced pressure at 30°C to afford (R)-3-(4,4-difluoropyrrolidin-2-yl)-5-fluoropyridine (840.00 mg, yield: 92.25%) as a white solid as bis HCl salt. 1H-NMR (400 MHz, MeOD) δ ppm 8.68-8.63 (m, 1H), 7.97 (d, 1H, J = 9.2 Hz), 5.26-5.21 (m, 1H), 4.03-3.90 (m, 2H), 3.13-2.92 (m, 2H).

(3S,5R)-5-(2,5-difluorophenyl)pyrrolidine-3-carbonitrile



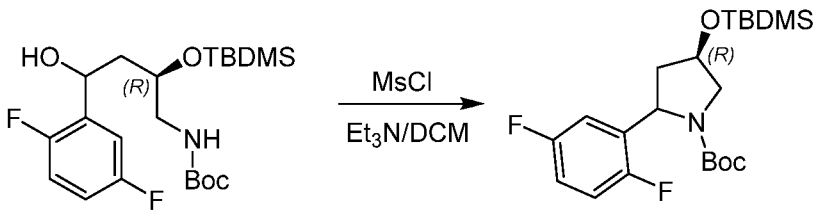

Step 1: tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(2,5-difluorophenyl)-4-hydroxybutyl)carbamate




To a solution of 2-bromo-1,4-difluoro-benzene (3.01 g, 15.60 mmol, 1.20 Eq) in THF (15 mL) was added isopropylmagnesium chloride complex (2.27 g, 15.60 mmol, 1.20 Eq) at 0°C dropwise under $N_2$. The reaction was stirred at 15°C for 1 hr to prepare (2, 5-difluorophenyl) magnesium bromide (23 mL). To a solution of tert-butyl (R)-4-((tert-butyldimethylsilyl)oxy)-2-oxopyrrolidine-1-carboxylate (4.10 g, 13.00 mmol, 1.00 Eq) in THF (50 mL) was added (2,5-difluorophenyl) magnesium bromide (23 mL) dropwise at 0°C over 30 mins. The reaction mixture was stirred at 0°C for 1 hr. Methanol (20 mL) was added to the mixture followed by $NaBH_4$ (738 mg, 19.50 mmol, 1.50 Eq) at 0°C. The mixture was stirred at 0°C for 1 hr then poured into 10% aqueous $NH_4Cl$. The mixture was extracted with EtOAc (20 mL*2), the combined organic layers

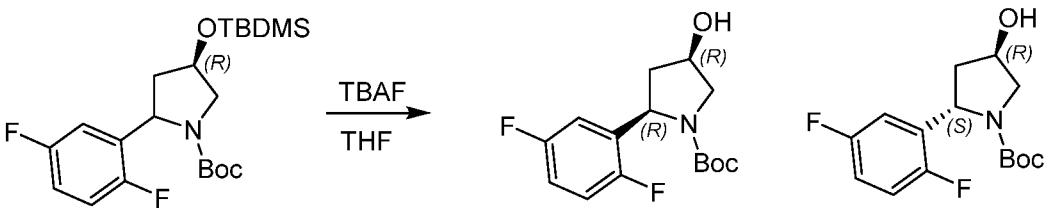
were washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by medium pressure liquid chromatography (MPLC) to give tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(2,5-difluorophenyl)-4-hydroxybutyl)carbamate (2.22 g, 5.14 mmol, 39.6% yield). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 7.17-7.15 (m, 1H), 6.86-6.79 (m, 2H), 5.11-5.06 (m, 1H), 4.70 (br.s, 1H), 4.02-3.98 (m, 1H), 3.69 (br.s, 0.5H), 3.46 (br.s, 0.5H), 3.33-3.14 (m, 2H), 1.80-1.69 (m, 2H), 1.35 (s, 9H), 0.84-0.82 (9H, m), 0.04-0.03 (6H, m).

Step 2: tert-butyl (4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate



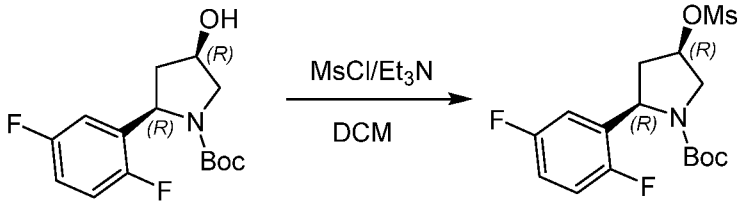

To a solution of tert-butyl ((2R)-2-((tert-butyldimethylsilyl)oxy)-4-(2,5-difluorophenyl)-4-hydroxybutyl)carbamate (13.40 g, 31.05 mmol, 1.00 Eq) and $Et_3N$ (9.43 g, 93.14 mmol, 3.00 Eq) in DCM (50 mL) was added dropwise methanesulfonyl chloride (5.33 g, 46.57 mmol, 1.50 Eq) at -60°C by under $N_2$. The mixture was stirred at -60°C for 2 hrs and 15°C for 16 hrs. LCMS showed the starting material was consumed completely. The reaction mixture was extracted with DCM (30 mL*2) and the combined organics were washed with brine (50 mL), dried over $Na_2SO_4$ and filtered, concentrated to give tert-butyl (4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate (12.00 g, 26.11 mmol, yield: 84.10%, 90% purity) which was used directly without further purification.

Step 3: tert-butyl (2R,4R)-2-(2,5-difluorophenyl)-4-hydroxypyrrolidine-1-carboxylate



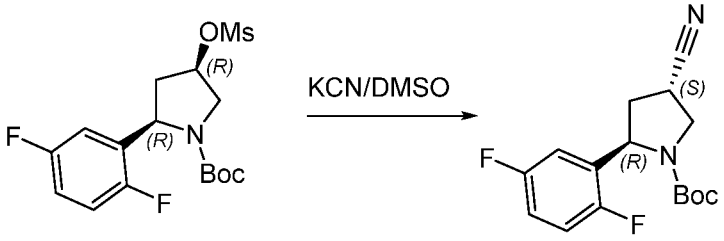
To a solution of tert-butyl (4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate (4.50 g, 10.88 mmol, 1.00 Eq) in THF (30 mL) was added TBAF/THF (1 M, 14.15 mL, 1.30 Eq) at 15°C. The mixture was stirred at 15°C for 16 hrs. TLC (PE:EtOAc = 3:1) showed the starting material was consumed completely. The reaction mixture was quenched by $H_2O$ (50 mL), extracted with EtOAc (30 mL*2) and the combined organics were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral *prep*-HPLC to afford tert-butyl (2R,4R)-2-(2,5-difluorophenyl)-4-hydroxypyrrolidine-1-carboxylate (1.00 g, 3.34 mmol, yield: 30.70%) as a white solid. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ ppm 7.04-6.80 (m, 3H), 5.10-5.00 (m, 1H), 4.43 (s, 1H), 3.75 (br.s, 1H), 3.53-3.49 (m, 1H), 2.53 (br.s, 1H), 1.93-1.90 (m, 1H), 1.40-1.16 (m, 9H).

Step 4: tert-butyl (2R,4R)-2-(2,5-difluorophenyl)-4-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate



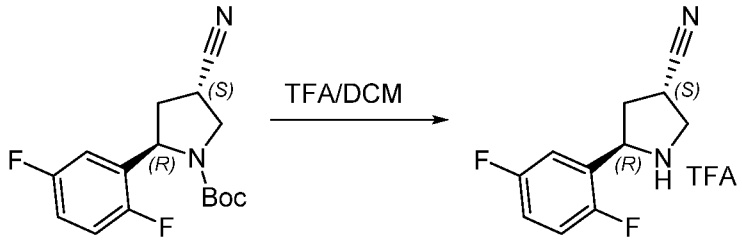

To a mixture of tert-butyl (2R,4R)-2-(2,5-difluorophenyl)-4-hydroxypyrrolidine-1-carboxylate (3.00 g, 10.02 mmol, 1.00 *eq*) and $Et_3N$ (2.03 g, 20.04 mmol, 2.00 *eq*) in DCM (80.00 mL) was added MsCl (1.61 g, 14.03 mmol, 1.40 *eq*) dropwise at 0°C. The mixture was stirred at 18°C for 2 hrs. The mixture was quenched by $H_2O$ (30 mL). The aqueous phase was extracted by DCM (50 mL*3). The combined organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. tert-Butyl (2R,4R)-2-(2,5-difluorophenyl)-4-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate (3.60 g, 9.54 mmol, yield: 95.20%) was obtained as a brown solid.

Step 5: tert-butyl (2R,4S)-4-cyano-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate



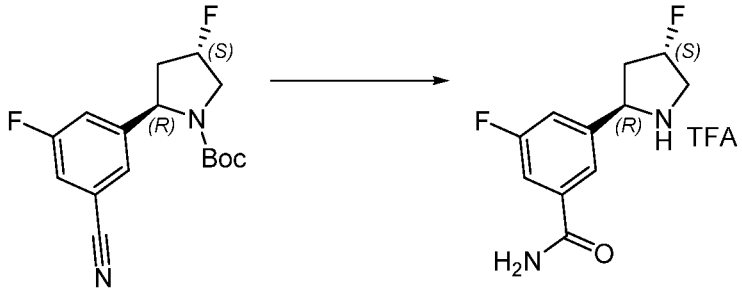
To a mixture of tert-Butyl (2R,4R)-2-(2,5-difluorophenyl)-4-((methylsulfonyl)oxy)pyrrolidine-1-carboxylate (3.60 g, 9.54 mmol, 1.00 eq) in DMSO (20.00 mL) was added KCN (745.49 mg, 11.45 mmol, 1.20 eq) in one portion. The mixture was stirred at 90°C for 3 hrs. 80 mL of H2O was added to the mixture, and the mixture was extracted by EtOAc (80 mL*4). The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc = 40:1, 30:1, 10:1). tert-Butyl (2R,4S)-4-cyano-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate (1.60 g, 5.19 mmol, yield: 54.40%) was obtained as light green liquid.

Step 6: (3S,5R)-5-(2,5-difluorophenyl)pyrrolidine-3-carbonitrile



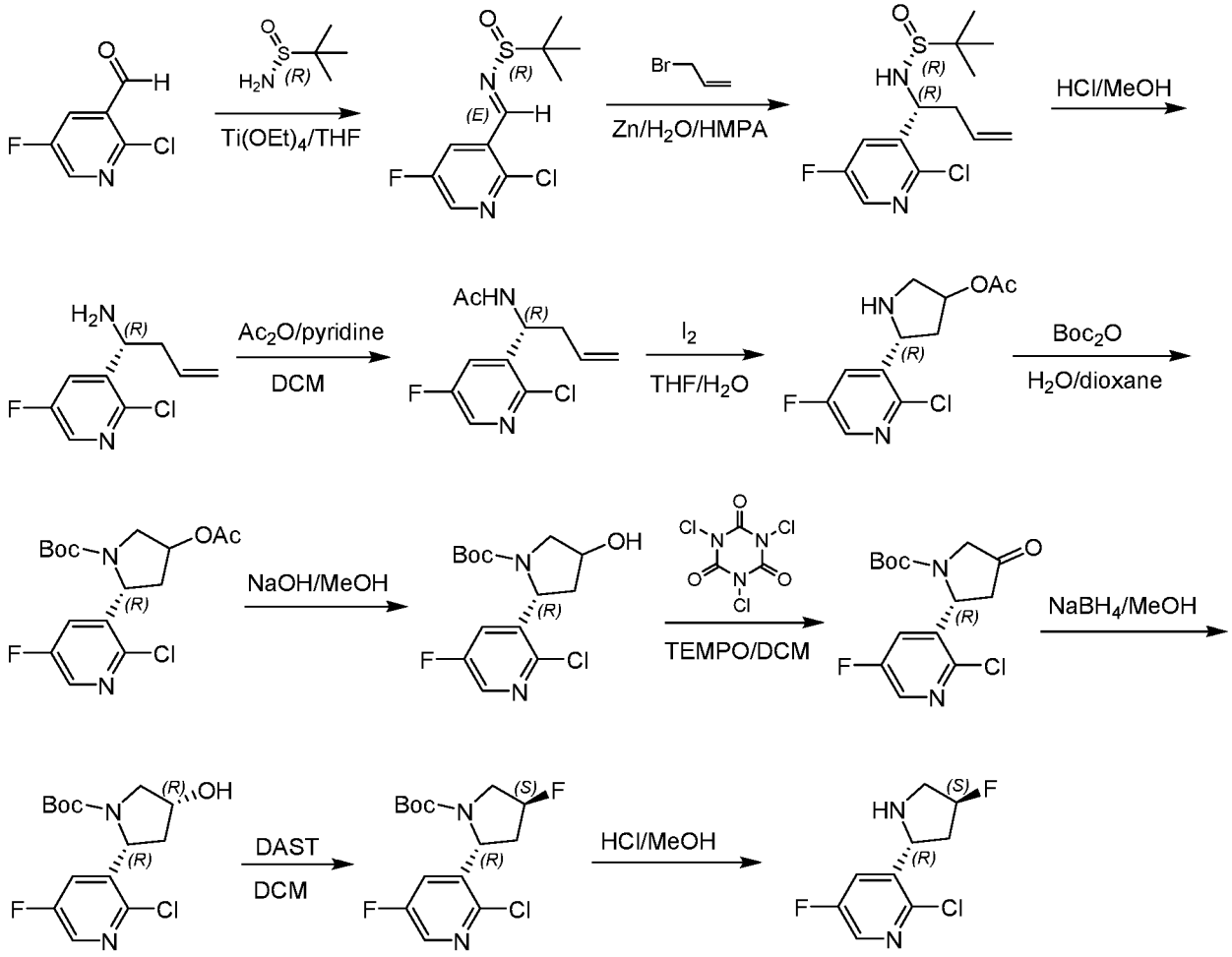

A mixture of tert-Butyl (2R,4S)-4-cyano-2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate (800.00 mg, 2.59 mmol, 1.00 eq) in TFA (4.00 mL)/DCM (20.00 mL) was stirred at 18°C for 3 hrs. The mixture was dried under $N_2$. (3S,5R)-5-(2,5-difluorophenyl)pyrrolidine-3-carbonitrile (780.00 mg, 2.42 mmol, yield: 93.44%) was obtained as a light yellow solid.

3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzamide

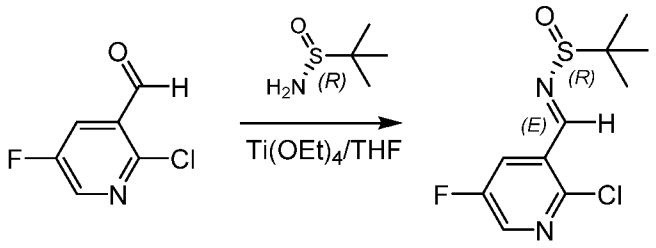



3-Fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzonitrile (0.050 g, 0.240 mmol) (Prepared as in WO 2012/034095) was taken up in TFA (0.800 ml, 10.38 mmol) and $H_2SO_4$ (0.200 ml, 3.75 mmol) and stirred overnight at room temperature. The reaction mixture was diluted with ice water (3ml) and the solid was isolated by filtration, and used directly.

2-chloro-5-fluoro-3-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine



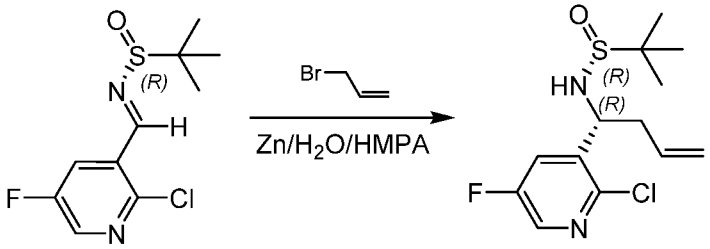

Step 1: (S,Z)-N-((2-chloro-5-fluoropyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide




2-chloro-5-fluoronicotinaldehyde (20 g, 125 mmol) was taken up in THF (150 ml) at 0 °C. (R)-2-Methylpropane-2-sulfinamide (16.71 g, 138 mmol) was added followed by dropwise addition

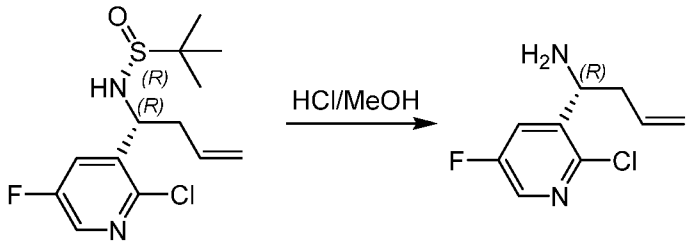
of titaniumtetraethanolate (22.88 ml, 150 mmol). The reaction mixture was stirred while warming to RT. After 3 hours the reaction mixture was cooled to 0 °C, and 150ml of brine was added and stirred for 20 minutes. The mixture was filtered through Celite. The aqueous layer was separated and discarded. The organic layer with dried over $Na_2SO_4$ and the solvent was removed to give (S,Z)-N-((2-chloro-5-fluoropyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (32 g, 122 mmol, 97 % yield), which was carried on without further purification. LCMS: 263 M+H.

Step 2: (R)-N-((R)-1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide



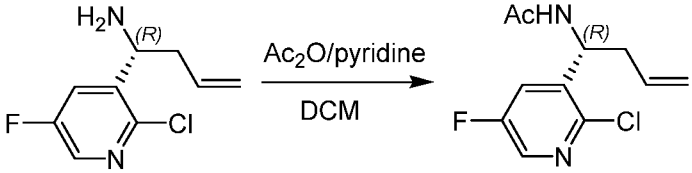

(R,E)-N-((2-chloro-5-fluoropyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (32.9 g, 125 mmol) was dissolved in HMPA (100 ml) and cooled to 0 °C. Zinc (16.37 g, 250 mmol), allyl bromide (21.67 ml, 250 mmol) and water (2.256 ml, 125 mmol) were added at 0 °C and the reaction mixture was allowed to warm to RT overnight. LCMS showed complete conversion to desired product. 100 ml of water was added at RT and stirred for 30 minutes. 30 ml of MBTE was added followed by 60 ml of 10% citric acid and the reaction mixture was stirred for 30 minutes. The mixture was filtered through Celite and washed with MTBE. The organic layer was washed with 10% citric acid, water and brine. The solvent was removed under vacuum to give (R)-N-((R)-1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (14.5 g, 47.6 mmol, 38.0 % yield) as an orange oil. LCMS: 305 M+H.

Step 3: (R)-1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-amine, HCl



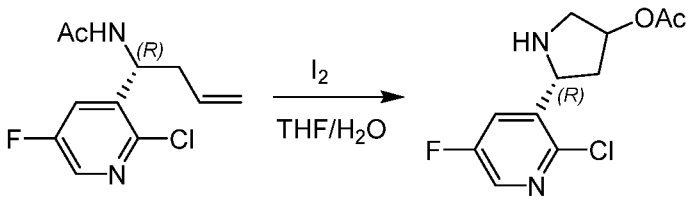
(R)-N-((R)-1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (7.5 g, 24.61 mmol) was taken up in 10 ml MeOH. HCl (4M in dioxane) (30.8 ml, 123 mmol) was added and stirred at RT for 1h. The solvent was removed under vacuum and the residue was diluted in DCM and washed with saturated aqueous NaHCO3. The layers were separated and the organic layer was dried with $Na_2SO_4$ and the solvent was removed under vacuum. Recovered (R)-1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-amine, HCl (5.83 g, 24.59 mmol, 100 % yield) as a solid. LCMS: 201 M+H.

Step 4: (R)-N-(1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-yl)acetamide




To (R)-1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-amine•HCl (5.83 g, 24.59 mmol) in DCM (70.3 ml) at 0 °C was added TEA (4.11 ml, 29.5 mmol) and acetic anhydride (2.320 ml, 24.59 mmol). The mixture was stirred for 2 hours. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Recovered (R)-N-(1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-yl)acetamide (5.97 g, 24.60 mmol, 100 % yield) and was carried on without further purification. LCMS: 243 M+H.

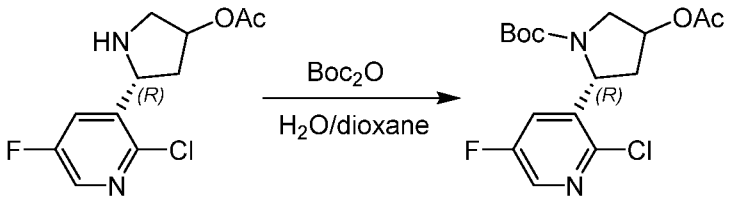
Step 5: (5R)-5-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-3-yl acetate




(R)-N-(1-(2-chloro-5-fluoropyridin-3-yl)but-3-en-1-yl)acetamide (5.97 g, 24.60 mmol) was taken up in THF (56.2 ml) and water (14.06 ml), followed by addition of $I_2$ (18.73 g, 73.8 mmol) and stirred overnight at RT. The crude reaction was diluted with saturated $NaHCO_3$ and $Na_2S_2O_3$ solutions and extracted twice with EtOAc. Aqueous layer was basified with saturated aqueous

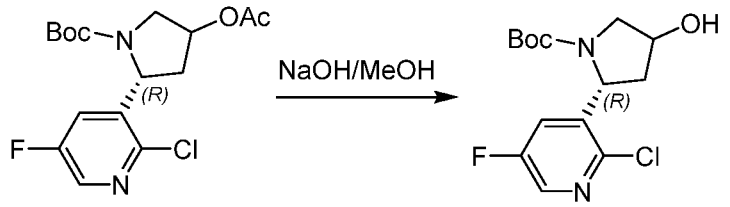
$NaHCO_3$ and extracted with EtOAc to obtain (5R)-5-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-3-yl acetate (5.9 g, 22.81 mmol, 93 % yield) as a light yellow oil. LCMS: 259 M+H.

Step 6: (2R)-tert-butyl 4-acetoxy-2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate



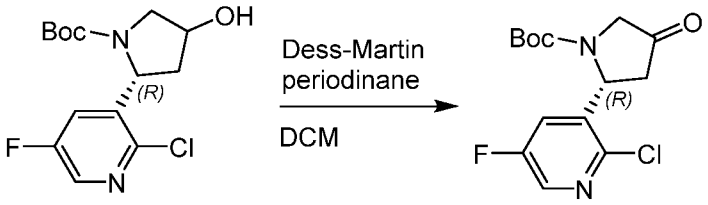

To a solution of (5R)-5-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-3-yl acetate (5.9 g, 22.81 mmol) in dioxane (76 ml) and water (76 ml) was added BOC-anhydride (7.94 ml, 34.2 mmol) followed by careful addition of 2N NaOH (7ml) to achieve pH ~9. The reaction mixture was stirred for 1 hour at RT. The reaction mixture was diluted with water and extracted with EtOAc three times. The organic layer was dried over $Na_2SO_4$ and the solvent was removed under vacuum to give (2R)-tert-butyl 4-acetoxy-2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (3.5 g, 9.75 mmol, 42.8 % yield), which was carried on without further purification. LCMS: 359 M+H.

Step 7: (2R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate



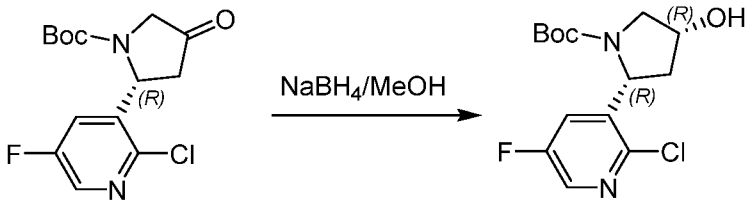

(2R)-tert-butyl 4-acetoxy-2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidine-1-carboxylate (3.5 g, 9.75 mmol) was taken up in MeOH (48.8 ml) followed by addition of 2M NaOH (5.37 ml, 10.73 mmol) and the reaction mixture was stirred at RT for 2 hours. The solvent was removed under vacuum and the aqueous layer was neutralized with 1N HCl, and extracted with EtOAc three times. The combined organic layers were dried over $Na_2SO_4$. The solvent was removed under vacuum and the residue was purified via silica gel chromatography (0-70% Hex/EtOAc) to give (2R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (2.1 g, 6.63 mmol, 68.0 % yield). LCMS: 317 M+H.

Step 8: (R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-oxopyrrolidine-1-carboxylate



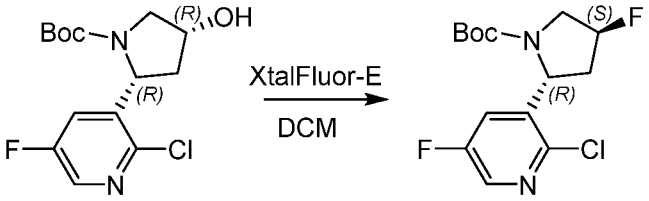

(2R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (2.1 g, 6.63 mmol) was taken up in DCM (66.3 ml) and $NaHCO_3$ (0.557 g, 6.63 mmol) was added followed by Dess-Martin periodinane (8.44 g, 19.89 mmol). The reaction mixture was stirred overnight. Water was added (0.119 ml, 6.63 mmol) followed by Dess-Martin periodinane (8.44 g, 19.89 mmol) and stirred for 18 hours. The pH wsa adjusted to ~7 with saturated aqueous $NaHCO_3$ and extracted with DCM x3. The organic layers were combined, dried over $Na_2SO_4$ and the solvent was removed under vacuum. The residue was purified via flash chromatography (0-70% Hex/EtOAc) to give (R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-oxopyrrolidine-1-carboxylate (1.6 g, 5.08 mmol, 77 % yield). LCMS: 315 M+H.

Step 9: (2R,4R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate



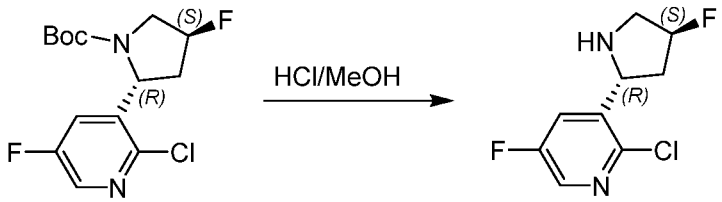

(R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-oxopyrrolidine-1-carboxylate (1.6 g, 5.08 mmol) was suspended in ethanol (33.9 ml) and cooled to 0°C. $NaBH_4$ was added portionwise (0.096 g, 2.54 mmol) and stirred for 45 minutes at 0°C. The reaction was quenched slowly with saturated $NH_4Cl$ and allowed to warm to RT, and the solution was extracted with DCM x3. The organic layers were combined and dried over $Na_2SO_4$. The residue was purified via flash chromatography (0-70% Hex/EtOAc) to give (2R,4R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (1.446 g, 4.57 mmol, 90 % yield). LCMS: 317 M+H.

Step 10: (2R,4S)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-fluoropyrrolidine-1-carboxylate



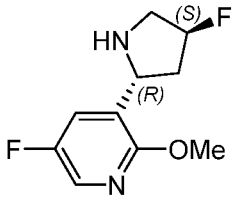

(2R,4R)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-hydroxypyrrolidine-1-carboxylate (1.0 g, 3.16 mmol) was taken up in DCM (25 ml) and cooled to -78°C. TEA-HF (1.098 ml, 9.47 mmol) was added and stirred for 10 minutes. XtalFluor-E (1.446 g, 6.31 mmol) was added and after 10 minutes the reaction mixture was transferred to an ice bath and allowed to warm to 0°C. After 2 hours the reaction mixture was diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The organic layers were separated, and the solvent was removed under vacuum. The residue was purified via ISCO (0-50% Hex/EtOAc; 12g column) to give (2R,4S)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-fluoropyrrolidine-1-carboxylate (0.805 g, 2.53 mmol, 80 % yield) as a white solid. LCMS: 319 M+H.

Step 11: 2-chloro-5-fluoro-3-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine, HCl




(2R,4S)-tert-butyl 2-(2-chloro-5-fluoropyridin-3-yl)-4-fluoropyrrolidine-1-carboxylate (0.805 g, 2.53 mmol, 80 % yield) was taken up in EtOAc (5ml) and 4N HCl/dioxane (3ml) was added. The reaction mixture was stirred at RT for 1 hour. The precipitate was filtered off, washed with ether, and dried under high vacuum overnight to give 2-chloro-5-fluoro-3-((2R,4S)-4-fluoropyrrolidin-2-yl)pyridine, HCl (0.612 g, 2.399 mmol, 76 % yield) as an off white solid. LCMS: 219 M+H.

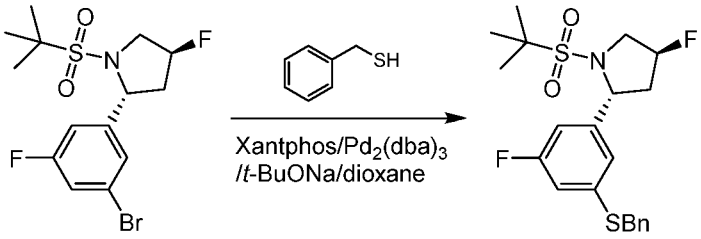
5-fluoro-3-((2R,4S)-4-fluoropyrrolidin-2-yl)-2-methoxypyridine



5-Fluoro-3-((2R,4S)-4-fluoropyrrolidin-2-yl)-2-methoxypyridine was prepared in the same way as 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzamide, substituting for 5-fluoro-2-methoxynicotinaldehyde for 2-chloro-5-fluoronicotinaldehyde.

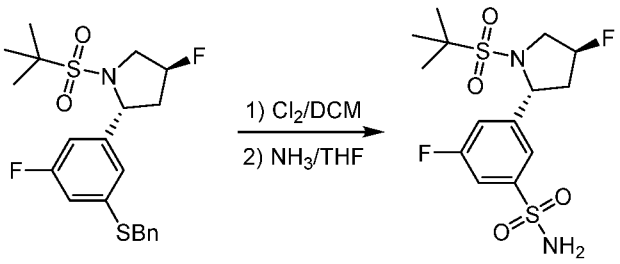
3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzenesulfonamide

Step 1: (2R,4S)-2-(3-(benzylthio)-5-fluorophenyl)-1-(tert-butylsulfonyl)-4-fluoropyrrolidine




To a mixture of (2R,4S)-2-(3-bromo-5-fluorophenyl)-1-(tert-butylsulfonyl)- 4-fluoropyrrolidine (1.00 g, 2.62 mmol, 1.00 *eq*) in dioxane (3.00 mL) was added *t*-BuONa (502.80 mg, 5.23 mmol, 2.00 *eq*), phenylmethanethiol (649.82 mg, 5.23 mmol, 613.04 uL, 2.00 *eq*), Xantphos (151.37 mg, 261.60 umol, 0.10 *eq*) and $Pd_2(dba)_3$ (239.55 mg, 261.60 umol, 0.10 *eq*). After addition, the mixture was stirred at 80°C for 16 hrs under $N_2$. The mixture was concentrated to give the crude product. The mixture was purified by column chromatography on silica gel (PE:EtOAc = 20:1-8:1) to give (2R,4S)-2-(3-(benzylthio)-5- fluorophenyl)-1-(tert-butylsulfonyl)-4-fluoropyrrolidine (700.00 mg, 1.64 mmol, yield: 62.78%) as a red oil.

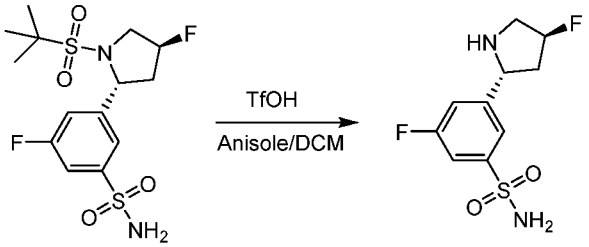
Step 2: 3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5- fluorobenzenesulfonamide




A steady stream of $Cl_2$ gas was bubbled through a mixture of (2R,4S)-2-(3-(benzylthio)-5-fluorophenyl)-1-(tert-butylsulfonyl)-4-fluoropyrrolidine (700.00 mg, 1.64 mmol, 1.00 *eq*) in DCM

(16.00 mL)/AcOH (8.00 mL)/$H_2O$ (4.00 mL) at 0°C for 6 mins. The reaction mixture was dissipated by sparging with $N_2$ gas for 6 mins. The resulting bis-sulfonyl chloride was then treated with excess $NH_3 \cdot H_2O$ until the pH of the aqueous phase was 9–10 and warmed to 25°C and stirred for 16 hrs. LCMS showed the reaction was complete. The mixture was extracted with DCM (20 mL * 3), the organic layer was concentrated to give 3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5-fluorobenzenesulfonamide (600.00 mg, crude) as a yellow oil.

Step 3: 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl)benzenesulfonamide




To a mixture of TfOH (706.35 mg, 4.71 mmol, 415.50 uL, 3.00 *eq*) in DCM (20.00 mL) was added anisole (254.48 mg, 2.36 mmol, 254.48 uL, 1.50 *eq*) at -40°C, then a solution of 3-((2R,4S)-1-(tert-butylsulfonyl)-4-fluoropyrrolidin-2-yl)-5- fluorobenzenesulfonamide (600.00 mg, 1.57 mmol, 1.00 *eq*) in DCM (10.00 mL) was added drop wise to the mixture at -40°C over 0.1 hr. After addition, the mixture was warmed to 25°C and stirred at 25°C for 1 hr. TLC (PE:EtOAc = 1:1) showed the starting material was consumed complete. The mixture was added to saturated *aq.* $K_2CO_3$ (100 mL) and stirred for 0.1 hr. The mixture was extracted with DCM (100 mL*2). The water layer was concentrated to give the crude product. The mixture was washed with DCM (10 mL*3), the organic layer was concentrated to give 3-fluoro-5-((2R,4S)-4-fluoropyrrolidin-2-yl) benzenesulfonamide (300.00 mg, crude) as a yellow oil.

The NMR and LC MS data obtained for compounds disclosed herein are also shown below.

| Compound Number | $^1$H NMR | MS (M+1) |
|---|---|---|
| **1** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.55 (br.s, 1H), 8.44 (d, 1H, J = 2.4 Hz), 8.10 (s, 1H), 7.83 (br.s, 1H), 6.69 (br.s, 1H), 6.24 (br.s, 1H), 5.55-5.43 (m, 2H), 4.25-4.16 (m, 2H), 2.95 (br.s, 1H), 2.40-2.26 (m, 1H) | 327 |
| **2** | $^1$H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 48.6 Hz, 1H), 8.33 (d, J = 37.6 Hz, 1H), 7.16 (d, J = 50.9 Hz, 3H), 6.47 (d, J = 238.1 Hz, 1H), 5.74 – 5.24 (m, 2H), 4.26 (d, J = 123.1 Hz, 2H), 2.80 (s, 1H), 2.27 (d, J = 40.7 Hz, 1H) | 344 |
| **3** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.57-8.53 (m, 3H), 8.12 (br.s, 1H), 7.91 (s, 1H), 6.56 (br.s, 1H), 5.70 (br.s, 1H), 4.46-4.41 (m, 1H), 4.38-4.24 (m, 1H), 3.25-3.11 (m, 1H), 2.69-2.58 (m, 1H) | 345 |
| **4** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.84 (d, 1H, J = 7.6 Hz), 8.66 (s, 1H), 8.49 (s, 1H), 8.11 (s, 1H), 8.00 (br.s, 1H), 5.60-5.57 (m, 1H), 5.49 (d, 1H, J = 52.4 Hz), 4.49-4.30 (m, 2H), 2.93-2.84 (m, 1H), 2.36-2.22 (m, 1H) | 345 |
| **5** | $^1$H-NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (br.s, 1H), 8.10 (s, 1H), 7.14-7.12 (m, 1H), 7.02 (br.s, 1.5H), 6.73 (br.s, 1.5H), 4.32 (br.s, 2H), 3.35 (br.s, 1H), 2.89 (br.s, 1.0H), 2.53 (br.s, 2H) | 350 |
| **6** | $^1$H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 63.8 Hz, 1H), 8.33 (d, J = 36.7 Hz, 1H), 7.73 (d, J = 39.9 Hz, 2H), 6.46 (d, J = 249.9 Hz, 1H), 5.50 (d, J = 56.3 Hz, 1H), 5.34 (t, 1H), 4.54 - 4.04 (m, 3H), 2.98 - 2.66 (m, 1H), 2.21 (d, J = 42.5 Hz, 1H) | 351 |
| **7** | $^1$H NMR (400 MHz, DMSO-d6) δ ppm 8.73 (dd, J = 59.6, 7.8 Hz, 1H), 8.32 (d, J = 41.5 Hz, 1H), 8.05 (d, J = 42.4 Hz, 1H), 7.65 (m, 1H), 6.76-6.13 (m, 1H), 5.64 – 5.24 (m, 2H), 4.42-4.15 (m, 2H), 3.92 (s, 3H), 2.94 – 2.65 (m, 1H), 2.25 (dt, J = 40.8, 10.7 Hz, 1H) | 357 |
| **8** | $^1$H NMR (400 MHz, DMSO-d6) δ ppm 8.73 (dd, J = 36.6, 7.7 Hz, 1H), 8.32 (d, J = 30.5 Hz, 1H), 7.90 (d, J = 38.4 Hz, 1H), 7.72 – 7.50 (m, 1H), 6.73-6.25 (m, 1H), 5.50 (dd, J = 53.0, 21.0 Hz, 1H), 5.36 – 5.12 (m, 1H), 4.37 (dd, J = 21.7, 13.8 Hz, 1H), 4.21 – 3.95 (m, 1H), 3.41 (d, 3H), 2.86 – 2.54 (m, 1H), 2.29 (m, 1H) | 357 |
| **9** | $^1$H NMR (400 MHz, Methanol-d4) δ 8.45 (s, 1H), 8.14 (s, 1H), 7.25 (d, J = 1.6 Hz, 1H), 7.09 (dt, J = 9.3, 1.9 Hz, 1H), 6.79 – 6.51 (m, 1H), 6.19 (s, 1H), 5.57 – 5.17 (m, 2H), 4.14 (d, J = 36.3 Hz, 2H), 2.92 (s, 1H), 2.24 (dddd, J = 40.9, 14.6, 9.4, 3.7 Hz, 1H) | 360 |
| **10** | $^1$H NMR (400 MHz, Methanol-d4) δ 8.57 (s, 1H), 8.26 – 8.04 (m, 2H), 7.61 (dd, J = 8.9, 2.8 Hz, 1H), 6.71 (d, J = | 361 |

| | | |
|---|---|---|
| | 7.5 Hz, 1H), 5.68 – 5.36 (m, 2H), 4.20 (d, J = 36.4 Hz, 2H), 2.38 – 2.14 (m, 2H) | |
| **11** | $^1$H NMR (400 MHz, Methanol-d4) δ 8.42 (s, 1H), 8.13 (s, 1H), 7.69 (t, J = 1.7 Hz, 1H), 7.51 (s, 1H), 7.34 (dt, J = 9.2, 2.0 Hz, 1H), 6.69 (s, 1H), 6.20 (s, 1H), 5.51 (d, J = 13.9 Hz, 1H), 5.40 (s, 1H), 4.18 (d, J = 36.7 Hz, 1H), 2.95 (s, 1H), 2.27 (dddd, J = 40.8, 13.9, 9.3, 3.7 Hz, 1H) | 369 |
| **12** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.81 (d, 1H, J = 7.2 Hz), 8.12 (s, 1H), 7.66 (s, 1H), 7.54 (d, 1H, J = 9.2 Hz), 7.40 (d, 1H, J = 7.6 Hz), 5.52-5.39 (m, 2H), 4.47-4.29 (m, 2H), 2.91-2.81 (m, 1H), 2.29-2.12 (m, 1H) | 369 |
| **13** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.54-8.43 (m, 1H), 8.10 (br.s, 1H), 6.96-6.77 (m, 3H), 5.51-5.38 (m, 2H), 4.05 (br.s, 5H), 2.83 (br.s, 1H), 2.20-2.03 (m, 1H) | 374 |
| **14** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.35 (br.s, 1H), 8.11 (s, 1H), 7.28 (s, 1H), 7.10 (d, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 8.8 Hz), 6.17 (br.s, 1H), 5.42 (d, 1H, J = 52.4 Hz), 5.23 (br.s, 1H), 4.16-4.08 (m, 1H), 2.91 (br.s, 1H), 2.31-2.17 (m, 1H), 1.47 (d, 6H, J = 3.6 Hz). | 384 |
| **15** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.76 (d, 1H, J = 7.2 Hz), 8.09 (s, 1H), 7.69 (s, 1H), 7.44 (d, 1H, J = 9.2 Hz), 7.36 (d, 1H, J = 8.4 Hz), 5.55-5.39 (m, 2H), 4.45-4.33 (m, 2H), 2.90-2.81 (m, 1H), 2.30-2.16 (m, 1H) | 387 |
| **16** | $^1$H-NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (br.s, 1H), 7.98 (s, 2H), 7.92 (d, 1H, J = 6.8 Hz), 7.02 (d, 1H, J = 6.4 Hz), 6.39 (br.s, 1H), 5.55-5.36 (m, 4H), 4.20-4.03 (m, 2H), 2.93 (br.s, 1H), 2.29-2.15 (m, 1H). | 405 |
| **17** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.49 (br.s, 1H), 8.08 (br.s, 1H), 7.36 (s, 1H), 7.08 (d, 2H, J = 8.4 Hz), 6.67 (br.s, 1H), 5.52 (br.s, 2H), 5.46 (d, 1H, J = 52.0 Hz), 4.17 (br.s, 1H), 4.09 (br.s, 1H), 4.87 (br.s, 1H), 2.32-2.16 (m, 1H) | 410 |
| **18** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.37 (br.s, 1H), 8.10 (br.s, 1H), 7.66 (s, 1H), 7.46 (br.s, 1H), 7.30 (br.s, 1H), 6.66 (br.s, 0.5H), 6.17 (br.s, 0.5H), 5.51-5.38 (m, 2H), 4.53 (br.s, 1H), 4.20-4.13 (m, 1H), 3.68-3.65 (m, 2H), 3.46-3.45 (m, 2H), 2.98-2.92 (m, 1H), 2.31-2.22 (m, 1H). | 413 |
| **19** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.39 (br.s, 1H), 8.12 (br.s, 1H), 7.65 (s, 1H), 7.47 (br.s, 1H), 7.32 (d, 1H, J = 8.8 Hz), 6.68 (br.s, 0.5H), 6.19 (br.s, 0.5H), 5.52-5.39 (m, 2H), 4.62 (br.s, 1H), 4.23-4.14 (m, 2H), 3.21 (d, 2H, J =6.8 Hz), 2.95 (br.s, 1H), 2.36-2.20 (m, 1H), 1.10-1.07 (m, 1H), 0.50 (d, 2H, J = 8.0 Hz), 0.26 (d, 2H, J = 4.4 Hz). | 423 |

| | | |
|---|---|---|
| **20** | $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.38 (br.s, 1H), 8.11 (br.s, 1H), 7.62 (s, 1H), 7.43 (br.s, 1H), 7.31 (d, 1H, $J$ = 9.2 Hz), 6.67-6.62 (m, 0.5H), 6.18 (br.s, 0.5H), 5.45 (d, 1H, $J$ = 52.8 Hz), 5.38 (br.s, 1H), 4.60 (br.s, 1H), 4.21-4.13 (m, 1H), 3.36 (br.s, 1H), 2.88 (s, 3H), 2.34-2.18 (m, 1H). | 383.1 |
| **21** | $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.41 (br.s, 1H), 8.09 (br.s, 1H), 7.20 (s, 2H), 7.05 (br.s, 1H), 6.66 (br.s, 0.5H), 6.18 (br.s, 0.5H), 5.43 (d, 1H, $J$ = 52.4 Hz), 5.36 (br.s, 1H), 4.54 (br.s, 0.5H), 4.19-4.05 (m, 1.5H), 3.08-2.88 (m, 7H), 2.32-2.18 (m, 1H). | 397.1 |
| **22** | $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.51-8.33 (m, 1H), 8.13-8.04 (m, 1H), 7.55 (br.s, 1H), 7.09-7.00 (m, 2H), 6.67-6.28 (m, 1H), 5.63-5.59 (m, 1H), 5.44 (d, 1H, $J$ = 52.8 Hz), 4.58-4.27 (m, 1H), 4.16-3.97 (m, 1H), 2.97 (br.s, 1H), 2.41-2.24 (m, 1H). | 369.0 |

NTRK1 Wild Type Assay at 1 mM ATP

In each well of a 384-well plate, 1 nM – 1.5 nM of wild type NTRK1 enzyme (BPS Bioscience; 40280) was incubated in a total of 12.5 µL of buffer (100 mM HEPES pH 7.5, 0.015% Brij 35, 10 mM $MgCl_2$, 1mM DTT) with 1-2 µM CSKtide (Tuft's University or Anaspec; FITC-AHA-KKKKD DIYFFFG-NH2) and 1 mM ATP at 25°C for 60 minutes in the presence or absence of a dosed concentration series of compound (1% DMSO final concentration). The reaction was stopped by the addition of 70 µL of Stop buffer (100 mM HEPES pH 7.5, 0.015% Brij 35, 35 mM EDTA and 0.2% of Coating Reagent 3 (Caliper Lifesciences)). The plate was then read on a Caliper EZReader 2 (protocol settings: -1.7 psi, upstream voltage -500, downstream voltage -3000, post sample sip 35s). Data was normalized to 0% and 100% inhibition controls and the $IC_{50}$ calculated using a 4-parameter fit in the CORE LIMS.

NTRK Wild Type and G595R Mutant Cellular Assays Protocol

KM12 wild type colon carcinoma cell line harboring the TPM3-NTRK1 fusion protein was obtained from the National Cancer Institute (NCI). This line has been previously shown to be dependent upon the NTRK activity derived from the NTRK fusion protein for growth and survival. The KM12 Cliff (G595R) cell line was generated by mutagenizing the wild type KM12 line with a DNA methylating agent and subsequently selecting for clones that were resistant to chronic

exposure to high concentration of a known NTRK inhibitor (Crizotinib). Cells were first plated in 384-well plates at 1000 cells/well in complete media (10% FBS and 1% pen/strep) and incubated overnight at $37^0$C. Cells were then dosed with test articles at varying concentrations using the Bravo liquid handling system. Concentrations ranged from 25uM down to 9.5pM (4-fold dilutions, 10 concentrations total). Each compound was run in duplicate per plate. DMSO and staurosporine (25uM) were included on each plate as negative and positive controls for growth inhibition. 72hr after dosing, assay plates were developed using CellTiter-Glo (Promega) and resultant luminescence was read on the Envision plate reader. $IC_{50}$ determinations were calculated using a 4-parameter curve fitting algorithm

The table below summarizes the results from the biological assays described above. The following designations are used to indicate activity: A < 10.00 nM; B = 10.01-100.0 nM; C = 100.01-1000.0 nM; and D > 1000.1 nM.

| Compound Number | NTRK1 $IC_{50}$ (nM) | KM12 $IC_{50}$ (nM) | G595R-KM12 $IC_{50}$ (nM) |
|---|---|---|---|
| **1** | A | A | B |
| **2** | A | A | A |
| **3** | B | B | C |
| **4** | A | A | A |
| **5** | B | B | C |
| **6** | A | A | A |
| **7** | A | A | A |
| **8** | B | B | C |
| **9** | A | A | A |
| **10** | A | A | A |
| **11** | A | A | B |
| **12** | A | A | A |
| **13** | A | A | A |
| **14** | B | B | C |
| **15** | A | B | B |
| **16** | A | B | B |
| **17** | A | A | A |
| **18** | B | B | B |
| **19** | A | B | B |
| **20** | B | B | B |
| **21** | B | B | C |
| **22** | B | B | C |

Incorporation by Reference

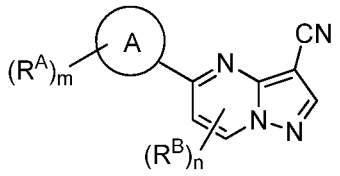
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:



I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -$N(R'')(R'')$, -$C(O)$-$N(R'')(R'')$, -$N(R'')(R'')$-$C(O)R'$, and -($C_1$-$C_6$ alkylene)-$N(R'')$-$C(O)R'$;

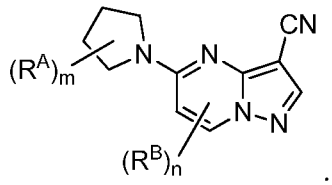
each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2;

provided that the compound is not (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

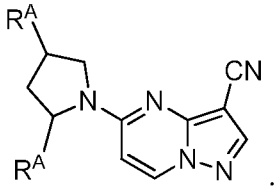
2. The compound of claim 1, having Formula (Ia-1):




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3. The compound of claim 1, wherein at least one $R^A$ is halo.

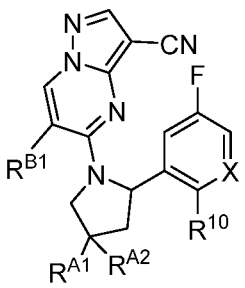
4. The compound of claim 1, having Formula (Ib):



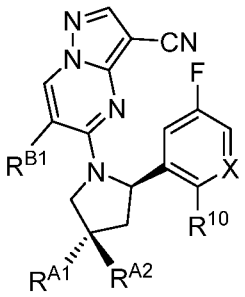

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5. The compound of claim 4, wherein one $R^A$ is halo and one $R^A$ is aryl or heteroaryl.

6. The compound of claim 1, having Formula Ic or Ic-1:



(Ic),



(Ic-1), or a pharmaceutically acceptable salt thereof, wherein:

X is N or C($R^9$);

$R^{A1}$ is fluoro or -CN;

$R^{A2}$ is fluoro or hydrogen;

$R^{B1}$ is hydrogen or fluoro;

$R^9$ is selected from hydrogen, halo, -CN, -$C_1$-$C_4$ alkyl, -C(O)N($R^{11}$)($R^{11}$), and -$S(O)_2$N($R^{11}$)($R^{11}$), wherein any alkyl portion of $R^9$ is optionally substituted with one or more substituents selected from -OH and -F;

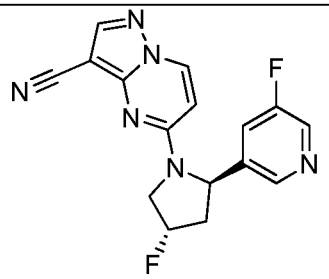
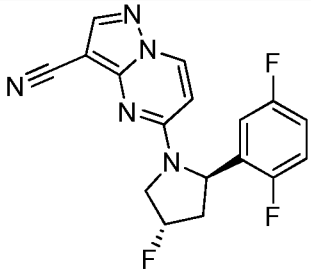
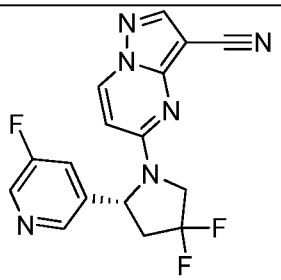
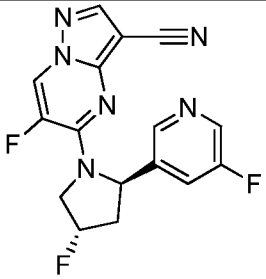
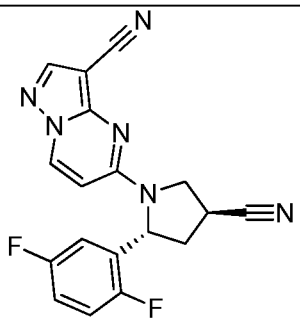
$R^{10}$ is is selected from hydrogen, halo, -O-($C_1$-$C_4$ alkyl) optionally substituted with one or more halo, and -C(O)N($R^{11}$)($R^{11}$); and

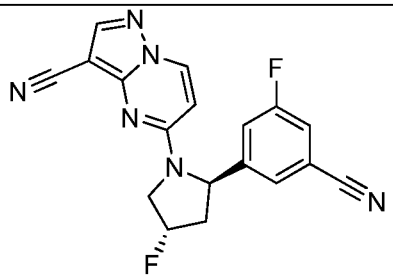
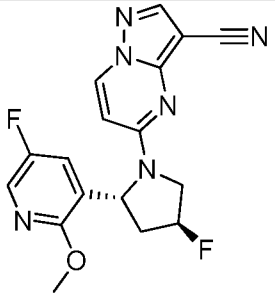
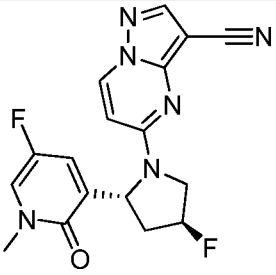
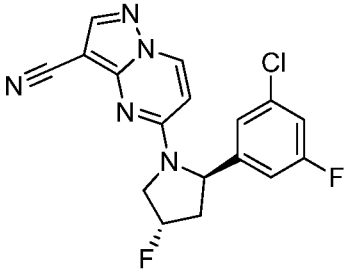
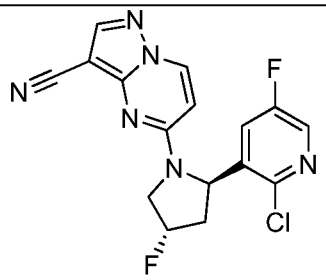
each $R^{11}$ is independently selected from hydrogen, and $C_1$-$C_4$ alkyl optionally substituted with one or more substituents selected from -OH and cyclopropyl.

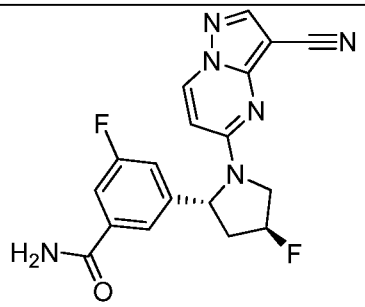
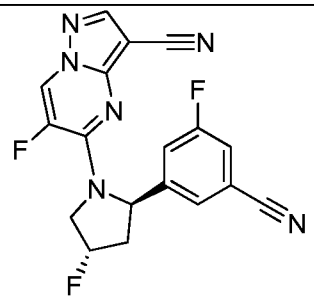
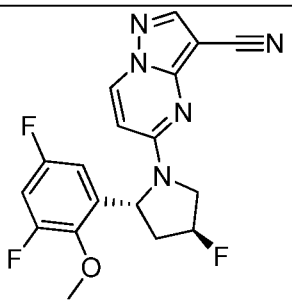
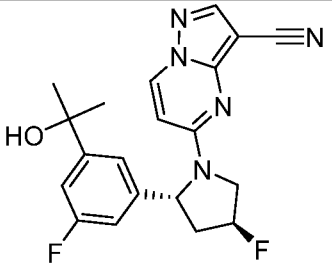
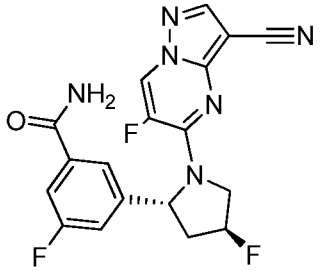
7. The compound of claim 6, wherein $R^9$ is selected from hydrogen, fluoro, chloro, -CN, -$C(O)NH_2$, -$C(O)NHCH_3$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_2CH_2OH$, -$C(OH)(CH_3)_2$, -$S(O)_2NH_2$, and N-(cyclopropylmethyl)carbamyl.

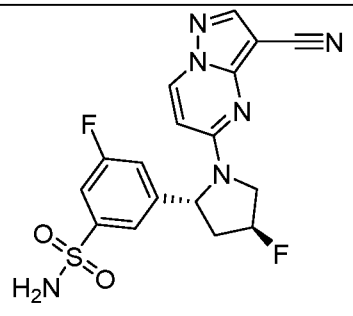
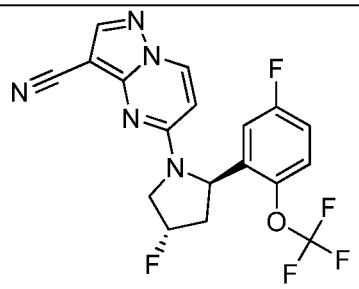
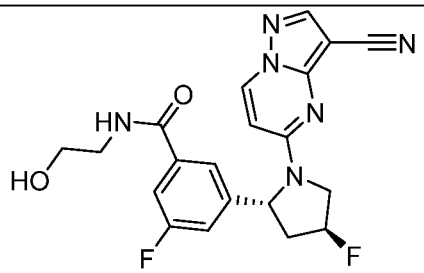
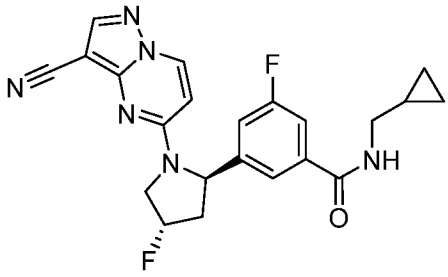
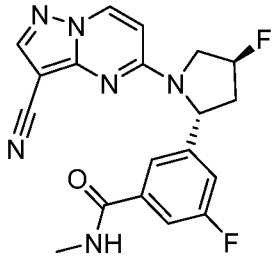
8. The compound of claim 6 or 7, wherein $R^{10}$ is selected from hydrogen, fluoro, chloro, -$OCH_3$, -$OCF_3$ and -$C(O)NH_2$.

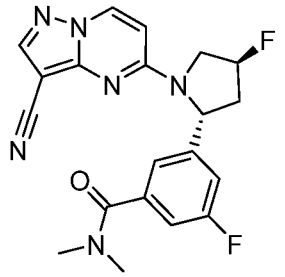
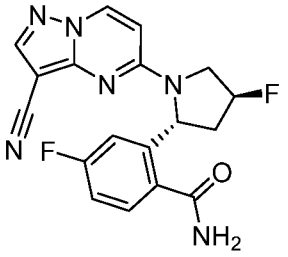
9. The compound of claim 1, selected from any one of the compounds in the table below:

| Compound Number | Structure |
|---|---|
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 |  |

| | |
|---|---|
| **6** |  |
| **7** |  |
| **8** |  |
| **9** |  |
| **10** |  |

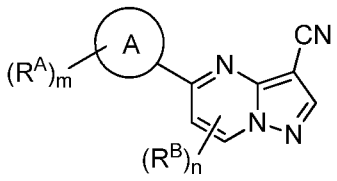
| | |
|---|---|
| **11** |  |
| **12** |  |
| **13** |  |
| **14** |  |
| **15** |  |

| | |
|---|---|
| **16** |  |
| **17** |  |
| **18** |  |
| **19** |  |
| **20** |  |

| | |
|---|---|
| 21 |  |
| 22 |  |

.

10. A pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, wherein:



I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

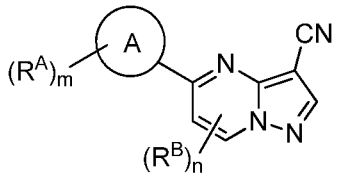
each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

11. A method for inhibiting NTRK activity in a cell or in a patient, said method comprising the step of contacting the cell or administering to the patient a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof, wherein:




I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$

alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -C(O)-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-C(O)$R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-C(O)$R^1$, -$NR^2S(O)_2R^1$, -P(O)($R^1$)($R^1$), and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

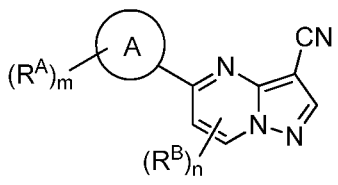
each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

12. A method for treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, comprising administering to the subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:




I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

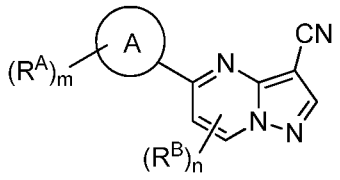
each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -$N(R'')(R'')$, -$C(O)$-$N(R'')(R'')$, -$N(R'')(R'')$-$C(O)R'$, and -($C_1$-$C_6$ alkylene)-$N(R'')$-$C(O)R'$;

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

13. A method for treating a subject who has developed resistance to a cancer treatment, comprising administering to the subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:



I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

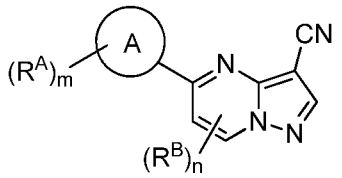
each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

14. A compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof for use in inhibiting NTRK activity in a cell or in a patient, wherein:




I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -$C(O)$-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

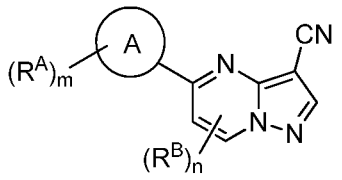
each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

15. A compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof for use in treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, wherein:




I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -C(O)-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$, -$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

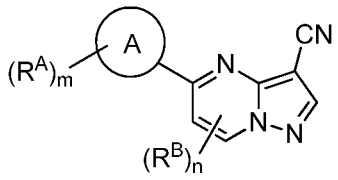
each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

16. A compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof for use in treating a subject who has developed resistance to a cancer treatment, wherein:




I

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each $R^A$ is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -$SR^1$, -$S(O)_2R^1$, -$S(O)_2$-$N(R^2)(R^2)$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R^2)(R^2)$, -C(O)-$N(R^2)(R^2)$, -$N(R^2)(R^2)$-$C(O)R^1$, -($C_1$-$C_6$ alkylene)-$N(R^2)$-$C(O)R^1$,

-$NR^2S(O)_2R^1$, -$P(O)(R^1)(R^1)$, and –$OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxyl, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of $R^a$;

each $R^B$ is independently selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, halo, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, -$N(R^1)(R^1)$, nitro, cyano, and –$OR^1$;

each $R^1$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of $R^b$;

each $R^2$ is independently selected from hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ heteroalkyl; or 2 $R^2$ together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of $R^b$;

each $R^a$ and $R^b$ is independently selected from halo, cyano, hydroxyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ haloalkoxyl, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -($C_1$-$C_6$ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and $C_1$-$C_6$ alkyl or $C_1$-$C_6$ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/062731

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519
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

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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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

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 January 2017 | 10/02/2017 |

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

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Form PCT/ISA/210 (second sheet) (April 2005)

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International application No
PCT/US2016/062731

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| X,P | WO 2016/133838 A1 (RIGEL PHARMACEUTICALS INC [US]; BRISTOL-MYERS SQUIBB COMPANY [US]) 25 August 2016 (2016-08-25) paragraph [0061]; claims 10,22,37; compounds 119,121,122 | 1,3,10, 12,13, 15,16 |

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Information on patent family members

International application No
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(71)申请人 蓝图药品公司
地址 美国马萨诸塞州
(72)发明人 史蒂文·M·翁劳斯基
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约瑟夫·L·基姆
(74)专利代理机构 永新专利商标代理有限公司 72002
代理人 过晓东
(51)Int.Cl.
*C07D 487/04*(2006.01)
*A61K 31/519*(2006.01)

权利要求书12页 说明书47页

(54)发明名称

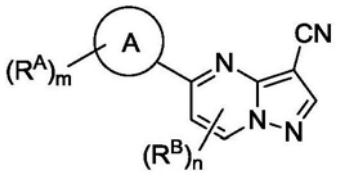
可用于治疗与NTRK相关的病症的化合物和组合物

(57)摘要

本发明涉及包含吡唑并[1,5-4]嘧啶-3-甲腈结构的NTRK抑制剂。所述抑制剂对野生型NTRK和其抗性突变体有活性。

CN 108431008 A

1.一种式I的化合物或其药学上可接受的盐,其中:



I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基;

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$亚烷基)-N($R^2$)-C(O)$R^1$、-N$R^2$S(O)$_2R^1$、-P(O)($R^1$)($R^1$)和-O$R^1$;其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代;

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基和-O$R^1$;

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基,其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代;

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基;或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环;

各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R';

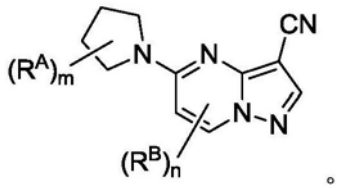
各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基;

m是0、1、2、3、4或5;并且

n是0、1或2;

前提是所述化合物不是(R)-5-(2-(2,5-二氟苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈。

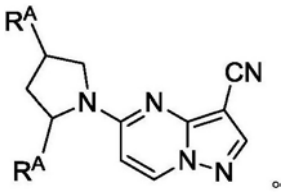
2.如权利要求1所述的化合物,其具有式(Ia-1):



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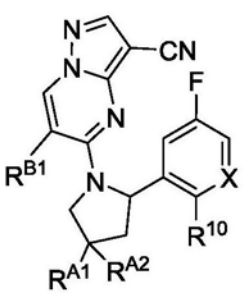
3.如权利要求1所述的化合物,其中至少一个$R^A$是卤代基。

4.如权利要求1所述的化合物,其具有式(Ib):

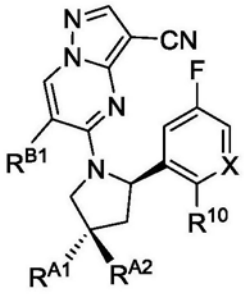


5.如权利要求4所述的化合物，其中一个$R^A$是卤代基并且一个$R^A$是芳基或杂芳基。

6.如权利要求1所述的化合物，其具有式Ic或Ic-1：



(Ic)、



(Ic-1)、

或其药学上可接受的盐，其中：

X是N或C($R^9$)；

$R^{A1}$是氟代基或-CN；

$R^{A2}$是氟代基或氢；

$R^{B1}$是氢或氟代基；

$R^9$选自氢、卤代基、-CN、-$C_1$-$C_4$烷基、-C(O)N($R^{11}$)($R^{11}$)和-S(O)$_2$N($R^{11}$)($R^{11}$)，其中$R^9$的任一烷基部分任选地被一个或多个选自-OH和-F的取代基取代；

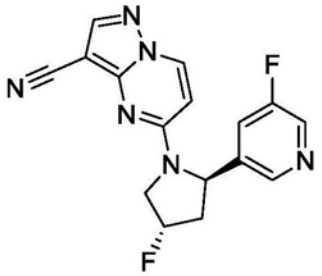
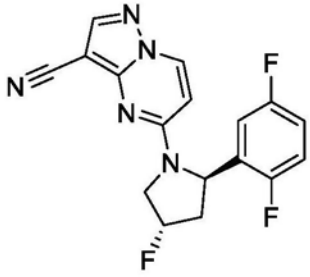
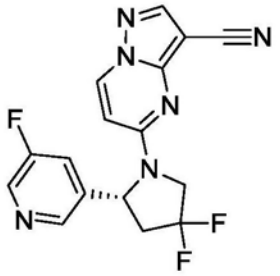
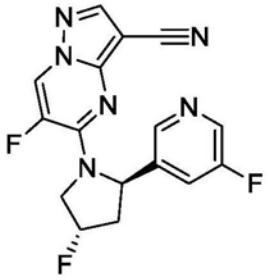
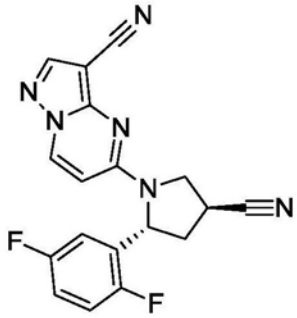
$R^{10}$选自氢、卤代基、任选地被一个或多个卤代基取代的-O-($C_1$-$C_4$烷基)和-C(O)N($R^{11}$)($R^{11}$)；并且

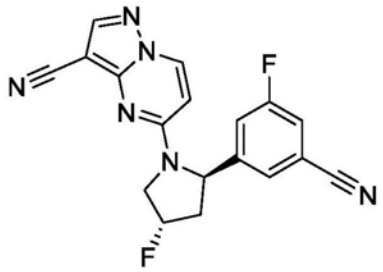
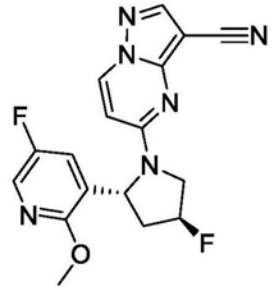
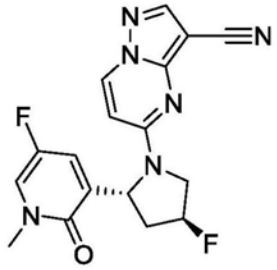
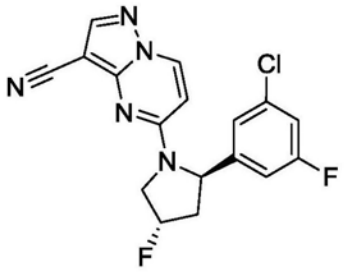
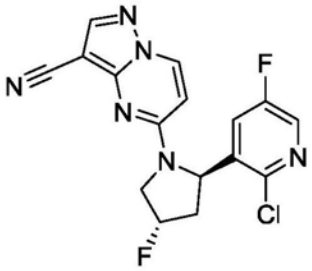
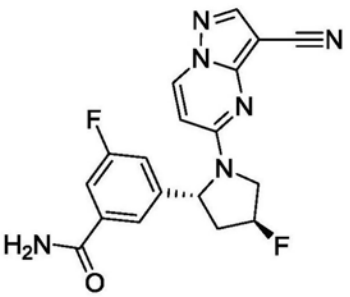
各$R^{11}$独立地选自氢和$C_1$-$C_4$烷基，所述$C_1$-$C_4$烷基任选地被一个或多个选自-OH和环丙基的取代基取代。

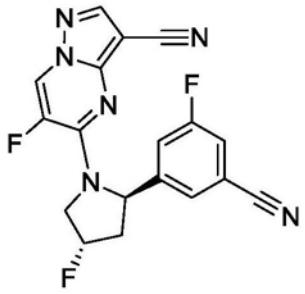
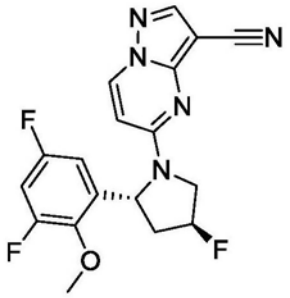
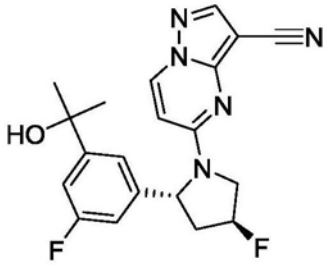
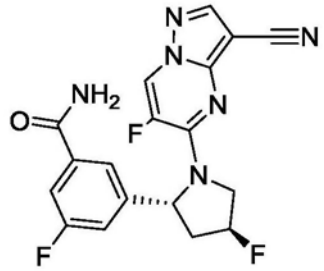
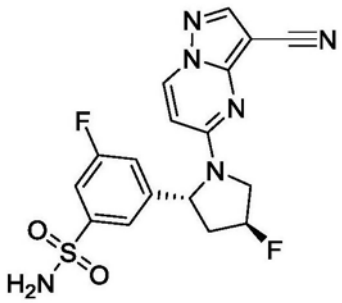
7.如权利要求6所述的化合物，其中$R^9$选自氢、氟代基、氯代基、-CN、-C(O)$NH_2$、-C(O)$NHCH_3$、-C(O)N($CH_3$)$_2$、-C(O)$NHCH_2CH_2OH$、-C(OH)($CH_3$)$_2$、-S(O)$_2NH_2$和N-(环丙基甲基)氨甲酰基。

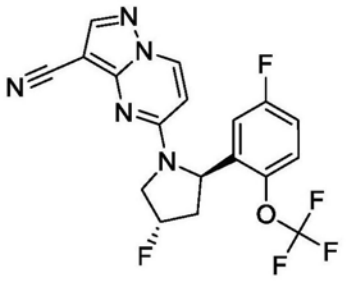
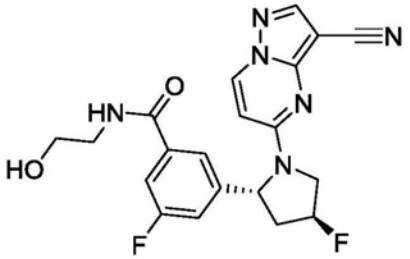
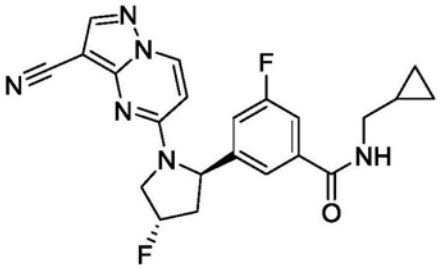
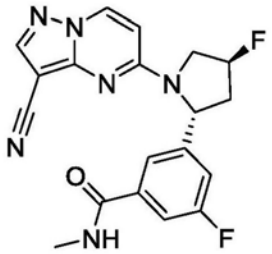
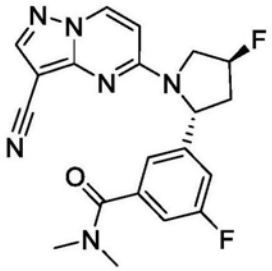
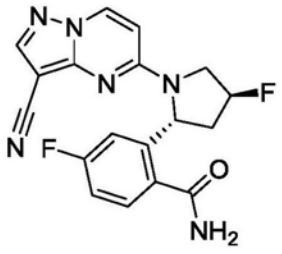
8.如权利要求6或7所述的化合物，其中$R^{10}$选自氢、氟代基、氯代基、-$OCH_3$、-$OCF_3$和-C(O)$NH_2$。

9.如权利要求1所述的化合物，其选自下表中的化合物中的任一种：

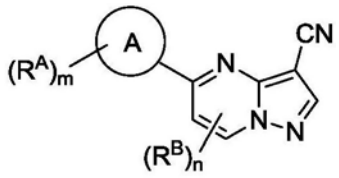
| 化合物编号 | 结构 |
| --- | --- |
| 1 |  |
| 2 |  |
| 3 |  |
| 4 |  |
| 5 |  |

| | |
|---|---|
| **6** |  |
| **7** |  |
| **8** |  |
| **9** |  |
| **10** |  |
| **11** |  |

| | |
|---|---|
| **12** |  |
| **13** |  |
| **14** |  |
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| **16** |  |

| | |
|---|---|
| **17** |  |
| **18** |  |
| **19** |  |
| **20** |  |
| **21** |  |
| **22** |  |

10.一种药物组合物,其包含式I的化合物或其药学上可接受的盐和药学上可接受的载剂,其中:



I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基；

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$亚烷基)-N($R^2$)-C(O)$R^1$、-N$R^2$S(O)$_2R^1$、-P(O)($R^1$)($R^1$)和-O$R^1$；其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代；

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基和-O$R^1$；

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基，其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代；

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基；或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环；

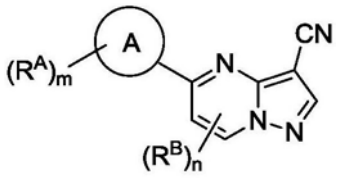
各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R'；

各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

m是0、1、2、3、4或5；并且

n是0、1或2。

11.一种抑制细胞或患者中的NTRK活性的方法，所述方法包括使所述细胞接触或向所述患者施用结构式I的化合物或其药学上可接受的盐或组合物的步骤，其中：



I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基；

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$

亚烷基)-N(R²)-C(O)R¹、-NR²S(O)₂R¹、-P(O)(R¹)(R¹)和-OR¹;其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代;

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N(R¹)(R¹)、硝基、氰基和-OR¹;

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基,其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代;

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基;或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环;

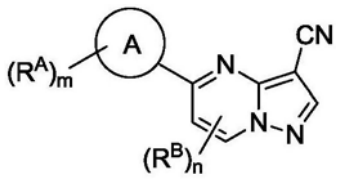
各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R';

各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基;

m是0、1、2、3、4或5;并且

n是0、1或2。

12.一种治疗罹患由异常的神经营养性酪氨酸受体激酶(NTRK)活性介导的病况的受试者的方法,所述方法包括向所述受试者施用治疗有效量的式I的化合物或其药学上可接受的盐,其中:




I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基;

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N(R¹)(R¹)、硝基、氰基、-C(O)R¹、-OC(O)R¹、-C(O)OR¹、-SR¹、-S(O)₂R¹、-S(O)₂-N(R²)(R²)、-($C_1$-$C_6$亚烷基)-S(O)₂-N(R²)(R²)、-C(O)-N(R²)(R²)、-N(R²)(R²)-C(O)R¹、-($C_1$-$C_6$亚烷基)-N(R²)-C(O)R¹、-NR²S(O)₂R¹、-P(O)(R¹)(R¹)和-OR¹;其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代;

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N(R¹)(R¹)、硝基、氰基和-OR¹;

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基,其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代;

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基;或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环;

各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N

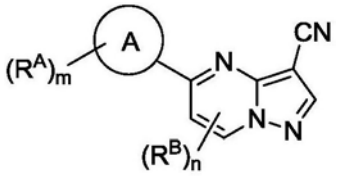
(R”)(R”)、-C(O)-N(R”)(R”)、-N(R”)(R”)-C(O)R’和-($C_1$-$C_6$亚烷基)-N(R”)-C(O)R’；

各R’和R”独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

m是0、1、2、3、4或5；并且

n是0、1或2。

13.一种治疗已对癌症治疗产生抗性的受试者的方法，所述方法包括向所述受试者施用治疗有效量的式I的化合物或其药学上可接受的盐，其中：




I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基；

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$亚烷基)-N($R^2$)-C(O)$R^1$、-N$R^2$S(O)$_2R^1$、-P(O)($R^1$)($R^1$)和-O$R^1$；其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代；

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基和-O$R^1$；

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基，其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代；

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基；或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环；

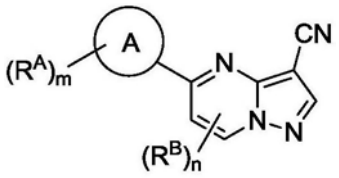
各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R”)(R”)、-C(O)-N(R”)(R”)、-N(R”)(R”)-C(O)R’和-($C_1$-$C_6$亚烷基)-N(R”)-C(O)R’；

各R’和R”独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

m是0、1、2、3、4或5；并且

n是0、1或2。

14.一种结构式I的化合物或其药学上可接受的盐或组合物，其用于抑制细胞或患者中的NTRK活性，其中：



I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基；

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$亚烷基)-N($R^2$)-C(O)$R^1$、-N$R^2$S(O)$_2R^1$、-P(O)($R^1$)($R^1$)和-O$R^1$；其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代；

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基和-O$R^1$；

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基，其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代；

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基；或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环；

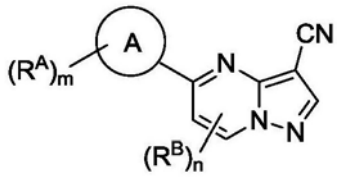
各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-(C1-$C_6$亚烷基)-N(R")-C(O)R'；

各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

m是0、1、2、3、4或5；并且

n是0、1或2。

15.一种结构式I的化合物或其药学上可接受的盐或组合物，其用于治疗罹患由异常的神经营养性酪氨酸受体激酶(NTRK)活性介导的病况的受试者，其中：



I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基；

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$

亚烷基)-N(R²)-C(O)R¹、-NR²S(O)₂R¹、-P(O)(R¹)(R¹)和-OR¹;其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代;

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N(R¹)(R¹)、硝基、氰基和-OR¹;

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基,其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代;

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基;或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环;

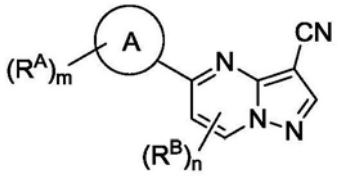
各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R';

各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基;

m是0、1、2、3、4或5;并且

n是0、1或2。

16.一种结构式I的化合物或其药学上可接受的盐或组合物,其用于治疗已对癌症治疗产生抗性的受试者,其中:




I

环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基;

各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N(R¹)(R¹)、硝基、氰基、-C(O)R¹、-OC(O)R¹、-C(O)OR¹、-SR¹、-S(O)₂R¹、-S(O)₂-N(R²)(R²)、-($C_1$-$C_6$亚烷基)-S(O)₂-N(R²)(R²)、-C(O)-N(R²)(R²)、-N(R²)(R²)-C(O)R¹、-($C_1$-$C_6$亚烷基)-N(R²)-C(O)R¹、-NR²S(O)₂R¹、-P(O)(R¹)(R¹)和-OR¹;其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代;

各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N(R¹)(R¹)、硝基、氰基和-OR¹;

各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基,其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代;

各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基;或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环;

各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N

(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R'；

各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

m是0、1、2、3、4或5；并且

n是0、1或2。

# 可用于治疗与NTRK相关的病症的化合物和组合物

[0001] 优先权要求

[0002] 本申请要求2015年11月19日提交的U.S.S.N.62/257,476的优先权,所述案件以引用的方式整体并入本文中。

[0003] 背景

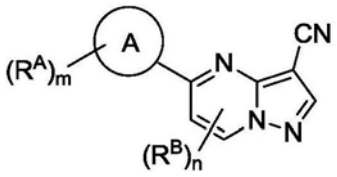
[0004] 神经营养性酪氨酸受体激酶(NTRK)1、2和3是活化参与细胞增殖和存活的多个下游途径的受体酪氨酸激酶(RTK)。由编码这些RTK的基因的异常染色体易位引起的各种基因融合与多种癌症的病因学相关,所述癌症包括高级和低级神经胶质瘤、胆管癌、乳头状甲状腺癌、结肠癌和非小细胞肺癌。对激酶融合概况的基因组学分析在许多其他癌症类型(包括头颈部鳞状细胞癌、胰腺癌、肉瘤和黑素瘤)中鉴别出了NTRK融合,从而提供了部署这些激酶的抑制剂来治疗多种肿瘤学适应症的其它治疗理念。

[0005] NTRK融合作为某些癌症的潜在原因的鉴别促进了发现和临床研发几种NTRK激酶抑制剂来治疗具有NTRK融合蛋白的肿瘤。早期的临床数据支持该方法在为特定的人恶性肿瘤患者提供益处方面的可行性。然而,最终,尽管有明显的临床活性迹象,但大多数患者的癌症将会变得对激酶抑制剂疗法具有抗性,从而导致疾病的复发和进展。当出现抗性时,患者的治疗选项通常非常有限。因此,需要抑制NTRK以及其抗性突变体的化合物。

## 发明概要

[0006] 本发明提供NTRK和NTRK突变体(例如,NTRK抗性突变体(如本文所定义))的抑制剂,例如,结构式(I)的抑制剂和其药学上可接受的盐和组合物。本发明进一步提供使用本发明的化合物和其药学上可接受的盐和组合物来抑制细胞或患者中NTRK或其突变体的活性的方法。本发明进一步提供使用本发明的化合物和其药学上可接受的盐和组合物来治疗罹患由异常的NTRK活性介导的病况(例如癌症)的受试者的方法。

[0007] 在一个方面,本发明特征在于式I的化合物或其药学上可接受的盐,其中:

[0008] 


I

[0009] 环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基;

[0010] 各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$亚烷基)-N($R^2$)-C(O)$R^1$、-N$R^2$S(O)$_2R^1$、-P(O)($R^1$)($R^1$)和-O$R^1$;其中芳基、杂芳基、环烷基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代;

[0011] 各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基和-$OR^1$；

[0012] 各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基，其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代；

[0013] 各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基；或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环；

[0014] 各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R'；

[0015] 各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

[0016] m是0、1、2、3、4或5；并且

[0017] n是0、1或2；

[0018] 前提是所述化合物不为(R)-5-(2-(2,5-二氟苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈。

[0019] 在另一方面，本发明提供药物组合物，其包含结构式(I)的化合物或其药学上可接受的盐和药学上可接受的载剂。

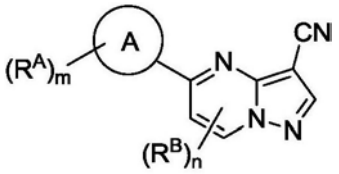
[0020] 在另一方面，本发明提供抑制细胞或患者中的NTRK活性的方法。在一些实施方案中，所述方法包括使细胞接触或向患者施用结构式(I)的化合物或其药学上可接受的盐或组合物的步骤。

[0021] 在另一方面，本发明提供治疗罹患由异常的NTRK活性介导的病况的受试者的方法。在一些实施方案中，所述方法包括向受试者施用治疗有效量的结构式(I)的化合物或其药学上可接受的盐或组合物。

[0022] 在另一方面，本发明提供治疗已对癌症治疗产生抗性的受试者的方法。在一些实施方案中，所述方法包括向受试者施用治疗有效量的结构式(I)的化合物或其药学上可接受的盐或组合物。

[0023] 发明实施方案

[0024] 在一个方面，本发明特征在于式I的化合物或其药学上可接受的盐，其中：

[0025] 


I

[0026] 环A选自单环或二环芳基、单环或二环杂芳基、环烷基和杂环基；

[0027] 各$R^A$独立地选自单环或二环芳基、单环或二环杂芳基、单环或二环环烷基、单环或二环杂环基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基、-C(O)$R^1$、-OC(O)$R^1$、-C(O)O$R^1$、-S$R^1$、-S(O)$_2R^1$、-S(O)$_2$-N($R^2$)($R^2$)、-($C_1$-$C_6$亚烷基)-S(O)$_2$-N($R^2$)($R^2$)、-C(O)-N($R^2$)($R^2$)、-N($R^2$)($R^2$)-C(O)$R^1$、-($C_1$-$C_6$亚烷基)-N($R^2$)-C(O)$R^1$、-N$R^2$S(O)$_2R^1$、-P(O)($R^1$)($R^1$)和-O$R^1$；其中芳基、杂芳基、环烷

基、杂环基、烷基、烷氧基、卤代烷基、羟烷基、杂烷基中的每一个独立地被0至5次出现的$R^a$取代；

[0028] 各$R^B$独立地选自$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、卤代基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、-N($R^1$)($R^1$)、硝基、氰基和-O$R^1$；

[0029] 各$R^1$独立地选自氢、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$卤代烷氧基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基，其中$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$羟烷基、$C_1$-$C_6$杂烷基、环烷基、环烷基烷基、杂环基和杂环基烷基中的每一个独立地被0至5次出现的$R^b$取代；

[0030] 各$R^2$独立地选氢、$C_1$-$C_6$烷基、$C_1$-$C_6$杂烷基；或2个$R^2$与其所连接的氮一起形成被0至5次出现的$R^b$取代的杂环基环；

[0031] 各$R^a$和$R^b$独立地选自卤代基、氰基、羟基、$C_1$-$C_6$烷基、$C_1$-$C_6$烷氧基、$C_1$-$C_6$卤代烷氧基、-N(R")(R")、-C(O)-N(R")(R")、-N(R")(R")-C(O)R'和-($C_1$-$C_6$亚烷基)-N(R")-C(O)R'；

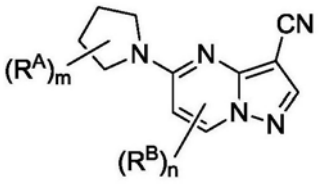
[0032] 各R'和R"独立地选自氢和$C_1$-$C_6$烷基或$C_1$-$C_6$羟烷基；

[0033] m是0、1、2、3、4或5；并且

[0034] n是0、1或2；

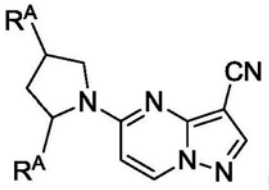
[0035] 前提是所述化合物不为(R)-5-(2-(2,5-二氟苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈。

[0036] 在一些实施方案中，所述化合物具有式(Ia-1)：

[0037] 
(Ia-1)。

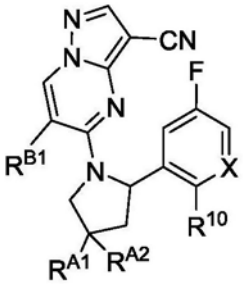
[0038] 在一些实施方案中，至少一个$R^A$是卤代基。

[0039] 在其它实施方案中，所述化合物具有式(Ib)：

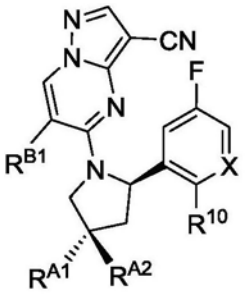
[0040] 
(Ib)。

[0041] 在一些实施方案中，一个$R^A$是卤代基并且一个$R^A$是芳基或杂芳基。

[0042] 在一些实施方案中，所述化合物具有式Ic：

[0043] 

(Ic)或式 Ic-1:

[0044]  其中：

(Ic-1),

[0045] X是N或C($R^9$)；

[0046] $R^{A1}$是氟代基或-CN；

[0047] $R^{A2}$是氟代基或氢；

[0048] $R^{B1}$是氢或氟代基；

[0049] $R^9$选自氢、卤代基、-CN、-$C_1$-$C_4$烷基、-C(O)N($R^{11}$)($R^{11}$)和-S(O)$_2$N($R^{11}$)($R^{11}$)，其中$R^9$的任一烷基部分任选地被一个或多个选自-OH和-F的取代基取代；

[0050] $R^{10}$选自氢、卤代基、任选地被一个或多个卤代基取代的-O-($C_1$-$C_4$烷基)和-C(O)N($R^{11}$)($R^{11}$)；并且

[0051] 各$R^{11}$独立地选自氢和$C_1$-$C_4$烷基，所述$C_1$-$C_4$烷基任选地被一个或多个选自-OH和环丙基的取代基取代。

[0052] 在式Ic的一些实施方案中，$R^9$选自氢、氟代基、氯代基、-CN、-C(O)$NH_2$、-C(O)$NHCH_3$、-C(O)N($CH_3$)$_2$、-C(O)$NHCH_2CH_2OH$、-C(OH)($CH_3$)$_2$、-S(O)$_2NH_2$和N-(环丙基甲基)氨甲酰基。

[0053] 在式Ic的一些实施方案中，$R^{10}$选自氢、氟代基、氯代基、-$OCH_3$、-$OCF_3$和-C(O)$NH_2$。

[0054] 在另一方面，本发明特征在于抑制细胞或患者中的NTRK活性的方法，所述方法包括使细胞接触或向患者施用本文所述的化合物(例如，表1中的化合物)或其药学上可接受的盐或其药物组合物的步骤。

[0055] 在另一方面，本发明特征在于治疗罹患由异常NTRK活性介导的病况的受试者的方法，所述方法包括向受试者施用治疗有效量的本文所述的化合物(例如，表1中的化合物)或其药学上可接受的盐或其药物组合物。

[0056] 在另一方面，本发明特征在于治疗已对癌症治疗产生抗性的受试者的方法，所述方法包括向受试者施用治疗有效量的本文所述的化合物(例如，表1中的化合物)或其药学上可接受的盐或其药物组合物。

[0057] 定义

[0058] 如本文所用，术语“患者”、“受试者”、“个体”和“宿主”是指罹患或怀疑罹患与异常的NTRK表达(即通过经由NTRK的信号传导造成的NTRK活性增加)或生物学活性相关的疾病或病症的人或非人动物。

[0059] “治疗(Treat和treating)”此类疾病或病症是指改善所述疾病或病症的至少一种症状。这些术语在与(例如)癌症的病况结合使用时是指以下各项中的一个或多个：阻止癌症的生长、使得癌症的重量或体积缩小、延长患者的预期存活时间、抑制肿瘤生长、减少肿瘤质量、减小转移性病灶的大小或数量、抑制新的转移性病灶的发展、延长存活、延长无进

展存活、延长进展前的时间和/或提高生活质量。

[0060] 术语“预防”在与(例如)癌症的病况或疾病结合使用时是指所述病况或疾病的症状的频率降低或发作延迟。因此,预防癌症包括(例如)相对于未治疗的对照群体,减少接受预防性治疗的患者群体中可检测癌性生长的数量,和/或相对于未治疗的对照群体,延迟被治疗群体中可检测癌性生长的出现,达到(例如)统计学上和/或临床上显著的量。

[0061] 术语“治疗效应”是指在动物、特别是哺乳动物且更特别是人中通过施用本发明的化合物或组合物引起的有益的局部或全身效应。短语“治疗有效量”意指以合理的益处/风险比有效地治疗由NTRK过表达或异常的NTRK生物活性造成的疾病或病况的本发明化合物或组合物的量。此类物质的治疗有效量将根据所治疗的受试者和疾病病况、受试者的重量和年龄、疾病病况的严重性、施用方式等而变化,其可容易地由本领域技术人员确定。

[0062] 如本文所用,“产生抗性”意味着当首次向患者施用药物时,患者的症状会改善,无论是由肿瘤体积的减小、新病灶数量的减少还是通过医师用来判断疾病进展的一些其它方式所测量;但那些症状在某一点会停止改善或者甚至会恶化。在那时,据称患者已发展对药物的抗性。

[0063] “脂族基团”意指直链、支链或环状烃基团并且包括饱和以及不饱和的基团,例如烷基、烯基和炔基。

[0064] “亚烷基”是指烷基的二价基团,例如,$-CH_2-$、$-CH_2CH_2-$和$CH_2CH_2CH_2-$。

[0065] “烯基”意指含有至少一个双键的脂族基团。

[0066] “烷氧基(Alkoxyl或alkoxy)”意指连接有氧自由基的烷基。代表性烷氧基包括甲氧基、乙氧基、丙氧基、叔丁氧基等。术语“卤代烷氧基”是指其中一个或多个氢原子被卤代基替代的烷氧基,并且包括其中所有的氢都被卤代基替代的烷氧基部分(例如,全氟烷氧基)。

[0067] “烷基”是指饱和直链或支链烃的单价基团,例如1至12个、1至10个或1至6个碳原子的直链或支链基团,其在本文分别称作$C_1-C_{12}$烷基、$C_1-C_{10}$烷基和$C_1-C_6$烷基。示例性的烷基包括(但不限于)甲基、乙基、丙基、异丙基、2-甲基-1-丙基、2-甲基-2-丙基、2-甲基-1-丁基、3-甲基-1-丁基、2-甲基-3-丁基、2,2-二甲基-1-丙基、2-甲基-1-戊基、3-甲基-1-戊基、4-甲基-1-戊基、2-甲基-2-戊基、3-甲基-2-戊基、4-甲基-2-戊基、2,2-二甲基-1-丁基、3,3-二甲基-1-丁基、2-乙基-1-丁基、丁基、异丁基、叔丁基、戊基、异戊基、新戊基、己基、庚基、辛基等。

[0068] “亚烯基”是指具有两个连接点的烯基。例如,“亚乙烯基”表示基团$-CH=CH-$。亚烯基还可呈未取代的形式或具有一个或多个取代基的被取代形式。

[0069] “炔基”是指含有2-12个碳原子且以具有一个或多个三键为特征的直链或支链烃链。炔基的实例包括(但不限于)乙炔基、炔丙基和3-己炔基。三键碳中的一个可任选地为炔基取代基的连接点。

[0070] “亚炔基”是指具有两个连接点的炔基。例如,“亚乙炔基”表示基团$-C\equiv C-$。亚炔基还可呈未取代的形式或具有一个或多个取代基的被取代形式。

[0071] “羟亚烷基”或“羟烷基”是指其中亚烷基或烷基氢原子被羟基替代的亚烷基或烷基部分。羟亚烷基或羟烷基包括其中一个以上氢原子已被羟基替代的基团。

[0072] “芳族环体系”是本领域公知的并且是指其中至少一个环是芳族环的单环、二环或

多环烃环体系。

[0073] “芳基”是指芳族环体系的单价基团。代表性芳基包括完全芳族环体系，例如苯基、萘基和蒽基；以及其中芳族碳环稠合至一个或多个非芳族碳环的环体系，例如二氢茚基、邻苯二甲酰亚氨基、萘二甲酰亚氨基或四氢萘基等。

[0074] “芳基烷基”或“芳烷基”是指其中烷基氢原子被芳基替代的烷基部分。芳烷基包括其中一个以上氢原子已被芳基替代的基团。“芳基烷基”或“芳烷基”的实例包括苄基、2-苯乙基、3-苯丙基、9-芴基、二苯甲基和三苯甲基。

[0075] “芳氧基”是指-O-(芳基)，其中杂芳基部分如本文所定义。

[0076] “卤代基”是指任一卤素的基团，例如，-F、-Cl、-Br或-I。

[0077] “卤代烷基”和“卤代烷氧基”是指被一个或多个卤代基或被其组合取代的烷基和烷氧基结构。例如，术语“氟代烷基”和“氟代烷氧基”分别包括其中卤代基是氟的卤代烷基和卤代烷氧基。

[0078] “卤代亚烷基”是指其中一个或多个氢原子被卤代基替代的二价烷基(例如，-$CH_2$-、-$CH_2CH_2$-和-$CH_2CH_2CH_2$-)并且包括其中所有氢都被卤代基替代的烷基部分。

[0079] “杂烷基”是指具有一个或多个选自除碳以外的原子(例如，氧、氮、硫、磷或其组合)的主链原子的任选取代的烷基。数值范围可以是给定的，例如$C_1$-$C_6$杂烷基，其是指在该实例中链中碳的数目包括1至6个碳原子。例如，-$CH_2OCH_2CH_3$基团被称为“$C_3$”杂烷基。连接至分子的其余部分可以经由杂烷基链中的杂原子或碳进行。“亚杂烷基”是指具有一个或多个选自除碳以外的原子(例如，氧、氮、硫、磷或其组合)的主链原子的二价任选取代的烷基。

[0080] “碳环体系”是指其中每一环为完全饱和或含有一个或多个不饱和单元但其中环都不为芳族环的单环、二环或多环烃环体系。

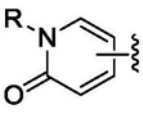
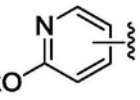
[0081] “碳环基”是指碳环体系的单价基团。代表性碳环基包括环烷基(例如，环戊基、环丁基、环戊基、环己基等)和环烯基(例如，环戊烯基、环己烯基、环戊二烯基等)。

[0082] “环烷基”是指具有3至12个碳的环状、双环、三环或多环非芳族烃基。任一可取代的环原子都可被取代(例如，被一个或多个取代基取代)。环烷基可含有稠环或螺环。稠环是共有共同碳原子的环。环烷基部分的实例包括(但不限于)环丙基、环己基、甲基环己基、金刚烷基和降冰片基。

[0083] “环烷基烷基”是指其中环烷基和烷基是如本文所公开的那样的-(环烷基)-烷基。“环烷基烷基”是经由环烷基键合至母体分子结构。

[0084] “杂芳族环体系”是本领域公知的并且是指如下的单环、二环或多环体系：其中至少一个环是芳族环并且包含至少一个杂原子(例如，N、O或S)；并且其中其它环都不为杂环基(如下文所定义)。在某些情况下，是芳族环并且包含杂原子的环在此类环中含有1个、2个、3个或4个环杂原子。

[0085] “杂芳基”是指杂芳族环体系的单价基团。代表性杂芳基包括如下的环体系：其中(i)每一环包含杂原子并且是芳族环，例如，咪唑基、噁唑基、噻唑基、三唑基、吡咯基、呋喃基、噻吩基吡唑基、吡啶基、吡嗪基、哒嗪基、嘧啶基、吲嗪基、嘌呤基、萘啶基和蝶啶基；(ii)每一环是芳族环或碳环基，至少一个芳族环包含杂原子并且至少一个其它环是烃环或(例如)吲哚基、异吲哚基、苯并噻吩基、苯并呋喃基、二苯并呋喃基、吲唑基、苯并咪唑基、苯并噻唑基、喹啉基、异喹啉基、噌啉基、酞嗪基、喹唑啉基、喹喔啉基、咔唑基、吖啶基、吩嗪基、

吩噻嗪基、吩噁嗪基、吡啶并[2,3-b]-1,4-噁嗪-3-(4H)-酮、5,6,7,8-四氢喹啉基和5,6,7,8-四氢异喹啉基;并且(iii)每一环是芳族环或碳环基,并且至少一个芳族环与另一芳族环(例如,4H-喹嗪基)共有桥头杂原子。在一些实施方案中,杂芳基可包括和,其中R是H或$C_{1-6}$烷基。

[0086] "杂环体系"是指其中至少一个环是饱和或部分不饱和的环(但不是芳族环)并且包含至少一个杂原子的单环、二环和多环环体系。杂环体系可在任一杂原子或碳原子处连接至其侧基从而产生稳定的结构,并且任一个环原子都可任选地被取代。

[0087] "杂环基"是指杂环体系的单价基团。代表性杂环基包括如下的环体系:其中(i)每个环是非芳族环并且至少一个环包含杂原子,例如,四氢呋喃基、四氢吡喃基、四氢噻吩基、吡咯烷基、吡咯烷酮基、哌啶基、吡咯啉基、十氢喹啉基、噁唑烷基、哌嗪基、二噁烷基、二氧戊环基、二氮呼基、氧氮呼基、硫氮呼基、吗啉基和奎宁环基;(ii)至少一个环是非芳族环并且包含杂原子,并且至少一个其它环是芳族碳环,例如,1,2,3,4-四氢喹啉基、1,2,3,4-四氢异喹啉基;并且(iii)至少一个环是非芳族环并且包含杂原子,并且至少一个其它环是芳族环并且包含杂原子,例如,3,4-二氢-1H-吡喃并[4,3-c]吡啶和1,2,3,4-四氢-2,6-萘啶。

[0088] "杂环基烷基"是指被杂环基取代的烷基。

[0089] "氰基"是指-CN基团。

[0090] "硝基"是指$-NO_2$。

[0091] "羟基(Hydroxy或hydroxyl)"是指-OH。

[0092] "羟烷基"是指其中一个或多个氢原子被羟基替代的二价烷基(例如,$-CH_2-$、$-CH_2CH_2-$和$-CH_2CH_2CH_2-$),并且包括其中所有氢都被羟基替代的烷基部分。

[0093] "取代的"无论前面是否有术语"任选地"都意味着指定部分的一个或多个氢被适合的取代基替代。除非另有指示,否则"任选地取代的"基团可在该基团的每一可取代位置具有适合的取代基,并且当任一给定结构中的一个以上位置可被一个以上选自指定基团的取代基取代时,则每一位置的取代基可以是相同或不同的。本发明所设想的取代基的组合优选是使得形成稳定或化学可行的化合物的那些组合。如本文所用,术语"稳定"是指化合物在经受允许其生产、检测和(在某些实施方案中)其回收、纯化和出于本文所公开的一个或多个目的的使用的条件时基本上不会发生改变。

[0094] 如本文所用,每一表述(例如,烷基、m、n等)在任一结构中出现一次以上时其定义意在独立于其在同一结构中其它地方的定义。

[0095] 本发明的某些化合物可以特定的几何或立体异构形式存在。本发明涵盖如属于本发明的范围的所有此类化合物,包括顺式-和反式-异构体、R-和S-对映异构体、非对映异构体、(D)-异构体、(L)-异构体、它们的外消旋混合物和它们的其它混合物。其它不对称的碳原子可以存在于例如烷基的取代基中。所有此类异构体以及其混合物都打算包括在本发明中。

[0096] 若需要(例如)本发明化合物的特定对映异构体,则所述对映异构体可以通过不对称合成或者通过用手性助剂衍生化来制备,其中分离所得非对映异构体混合物并裂解辅助基团以得到纯净的所需对映异构体。或者,倘若分子含有碱性官能团(例如氨基)或酸性官

能团(例如羧基),则可用适当的光学活性酸或碱形成非对映异构体盐,随后通过本领域众所周知的分离结晶或色谱手段来拆分由此形成的非对映异构体,并且随后回收纯净的对映异构体。

[0097] 除非另有指示,否则当所公开的化合物是通过结构来命名或绘示而不指定立体化学并且具有一个或多个手性中心时,则应理解表示所述化合物的所有可能的立体异构体以及其对映异构体混合物。可使用下文所显示的等式计算组合物的"对映异构体过量"或"对映异构体过量%"。在下文所显示的实例中,组合物含有90%的一种对映异构体(例如,S对映异构体)和10%的另一种对映异构体(即,R对映异构体)。

[0098] ee=(90-10)/100=80%。

[0099] 因此,据称含有90%的一种对映异构体和10%的另一种对映异构体的组合物具有80%的对映异构体过量。

[0100] 本文所述的化合物或组合物可含有至少50%、75%、90%、95%或99%的对映异构体过量的一种形式的化合物(例如,S对映异构体)。换句话说,此类化合物或组合物所含有的S对映异构体的对映异构体过量高于R对映异构体。

[0101] 本文所述的化合物还可以在构成此类化合物的一个或多个原子处含有非天然比例的原子同位素。例如,所述化合物可以被放射性同位素(例如氘($^{2}H$)、氚($^{3}H$)、碳-13($^{13}C$)或碳-14($^{14}C$))放射标记。本文公开的化合物的所有同位素变化形式(无论是否是放射性的)都打算涵盖在本发明的范围内。此外,本文所述的化合物的所有互变异构形式都打算涵盖在本发明的范围内。

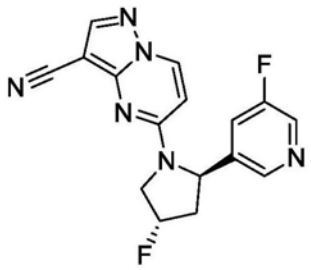
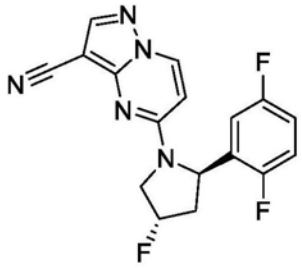
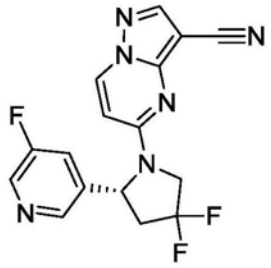
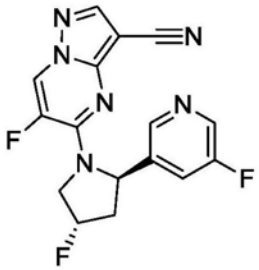
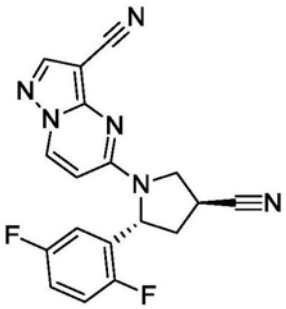
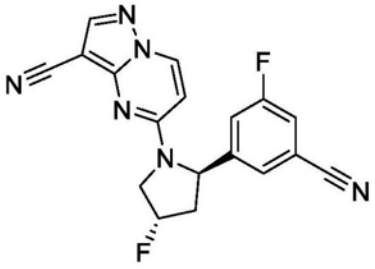
[0102] 所述化合物可以作为游离碱或盐来使用。代表性的盐包括氢溴酸盐、盐酸盐、硫酸盐、硫酸氢盐、磷酸盐、硝酸盐、乙酸盐、戊酸盐、油酸盐、棕榈酸盐、硬脂酸盐、月桂酸盐、苯甲酸盐、乳酸盐、磷酸盐、甲苯磺酸盐、柠檬酸盐、马来酸盐、富马酸盐、琥珀酸盐、酒石酸盐、萘酸盐(napthylate)、甲磺酸盐、葡庚糖酸盐、乳糖酸盐和月桂基磺酸盐等。(例如参见,Berge等(1977)"Pharmaceutical Salts",J.Pharm.Sci.66:1-19)。

[0103] 下表1显示了本文所述化合物的结构。

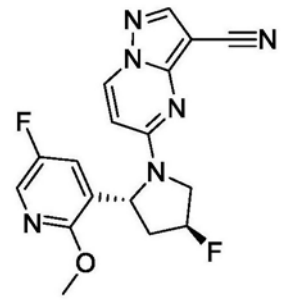
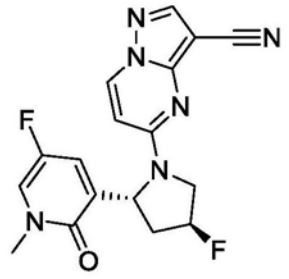
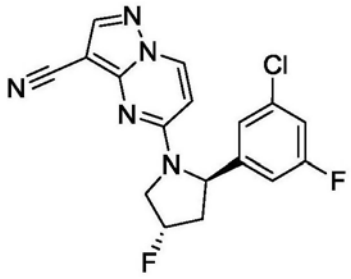
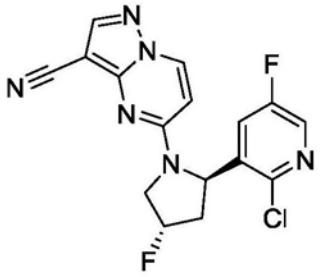
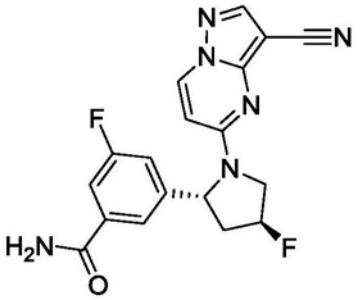
[0104]

| 化合物编号 | 结构 |
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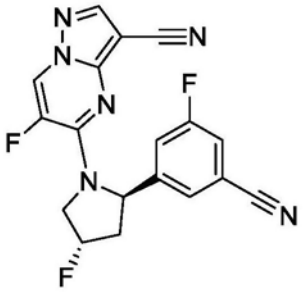
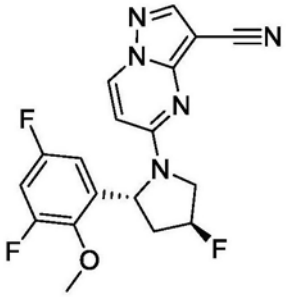
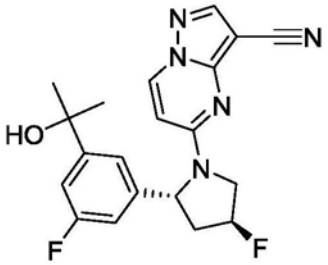
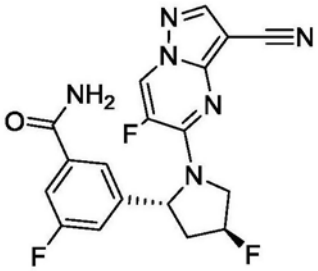
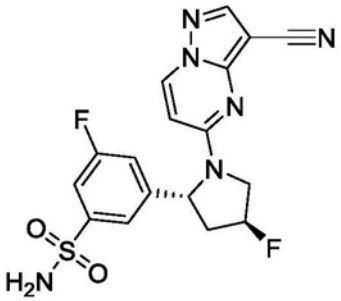
[0105]

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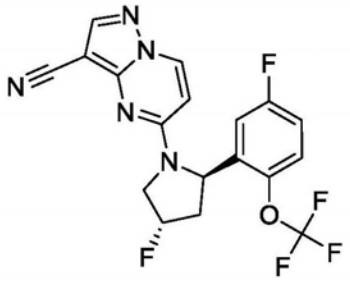
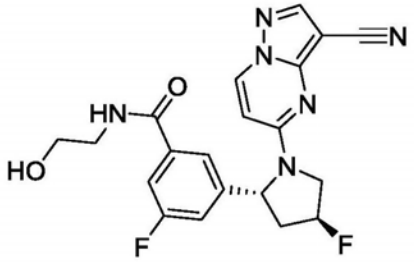
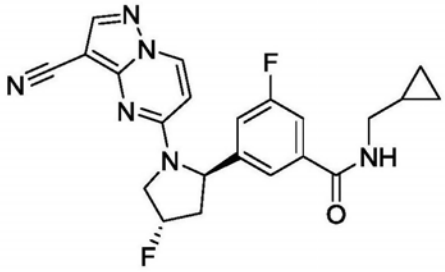
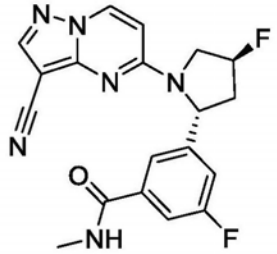
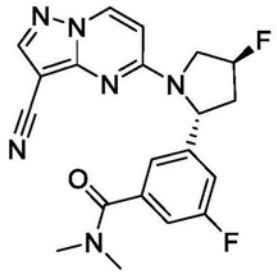
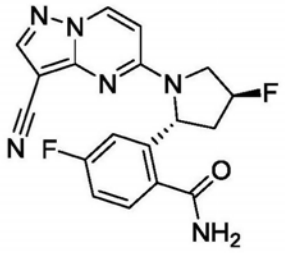
[0106]

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[0109] 预期这些化合物的药学上可接受的盐也可用于本文所述的用途。

[0110] “药学上可接受的盐”是指本发明化合物的保留其生物学性质并且没有毒性或换

句话说对于药学使用来说不会不合意的任何盐。药学上可接受的盐可以衍生自本领域公知的各种有机和无机反离子并且包括以下盐。此类盐包括：(1)用有机或无机酸形成的酸加成盐，所述酸例如盐酸、氢溴酸、硫酸、硝酸、磷酸、氨基磺酸、乙酸、三氟乙酸、三氯乙酸、丙酸、己酸、环戊基丙酸、乙醇酸、戊二酸、丙酮酸、乳酸、丙二酸、琥珀酸、山梨酸、抗坏血酸、苹果酸、马来酸、富马酸、酒石酸、柠檬酸、苯甲酸、3-(4-羟基苯甲酰基)苯甲酸、苦味酸、桂皮酸、苦杏仁酸、邻苯二甲酸、月桂酸、甲磺酸、乙磺酸、1,2-乙烷-二磺酸、2-羟基乙磺酸、苯磺酸、4-氯苯磺酸、2-萘磺酸、4-甲苯磺酸、樟脑酸、樟脑磺酸、4-甲基双环[2.2.2]-辛-2-烯-1-甲酸、葡萄庚酸、3-苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡萄糖酸、苯甲酸、谷氨酸、羟基萘甲酸、柳酸、硬脂酸、环己基氨基磺酸、奎尼酸、粘康酸等酸；或(2)在下列两种情况下形成的盐：存在于母体化合物中的酸性质子(a)被金属离子(例如，碱金属离子、碱土金属离子或铝离子)或碱金属或碱土金属的氢氧化物(例如钠、钾、钙、镁、铝、锂、锌和钡的氢氧化物)、氨替代，或者(b)与有机碱配位，所述有机碱例如脂族、脂环族或芳族有机胺，例如氨、甲胺、二甲胺、二乙胺、甲吡啶、乙醇胺、二乙醇胺、三乙醇胺、乙二胺、赖氨酸、精氨酸、鸟氨酸、胆碱、N,N'-二苄基亚乙基-二胺、氯普鲁卡因(chloroprocaine)、二乙醇胺、普鲁卡因、N-苄基苯乙胺、N-甲基葡糖胺哌嗪、三(羟甲基)-氨基甲烷、氢氧化四甲铵等。仅举例来说，药学上可接受的盐进一步包括钠盐、钾盐、钙盐、镁盐、铵盐、四烷基铵盐等，并且当所述化合物含有碱性官能团时，进一步包括无毒有机或无机酸的盐，例如盐酸盐、氢溴酸盐、酒石酸盐、甲磺酸盐、苯磺酸盐、乙酸盐、马来酸盐、草酸盐等。

[0111] 药物组合物

[0112] 本发明的药物组合物包含一种或多种本发明化合物和一种或多种生理学上或药学上可接受的载剂。术语“药学上可接受的载剂”是指参与携载或运输任何主体组合物或其组分的药学上可接受的材料、组合物或媒介物，例如液体或固体填充剂、稀释剂、赋形剂、溶剂或封装材料。每一载剂必须是“可接受的”意味着其与主体组合物和其组分应相容并且对患者没有害处。可用作药学上可接受的载剂的材料的一些实例包括：(1)糖，例如乳糖、葡萄糖和蔗糖；(2)淀粉，例如玉米淀粉和马铃薯淀粉；(3)纤维素和其衍生物，例如羧甲基纤维素钠、乙基纤维素和乙酸纤维素；(4)粉状黄蓍胶和；(5)麦芽；(6)明胶；(7)滑石；(8)赋形剂，例如可可脂和栓剂蜡；(9)油，例如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；(10)二醇，例如丙二醇；(11)多元醇，如甘油、山梨醇、甘露醇和聚乙二醇；(12)酯，如油酸乙酯和月桂酸乙酯；(13)琼脂；(14)缓冲剂，如氢氧化镁和氢氧化铝；(15)海藻酸；(16)无热源水；(17)等渗盐水；(18)林格氏溶液(Ringer'ssolution)；(19)乙醇；(20)磷酸盐缓冲溶液；和(21)用于药物调配物中的其它无毒相容性物质。

[0113] 本发明的组合物可经口、肠胃外、通过吸入喷雾、经局部、经直肠、经鼻、经颊、经阴道或经由所植入储器施用。如本文所用，术语“肠胃外”包括皮下、静脉内、肌内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内和颅内注射或输注技术。在一些实施方案中，本发明的组合物是经口、经腹膜内或经静脉内施用。本发明组合物的无菌可注射形式可以是水性或油性的悬浮液。这些悬浮液可根据本领域已知的技术使用适合的分散剂或润湿剂和悬浮剂来调配。无菌可注射制剂还可为于无毒的肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液，例如，呈于1,3-丁二醇中的溶液形式。可采用的可接受的媒介物和溶剂包括水、林格氏溶液和等渗氯化钠溶液。另外，常规采用无菌的不挥发油作为溶剂或悬浮介质。

[0114] 出于这个目的，可采用任何温和的不挥发油，包括合成的甘油单酯或甘油二酯。脂肪酸(例如油酸和其甘油酯衍生物)可用于制备注射剂，天然的药学上可接受的油(例如橄榄油或蓖麻油，尤其是它们的聚氧乙基化型式)同样也可用于制备注射剂。这些油溶液或悬浮液还可含有长链醇稀释剂或分散剂，例如羧甲基纤维素或通常用于制备药学上可接受的剂型(包括乳液和悬浮液)的类似分散剂。出于调配的目的还可使用其它的常用表面活性剂(例如Tween、Spans)和通常用于制造药学上可接受的固体、液体或其它剂型的其它乳化剂或生物利用度增强剂。

[0115] 本发明的药学上可接受的组合物可以任何经口可接受的剂型(包括(但不限于)胶囊、片剂、水性悬浮液或溶液)经口施用。在用于口服使用的片剂的情况下，通常使用的载剂包括乳糖和玉米淀粉。通常还添加润滑剂，例如硬脂酸镁。对于胶囊形式的口服施用，有用的稀释剂包括乳糖和干燥的玉米淀粉。当口服使用需要水性悬浮液时，将活性成分与乳化剂和悬浮剂组合。如果需要，还可添加某些甜味剂、调味剂或着色剂。

[0116] 或者，本发明的药学上可接受的组合物可以用于直肠施用的栓剂形式来施用。这些栓剂可通过将药剂与适合的非刺激性赋形剂混合来制备，所述赋形剂在室温下为固体而在直肠温度下为液体，从而会在直肠中融化以释放药物。此类材料包括可可脂、蜂蜡和聚乙二醇。

[0117] 本发明的药学上可接受的组合物还可以局部施用，尤其是在治疗目标包括通过局部施加容易接近的区域或器官的情况下，所述治疗目标包括眼睛、皮肤或下肠道的疾病。针对这些区域或器官中的每一个可易于制备适合的局部调配物。用于下肠道的局部施加可以直肠栓剂调配物(参见上文)或适合的灌肠调配物来进行。还可使用局部透皮贴片。

[0118] 对于局部施加，可将药学上可接受的组合物调配在适合的软膏中，所述软膏含有悬浮或溶解于一种或多种载剂中的活性组分。用于局部施用本发明化合物的载剂包括(但不限于)矿物油、液体矿脂、白凡士林、丙二醇、聚氧乙烯、聚氧丙烯化合物、乳化蜡和水。或者，可将药学上可接受的组合物调配在适合的洗剂或霜剂中，所述洗剂或霜剂含有悬浮或溶解于一种或多种药学上可接受的载剂中的活性组分。适合的载剂包括(但不限于)矿物油、山梨糖醇酐单硬脂酸酯、聚山梨糖醇酯60、鲸蜡基酯蜡、鲸蜡硬脂醇、2-辛基十二烷醇、苄醇和水。

[0119] 本发明的药学上可接受的组合物还可通过鼻气溶胶或吸入来施用。此类组合物可根据药物调配物领域熟知的技术来制备，并且可采用苄醇或其他适合的防腐剂、增强生物利用度的吸收促进剂、氟碳和/或其它常规增溶剂或分散剂以盐水中的溶液形式来制备。

[0120] 可与载剂材料组合以产生单一剂型组合物的本发明化合物的量将根据所治疗宿主、具体施用模式而变化。

[0121] 剂量

[0122] 本发明化合物(包括药学上可接受的盐和氘化变体形式)的毒性和治疗功效可在细胞培养物或实验动物中通过标准药物程序来测定。$LD_{50}$是对50％群体致死的剂量。$ED_{50}$是在50％群体中治疗有效的剂量。毒性与治疗效应之间的剂量比($LD_{50}/ED_{50}$)是治疗指数。展现大治疗指数的化合物是优选的。尽管可使用展现毒副作用的化合物，但应注意设计一种将此类化合物靶向受影响组织位点的递送系统，以便使对未感染细胞的潜在损害减至最少，从而减少副作用。

[0123] 从细胞培养测定和动物研究获得的数据可用于调配剂量范围以供人使用。此类化合物的剂量可以在包括$ED_{50}$而几乎没有或没有毒性的循环浓度范围内。剂量可根据所采用的剂型和所利用的施用途径而在该范围内变化。对于任何化合物，治疗有效剂量最初都可以根据细胞培养测定来估计。可以在动物模型中调配剂量以实现包括如在细胞培养中确定的$IC_{50}$(即，达成症状半最大抑制的测试化合物浓度)的循环血浆浓度范围。此类信息可以用来更准确地确定人中有用的剂量。可以通过(例如)高效液相色谱来测量血浆中的水平。

[0124] 还应理解，任一特定患者的具体剂量和治疗方案将取决于各种因素，包括所采用的特定化合物的活性、年龄、体重、一般健康状况、性别、膳食、施用时间、排泄速率、药物组合和治疗医师的判断以及所治疗的特定疾病的严重性。所述组合物中本发明化合物的量还将取决于所述组合物中的特定化合物。

[0125] 治疗

[0126] NTRK融合与几种类型的癌症相关。这些融合具有与受体的天然或野生型形式相同的完整的NTRK激酶结构域；因此，如本文所用，具有与野生型NTRK相同的激酶结构域的任何NTRK蛋白(NTRK1、2或3)将被称为“野生型NTRK”。突变可能发生在NTRK激酶结构域中，产生对激酶抑制剂疗法有抗性的突变体。这些抗性突变可以使用结构生物学和计算分析以及通过检查其中序列变化产生不同氨基酸的密码子的密码子序列来预测。或者，给定抑制剂的抗性突变可以通过施用该抑制剂(例如，已知NTRK野生型抑制剂)并使细胞暴露于突变促进剂(如ENU(N-乙基-N-亚硝基脲))以实验方式来鉴别。洗涤细胞，并且然后与增加的浓度(2-100×增殖$IC_{50}$)的所选化合物进行平铺。然后在3-4周后收集具有细胞生长晕(outgrowth)的孔。具体而言，经由两种方法鉴别了NTRK融合内氨基酸位置595(NTRK1wt编号)处的突变，实现了从甘氨酸到精氨酸残基的改变(迄今命名为‘G595R’)。随后证实了该突变可赋予对正处于临床评估的两种NTRK抑制剂显著的抗性(显示在下表中)。如表中所示，所述化合物对野生型NTRK有活性，但对NTRK融合的G595R突变体形式的活性明显更低。

[0127]

| 化合物 | NTRK wt 酶测定 $IC_{50}$ (nM) | NTRK wt 细胞 $GI_{50}$ (nM) | NTRK G595R 细胞 $GI_{50}$ (nM) |
|---|---|---|---|
| 恩曲替尼(Entrectinib) | 0.6 | 2 | 2700 |
| TSR-011 | 2.3 | 32 | 12000 |
| 克唑替尼(Crizotinib) | 9.3 | 87 | 9000 |

[0128] 本发明提供抑制野生型NTRK和其突变体(包括G595R突变体)的化合物。此外，与其它激酶相比，抑制剂对野生型NTRK可能具有选择性，从而使得与抑制其他激酶相关的毒性降低。由于本文所述的化合物对野生型和突变NTRK具有活性，因此所述化合物可用于治疗患有与异常NTRK活性相关的病况的患者。它们还可用于治疗多种癌症。在一些实施方案中，癌症选自非小细胞肺癌、乳腺癌、黑素瘤、低级和高级神经胶质瘤、神经胶质母细胞瘤、小儿星细胞瘤、结直肠癌、甲状腺癌、胰腺癌、胆管癌、头颈癌、原发性CNS肿瘤、胆道癌、急性骨髓性白血病、乳腺癌、唾液腺癌、肉瘤和spitz样赘瘤(spitzoid neoplasm)。

[0129] 所述化合物还可用于治疗已对野生型NTRK抑制剂产生抗性的患者或具有NTRK的突变形式(例如G595R突变体)的患者。所述方法包括施用对NTRK抗性突变体有活性的本发明化合物或组合物的步骤。“活性”意味着当在生物化学测定中测量时，化合物对至少一种

抗性突变体的$IC_{50}$小于1μM、500nM、250nM、100nM、75nM、50nM、25nM、10nM或5nM。

[0130] 本文所述的化合物和组合物可单独施用或与其它化合物(包括其它NTRK调节化合物或其它治疗剂)组合施用。在一些实施方案中,本发明的化合物或组合物可以与一种或多种选自以下各项的化合物组合施用:卡博替尼(Cabozantinib)(COMETRIQ)、凡德他尼(Vandetanib)(CALPRESA)、索拉非尼(Sorafenib)(NEXAVAR)、舒尼替尼(Sunitinib)(SUTENT)、瑞格非尼(Regorafenib)(STAVARGA)、普纳替尼(Ponatinib)(ICLUSIG)、贝伐珠单抗(Bevacizumab)(AVASTIN)、克唑替尼(XALKORI)或吉非替尼(Gefitinib)(IRESSA)。本发明的化合物或组合物可以通过相同或不同的施用途径与其它治疗剂同时或依序施用。本发明的化合物可与其它治疗剂一起包括在单一调配物或包括在分开的调配物中。

[0131] 合成

[0132] 本发明的化合物(包括其盐和N-氧化物)可以使用已知的有机合成技术来制备,并且可以根据许多可能的合成途径中的任何一条(例如下文方案中的那些)来合成。用于制备本发明化合物的反应可以在适合的溶剂中进行,所述溶剂可以由有机合成领域的技术人员容易地选择。适合的溶剂在进行反应的温度(例如可在溶剂的冷冻温度至溶剂的沸腾温度范围内的温度)下与起始材料(反应物)、中间体或产物基本上不反应。给定的反应可以在一种溶剂或一种以上溶剂的混合物中进行。取决于特定的反应步骤,本领域技术人员可以选择用于特定反应步骤的适合溶剂。

[0133] 本发明化合物的制备可涉及多种化学基团的保护和去保护。本领域技术人员可容易地确定保护和去保护的需要以及适当保护基团的选择。保护基团的化学可参见(例如)Wuts和Greene,Protective Groups in Organic Synthesis,第4版,John Wiley&Sons:New Jersey,(2006),所述文献以引用的方式整体并入本文中。

[0134] 可根据本领域已知的任何适合的方法来监测反应。例如,产物形成可以通过光谱手段(例如核磁共振(NMR)光谱法(例如$^{1}H$或$^{13}C$)、红外(IR)光谱法、分光光度法(例如,UV可见光)、质谱法(MS))或通过色谱法(例如高效液相色谱(HPLC)或薄层色谱(TLC))来监测。用于化合物表征的分析仪器和方法:

[0135] LC-MS:除非另有指示,否则所有液相色谱-质谱(LC-MS)数据(分析样品的纯度和同一性)都是在22.4℃下利用Agilent 1260型LC系统获得的,所述系统使用利用ES-API电离的Agilent 6120型质谱仪且安装有Agilent Poroshel 120(EC-C18,2.7um粒径,3.0×50mm尺寸)反相柱。流动相由溶剂0.1%甲酸的水溶液和0.1%甲酸的乙腈溶液的混合物组成。利用在4分钟的过程中95%水性/5%有机至5%水性/95%有机流动相的恒定梯度。流速恒定为1mL/min。

[0136] 制备型LC-MS:制备型HPLC是在22.4℃下在安装有Luna 5u C18(2)100A,AXIA填充的250×21.2mm反相柱的Shimadzu Discovery VP®制备型系统上进行。流动相由溶剂0.1%甲酸的水溶液和0.1%甲酸的乙腈溶液的混合物组成。利用在25分钟的过程中95%水性/5%有机至5%水性/95%有机流动相的恒定梯度。流速恒定为20mL/min。在微波中进行的反应是在Biotage Initiator微波单元中进行。

[0137] 手性HPLC:用来解析手性混合物的制备型HPLC是在安装有Chiralpak AS-H柱(5mm,3.0cm内径×25cm L)的Thar SFC Pre-80仪器上进行。流动相由SFC $CO_2$(A)和MeOH/0.1%$NH_4OH$(B)组成。以65g/min的流速维持67%至33%(B)的恒定梯度,其中系统背压为

100巴(bar)。通过在220nm波长处的UV检测来监测分离进展。

[0138] 硅胶色谱:硅胶色谱是在Teledyne Isco CombiFlash® Rf单元或 Biotage® Isolera Four单元上进行。

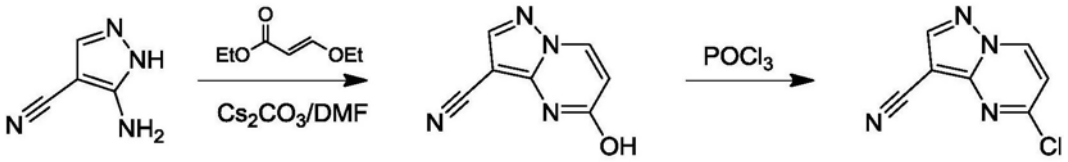
[0139] 质子NMR:除非另有指示,否则所有$^1$H NMR光谱都是利用Varian 400MHz Unity Inova 400MHz NMR仪器(获取时间=3.5秒并且延迟1秒;16至64次扫描)获得的。倘若表征,则所有质子都是在DMSO-$d_6$溶剂中以相对于残留DMSO(2.50ppm)的百万分率(ppm)来报告。

## 实施例

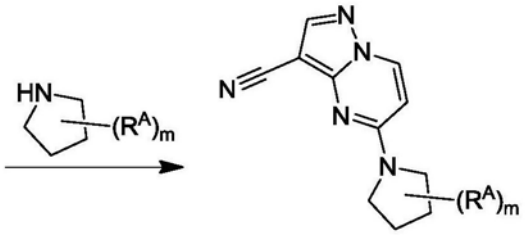
[0140] 以下实施例意在说明,并且并非打算以任一方式进行限制。

[0141] 下文方案意在提供关于制备本发明化合物的一般指导。本领域技术人员应当理解,可使用有机化学的常识对所述方案中所显示的制备进行改进或优化以制备本发明的多种化合物。

[0142] 合成方案1

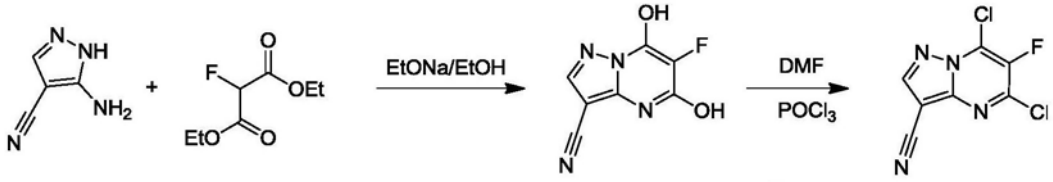



[0143]

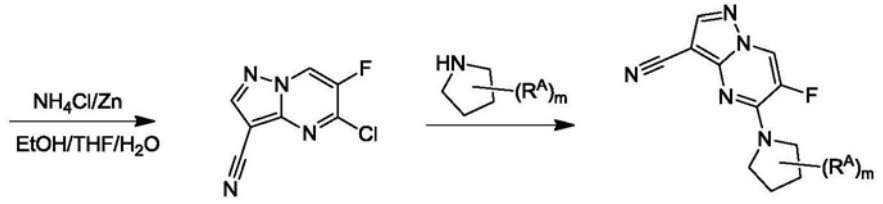



[0144] 一般合成方案1涉及在热条件下在例如碳酸铯的碱存在时经由5-氨基-1H-吡唑-4-甲腈和(E)-3-乙氧基丙烯酸乙酯或适合等效物的环化形成5-羟基吡唑并[1,5-a]嘧啶-3-甲腈。通过与氧氯化磷发生反应将羟基转化为例如氯离子的离去基团。在溶剂(例如二噁烷或正丁醇)中在碱(例如DIPEA)存在时或者经由(例如)Buchwald条件下的Pd催化的交叉偶合将氯基置换为胺,以得到所需的产物。

[0145] 合成方案2



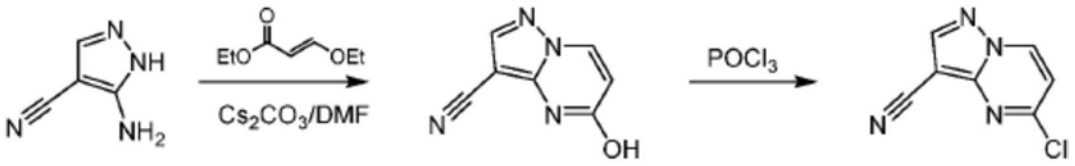

[0146]



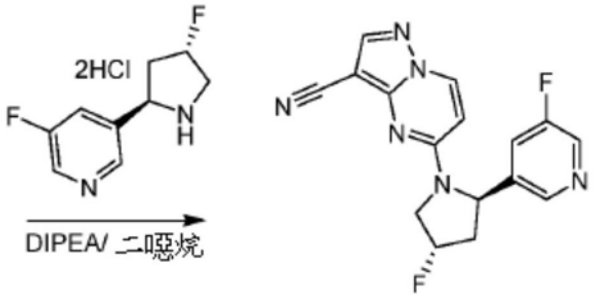

[0147] 一般合成方案2涉及经由5-氨基-1H-吡唑-4-甲腈和2-氟丙二酸二乙酯或合适等效物的环化来形成6-氟-5,7-二羟基吡唑并[1,5-a]嘧啶-3-甲腈。通过与氧氯化磷发生反

应将羟基转化为氯化物。在5-氯基存在时在还原剂(例如锌)存在时可选择性地还原7-氯基。在例如二噁烷或正丁醇的溶剂中在例如DIPEA的碱存在时或者通过(例如)Buchwald条件下的Pd催化的交叉偶合将剩余的氯基团置换为胺,以得到所需的产物。

[0148] 实施例1:5-((2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物1)

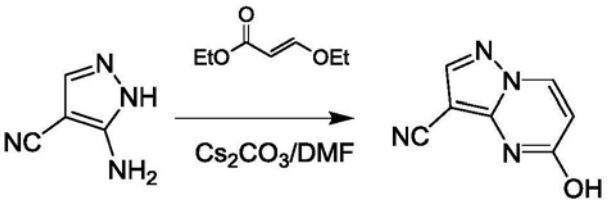



[0149]




[0150] 步骤1:5-羟基吡唑并[1,5-a]嘧啶-3-甲腈的合成

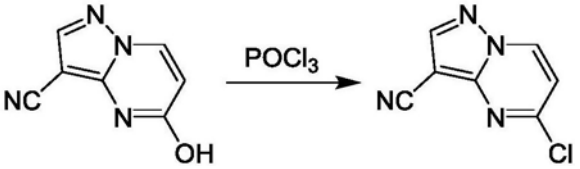
[0151]




[0152] 向5-氨基-1H-吡唑-4-甲腈(10.00g,92.51mmol)于DMF(350.00mL)中的混合物中添加(E)-3-乙氧基丙烯酸乙酯(13.34g,92.51mmol)和$Cs_2CO_3$(60.38g,185.02mmol)。将混合物在100℃搅拌2小时。LCMS显示反应完成后,使反应混合物冷却至25℃,然后添加至水(300mL)中,用HCl(1M)酸化至pH=4,然后过滤。在真空中干燥滤饼以得到呈白色固体的5-羟基吡唑并[1,5-a]嘧啶-3-甲腈(10.00g,产率:67.51%)。

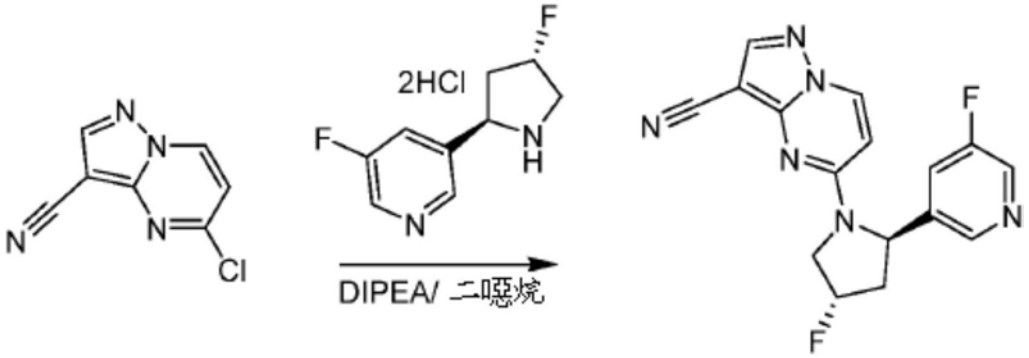
[0153] 步骤2:5-氯吡唑并[1,5-a]嘧啶-3-甲腈的合成

[0154]



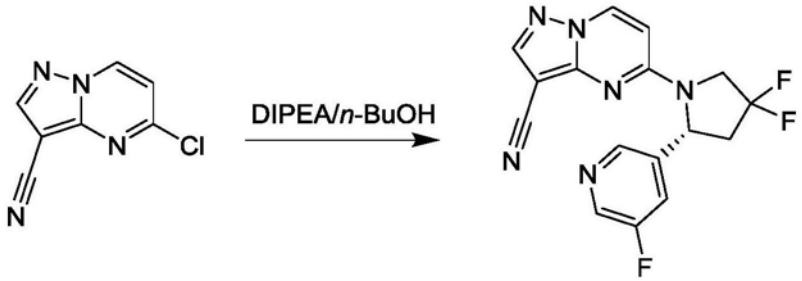

[0155] 将5-羟基吡唑并[1,5-a]嘧啶-3-甲腈(10.00g,62.45mmol)于$POCl_3$(200.00mL)中的混合物加热至150℃并保持4小时。TLC(PE:EtOAc=1:1)显示反应完成后,浓缩混合物以去除$POCl_3$,然后溶解于DCM(100mL)中,浓缩并通过硅胶(DCM)上的柱色谱纯化,以得到呈白色固体的5-氯吡唑并[1,5-a]嘧啶-3-甲腈(6.00g,产率:53.80%)。

[0156] 步骤3:5-((2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈的合成

[0157] 

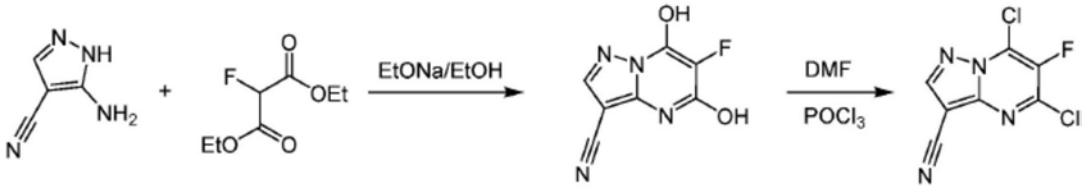

[0158] 向5-氯吡唑并[1,5-a]嘧啶-3-甲腈(86.00mg,334.49umol,1.20当量)和3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶HCl(49.78mg,278.74umol,1.00当量)于二噁烷(6.00mL)中的混合物中一次性添加DIPEA(108.07mg,836.23umol,3.00当量)。将混合物在130℃下搅拌16小时。LCMS显示反应完成。通过酸性制备型HPLC来纯化反应混合物,以得到呈黄色油状的5-((2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(90.60mg,163.43umol,产率:58.63%)。

[0159] 实施例2:(R)-5-(4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物3)

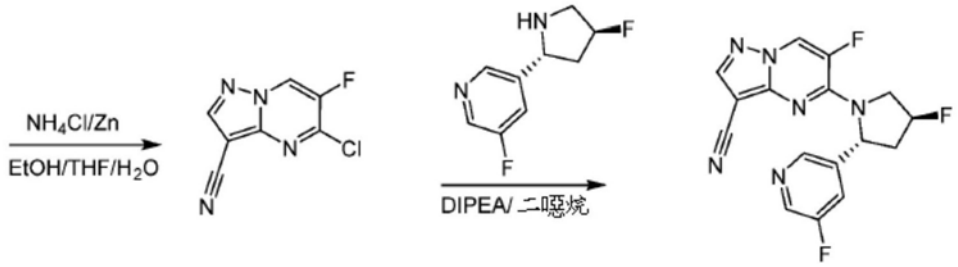
[0160] 


[0161] 向5-氯吡唑并[1,5-a]嘧啶-3-甲腈(40.00mg,223.99umol,1.00当量)和3-[(2R)-4,4-二氟吡咯烷-2-基]-5-氟-吡啶(61.62mg,223.99umol,1.00当量)于n-BuOH(2.00mL)中的混合物中添加DIPEA(144.74mg,1.12mmol,5.00当量)。将所得混合物在100℃下搅拌16小时。浓缩混合物并通过酸性制备型HPLC(TFA系统)来纯化粗制产物。获得呈棕色固体的(R)-5-(4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(48.70mg,85.09umol,产率:38%)。

[0162] 实施例3:6-氟-5-((2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物4)

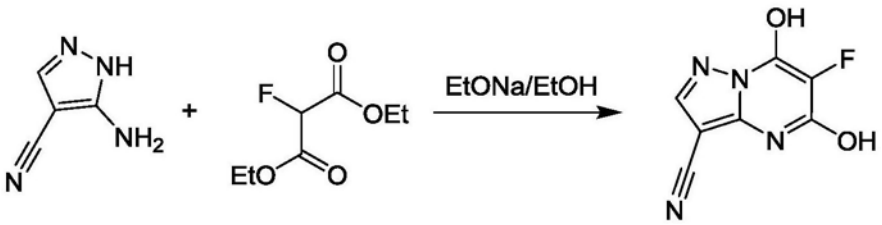



[0163]




[0164] 步骤1:6-氟-5,7-二羟基吡唑并[1,5-a]嘧啶-3-甲腈

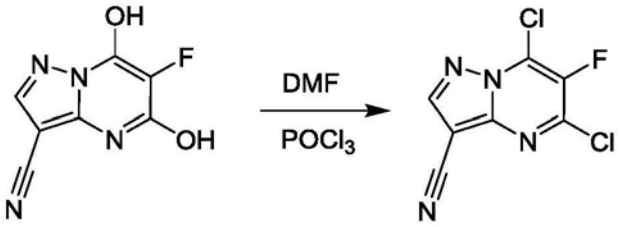
[0165]




[0166] 在20℃下向新鲜制备的NaOEt(4.34g,63.83mmol,1.38当量)于无水EtOH(100.00mL)中的混合物中添加5-氨基-1H-吡唑-4-甲腈(5.00g,46.25mmol,1.00当量)和2-氟丙二酸二乙酯(8.65g,48.56mmol,1.05当量)。将所得混合物加热至120℃并保持32小时。浓缩混合物以去除EtOH,并将所得残余物溶解于水(50mL)中。通过HCl(1M)将水层酸化至pH=2至3并且产生白色沉淀物。通过过滤收集固体并在真空中干燥,以得到呈白色固体的粗制6-氟-5,7-二羟基吡唑并[1,5-a]嘧啶-3-甲腈(4.00g,产率:44.54%)。$^1$H-NMR(400MHz,DMSO-$d_6$)δppm 7.92(s,1H)。

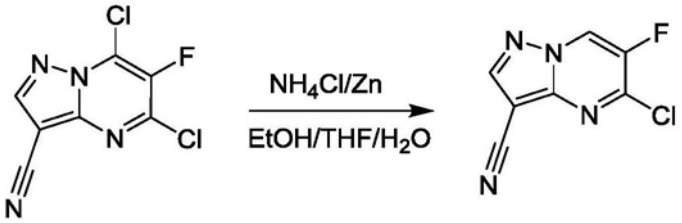
[0167] 步骤2:5,7-二氯-6-氟吡唑并[1,5-a]嘧啶-3-甲腈

[0168]



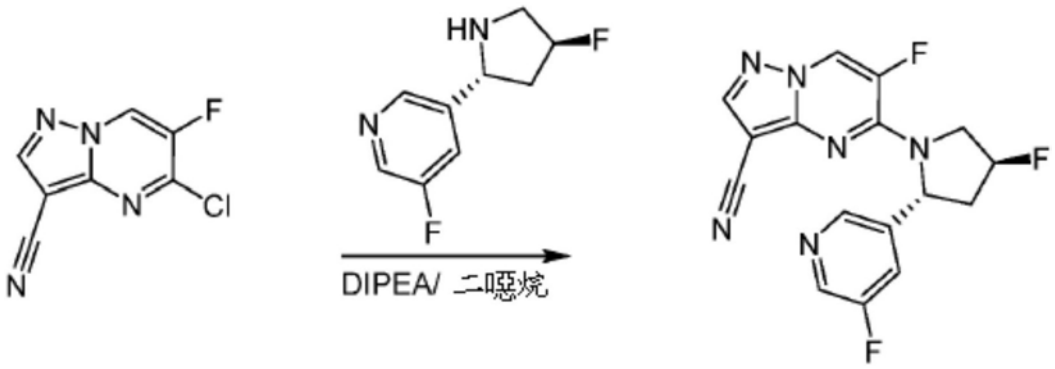

[0169] 向6-氟-5,7-二羟基吡唑并[1,5-a]嘧啶-3-甲腈(4.00g,20.61mmol,1.00当量)于$POCl_3$(80.00mL)中的混合物中添加DMF(150.61mg,2.06mmol,158.53uL,0.10当量),并将混合物加热至100℃并保持16小时。浓缩混合物以得到粗制产物。通过硅胶(DCM)上的急速柱色谱纯化该粗制产物,以得到呈黄色固体的5,7-二氯-6-氟吡唑并[1,5-a]嘧啶-3-甲腈(1.30g,产率:27.32%)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 8.48(s,1H)。

[0170] 步骤3:5-氯-6-氟吡唑并[1,5-a]嘧啶-3-甲腈

[0171] 

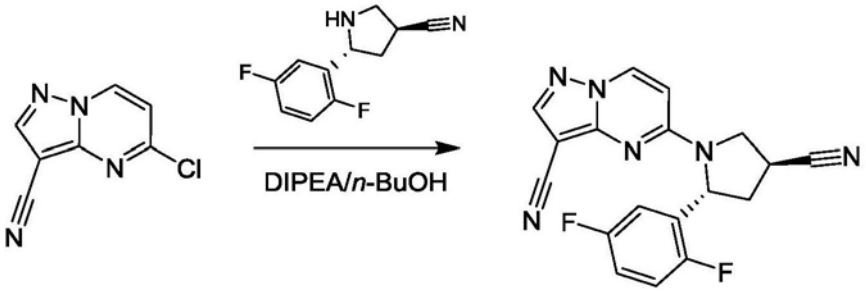

[0172] 向5,7-二氯-6-氟吡唑并[1,5-a]嘧啶-3-甲腈(1.30g,5.63mmol,1.00当量)于EtOH/THF/$H_2O$(50.00mL,V/V/V=3/1/2)中的混合物中添加Zn粉末(1.84g,28.14mmol,5.00当量)和$NH_4Cl$(1.20g,22.51mmol,786.96uL,4.00当量)。将混合物在20℃下搅拌0.1小时。浓缩混合物以去除EtOH和THF。用EtOAc(10mL*2)萃取混合物,将有机层经$Na_2SO_4$干燥,并浓缩以得到呈黄色固体的5-氯-6-氟吡唑并[1,5-a]嘧啶-3-甲腈(1.00g,粗制物)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 8.75(d,1H,J=2.4Hz),8.40(s,1H)。

[0173] 步骤4:6-氟-5-((2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈

[0174] 


[0175] 向5-氯-6-氟吡唑并[1,5-a]嘧啶-3-甲腈(200.50mg,1.02mmol,1.00当量)于二噁烷(5.00mL)中的混合物中添加DIPEA(395.47mg,3.06mmol,3.00当量)和3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶(187.87mg,1.02mmol,1.00当量)。将混合物在100℃搅拌2小时。浓缩混合物以得到粗制产物。通过制备型HPLC(TFA系统)纯化粗制产物以得到呈黄色油状的6-氟-5-((2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(163.30mg,产率:46.50%)。

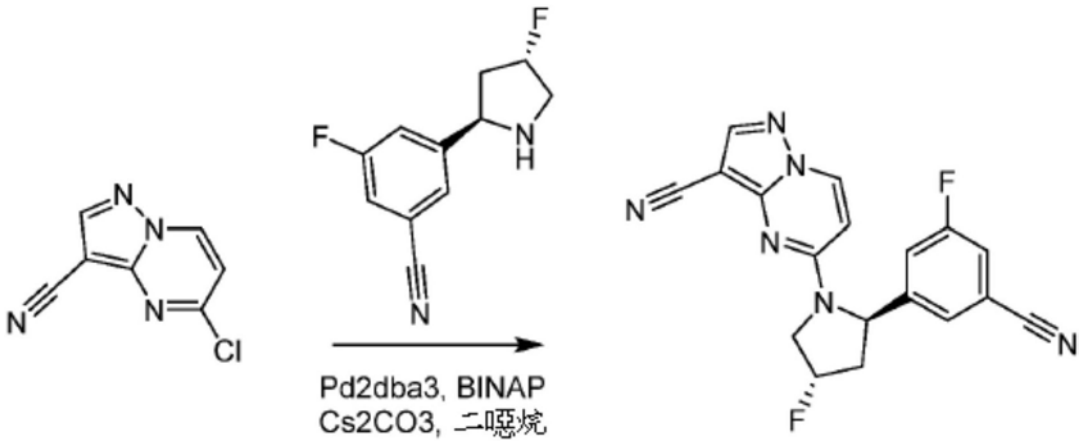
[0176] 实施例4:5-((2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物5)

[0177] 


[0178] 向5-氯吡唑并[1,5-a]嘧啶-3-甲腈(50.00mg,279.99umol)于n-BuOH(3.00mL)中的混合物中添加DIPEA(72.37mg,559.98umol)和(3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-甲腈(58.30mg,279.99umol)。将混合物在100℃下搅拌16小时。LCMS显示反应完成。浓缩反应混合物以得到粗制产物。通过中性制备型HPLC纯化该粗制产物,以得到呈白色固体的5-

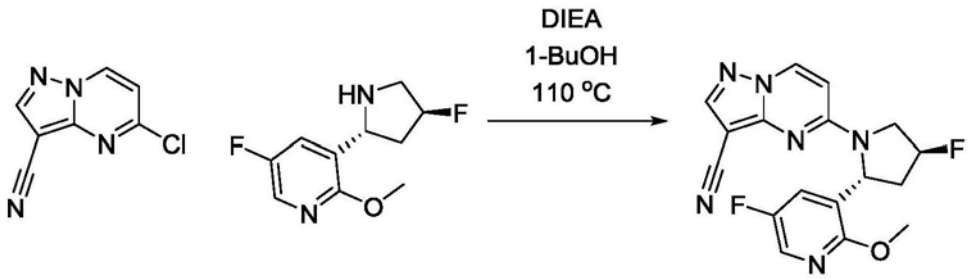
((2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(10.60mg,30.26umol,产率:10.81%)。

[0179] 实施例5:5-((2R,4S)-2-(3-氰基-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物6)

[0180] 

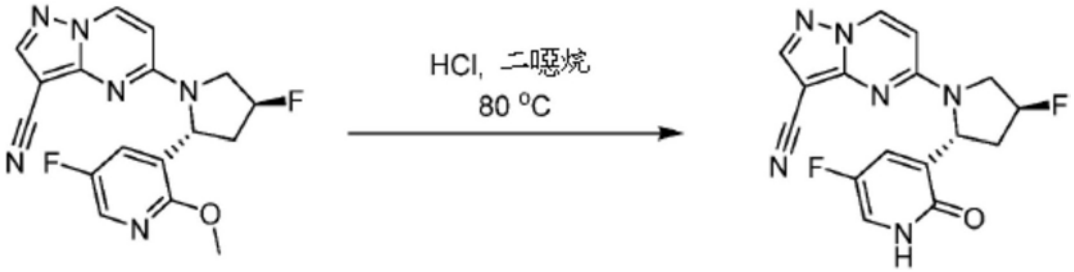

[0181] 将5-氯吡唑并[1,5-a]嘧啶-3-甲腈(0.075g,0.420mmol)、3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲腈(0.096g,0.462mmol)和Cs2CO3(0.411g,1.260mmol)吸收于二噁烷(2ml)中。添加Pd2(dba)3(0.038g,0.042mmol)和BINAP(0.052g,0.084mmol)并在110℃下搅拌4小时。在真空中除去溶剂。通过反相色谱(0-100%ACN/H2O)纯化残余物,以得到呈白色泡沫的5-((2R,4S)-2-(3-氰基-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(0.015g,0.043mmol,10.20%产率)。

[0182] 实施例6:5-((2R,4S)-4-氟-2-(5-氟-2-甲氧基吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物7)

[0183] 

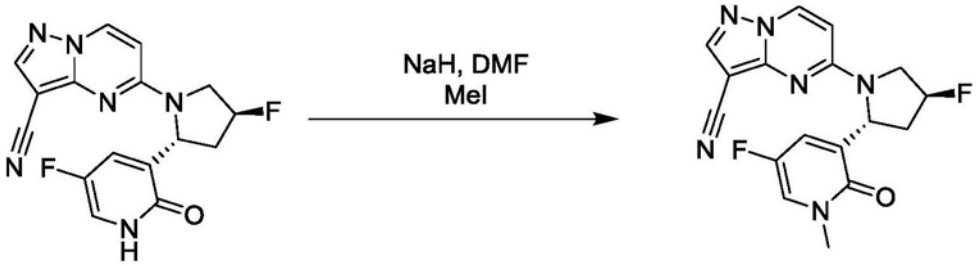

[0184] 将5-氯吡唑并[1,5-a]嘧啶-3-甲腈(88.5mg,0.50mmol)、5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)-2-甲氧基吡啶盐酸盐(124mg,0.50mmol)和DIEA(0.26mL,1.50mmol)于正丁醇(2.5mL)中的混合物在微波反应器中在110℃下加热60分钟。浓缩混合物以去除溶剂并通过硅胶上的柱色谱来纯化残余物,以得到呈白色固体的5-((2R,4S)-4-氟-2-(5-氟-2-甲氧基吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(168mg,产率:95%)。

[0185] 实施例7:5-((2R,4S)-4-氟-2-(5-氟-1-甲基-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物8)

[0186] 


[0187] 步骤1:5-((2R,4S)-4-氟-2-(5-氟-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈

[0188] 将5-((2R,4S)-4-氟-2-(5-氟-2-甲氧基吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(110mg,0.31mmol)和HCl(4M,0.4mL,1.50mmol)于二噁烷中于二噁烷(1.2mL)中的混合物在85℃下加热8小时。用饱和$NaHCO_3$溶液淬灭混合物并用EtOAc萃取。将合并的有机层经$Na_2SO_4$干燥并浓缩,以得到粗制产物,其不经进一步纯化即用于下一步骤。在0℃下向5-((2R,4S)-4-氟-2-(5-氟-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(100mg,0.29mmol)于DMF(1.5mL)中的溶液中添加NaH(60%分散液,14mg,0.35mmol)并使溶液在室温下升温15分钟。使反应混合物再次冷却至0℃,添加MeI(0.022mL,0.35mmol)并升温至室温过夜。LCMS显示起始材料被消耗。用水稀释混合物并用EtOAc(2×)萃取。用水(3×)洗涤合并的有机层,经$Na_2SO_4$干燥并浓缩以得到粗制产物,通过硅胶上的柱色谱纯化该粗制产物,以得到呈白色固体的5-((2R,4S)-4-氟-2-(5-氟-1-甲基-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(86mg,产量:83%)。

[0189] 

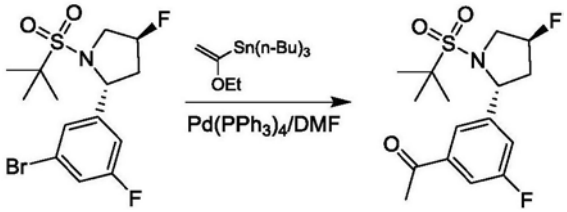

[0190] 步骤2:5-((2R,4S)-4-氟-2-(5-氟-1-甲基-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈的合成

[0191] 在0℃下向5-((2R,4S)-4-氟-2-(5-氟-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(100mg,0.29mmol)于DMF(1.5mL)中的溶液中添加NaH(60%分散液,14mg,0.35mmol)并使溶液在室温下升温15分钟。使反应混合物再次冷却至0℃,添加MeI(0.022mL,0.35mmol)并升温至室温过夜。LCMS显示起始材料被消耗。用水稀释混合物并用EtOAc(2×)萃取。用水(3×)洗涤合并的有机层,经$Na_2SO_4$干燥并浓缩以得到粗制产物,通过硅胶上的柱色谱纯化该产物,以得到呈白色固体的5-((2R,4S)-4-氟-2-(5-氟-1-甲基-2-氧代-1,2-二氢吡啶-3-基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(86mg,产量:83%)。

[0192] 实施例8:5-((2R,4S)-4-氟-2-(3-氟-5-(2-羟基丙-2-基)苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(化合物14)

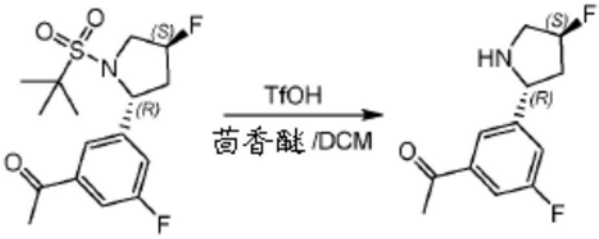
[0193] 步骤1:1-(3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯基)乙烷-

1-酮

[0194] 

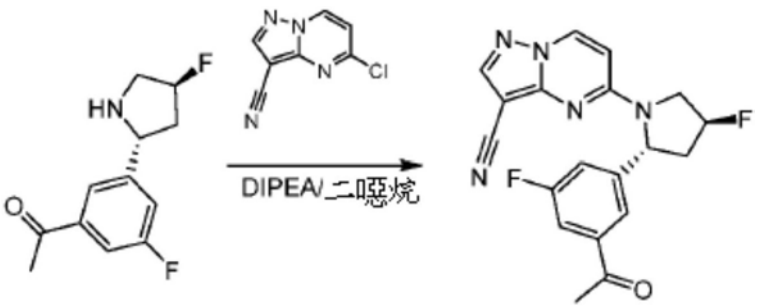

[0195] 向(2R,4S)-2-(3-溴-5-氟苯基)-1-(叔丁基磺酰基)-4-氟吡咯烷(200.00mg,523.20umol,1.00当量)于甲苯(5.00mL)中的混合物中添加Pd(PPh3)4(60.46mg,52.32umol,0.10当量)和三丁基(1-乙氧基乙烯基)锡烷(226.74mg,627.84umol,211.91uL,1.20当量)。将混合物在110℃和N2下搅拌16小时。浓缩混合物以得到粗制产物。通过制备型TLC(PE:EtOAc=3:1)纯化该粗制产物,以得到呈黄色油状的1-(3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯基)乙烷-1-酮(150.00mg,434.28umol,产率:83.00%)。

[0196] 步骤2:1-(3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯基)乙烷-1-酮

[0197] 


[0198] 在-40℃下向TfOH(195.53mg,1.30mmol,115.02uL,3.00当量)于DCM(5.00mL)中的混合物中添加茴香醚(70.44mg,651.42umol,70.44uL,1.50当量)。然后将1-(3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯基)乙烷-1-酮(150.00mg,434.28umol,1.00当量)于DCM(5.00mL)中的溶液添加至上述溶液中。添加后,将混合物在25℃下搅拌2小时。TLC(PE:EtOAc=3:1)显示反应完成。将饱和K2CO3水溶液(3mL)添加至混合物中,然后用DCM(3mL*2)对其进行萃取。浓缩有机层以得到呈黄色油状的1-(3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯基)乙烷-1-酮(100.00mg,粗制物)。

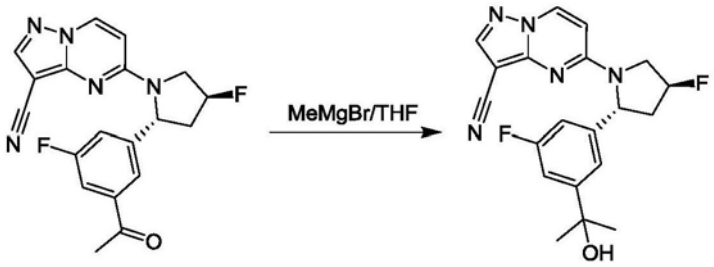
[0199] 步骤3:5-((2R,4S)-2-(3-乙酰基-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈

[0200] 


[0201] 向5-氯吡唑并[1,5-a]嘧啶-3-甲腈(80.00mg,447.98umol,1.00当量)于二噁烷(5.00mL)中的混合物中添加DIPEA(173.69mg,1.34mmol,234.72uL,3.00当量)和1-(3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯基)乙烷-1-酮(99.89mg,443.50umol,0.99当量)。将混合物在100℃下搅拌2小时。LCMS显示反应完成。浓缩混合物以得到粗制产物。通过制备型TLC(PE:EtOAc=1:1)纯化该粗制产物,以得到呈黄色油状的5-((2R,4S)-2-(3-乙酰基-5-氟苯

基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(100.00mg,272.22umol,产率:60.77%)。

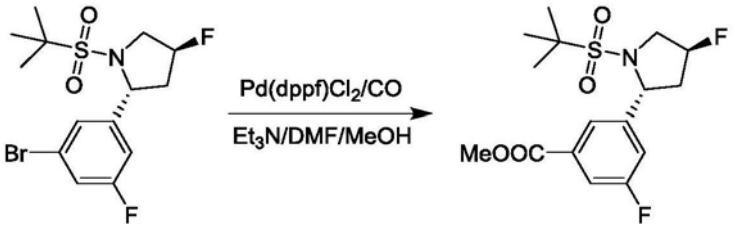
[0202] 步骤4:5-((2R,4S)-4-氟-2-(3-氟-5-(2-羟基丙-2-基)苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈

[0203] 


[0204] 在-78℃下向5-((2R,4S)-2-(3-乙酰基-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(50.00mg,136.11umol,1.00当量)于THF(5.00mL)中的混合物中逐滴添加MeMgBr(3M,136.11uL,3.00当量)。添加后,将混合物在25℃下搅拌16小时。HPLC显示起始料消耗约60%。将混合物添加至MeOH(2mL)中并且然后浓缩以得到粗制产物。通过制备型HPLC(TFA)纯化该粗制产物,以得到呈白色固体的5-((2R,4S)-4-氟-2-(3-氟-5-(2-羟基丙-2-基)苯基)吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(14.00mg,36.52umol,产率:26.83%)。$^{1}$H-NMR(400MHz,$CD_3OD$)δppm 8.35(br.s,1H),8.11(s,1H),7.28(s,1H),7.10(d,1H,J=8.0Hz),6.91(d,1H,J=8.8Hz),6.17(br.s,1H),5.42(d,1H,J=52.4Hz),5.23(br.s,1H),4.16-4.08(m,1H),2.91(br.s,1H),2.31-2.17(m,1H),1.47(d,6H,J=3.6Hz)。MS计算值:383.4,MS实验值:384.1,406.0([M+1]$^+$和[M+23]$^+$)。

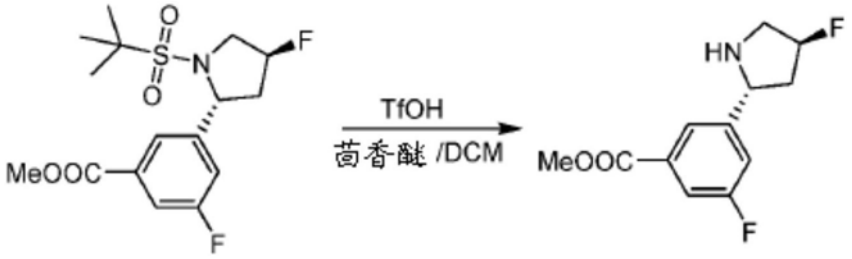
[0205] 实施例9:3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟-N-甲基苯甲酰胺(化合物20)

[0206] 步骤1:3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯甲酸甲酯

[0207] 

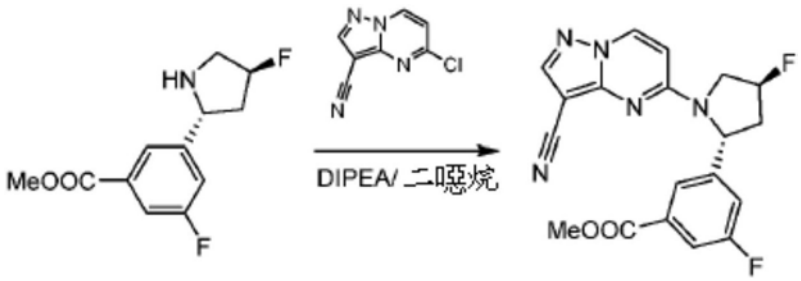

[0208] 向(2R,4S)-2-(3-溴-5-氟苯基)-1-(叔丁基磺酰基)-4-氟吡咯烷(2.00g,5.23mmol,1.00当量)于MeOH(10.00mL)中的混合物中添加$Et_3N$(1.59g,15.70mmol,3.00当量)、Pd(dppf)$Cl_2$(191.41mg,261.60umol,0.05当量)。将混合物在CO(50Psi)下在70℃下搅拌16小时。过滤混合物并浓缩滤液以得到粗制产物。通过硅胶上的柱色谱(PE:EtOAc=15:1-8:1)纯化该粗制产物,以得到呈红色固体的3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯甲酸甲酯(1.20g,3.32mmol,产率:63.46%)。

[0209] 步骤2:3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酸甲酯

[0210] 

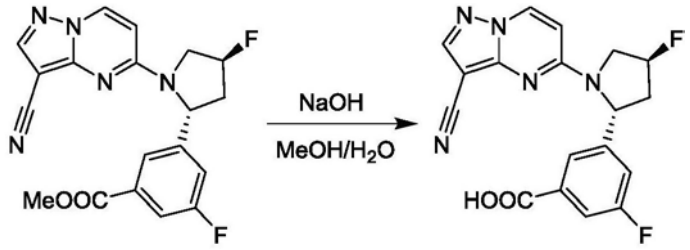

[0211] 在-40℃向TfOH(1.37g,9.12mmol,3.00当量)于DCM(50.00mL)中的混合物中添加茴香醚(493.12mg,4.56mmol,1.50当量)。然后在-40℃下经0.1小时将3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯甲酸甲酯(1.10g,3.04mmol,1.00当量)于DCM(30.00mL)中的溶液逐滴添加至混合物中。添加后,使混合物升温至0℃并在0℃下搅拌1小时。将混合物添加至$K_2CO_3$(水溶液,10mL)中并搅拌0.1小时。用DCM(10mL*2)萃取混合物。浓缩有机层并且然后添加HCl/EtOAc(10mL,4M)。将所得混合物在20℃下搅拌0.5小时并过滤。在真空中干燥滤饼,以得到呈黄色固体的3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酸甲酯(550.00mg,粗制物,HCl)。

[0212] 步骤3:3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟苯甲酸甲酯

[0213] 


[0214] 向3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酸甲酯(400.00mg,2.24mmol,1.00当量)于二噁烷(50.00mL)中的混合物中添加DIPEA(868.45mg,6.72mmol,3.00当量)和5-氯吡唑并[1,5-a]嘧啶-3-甲腈(540.00mg,2.24mmol,1.00当量)。将混合物在100℃下搅拌16小时。浓缩混合物以得到粗制产物。通过硅胶上的柱色谱(PE:EtOAc=10:1-3:1)纯化该粗制产物,以得到呈黄色油状的3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟苯甲酸甲酯(650.00mg,1.70mmol,产率:75.89%)。$^1$H-NMR(400MHz,$CD_3OD$)δ ppm 8.30-8.24(m,1H),6.94-6.83(m,2H),5.64(t,1H,J=9.2Hz),5.41(d,1H,J=52.0Hz),4.48-4.38(m,2H),3.97(s,3H),2.79-2.69(m,1H),2.20-2.06(m,1H)。

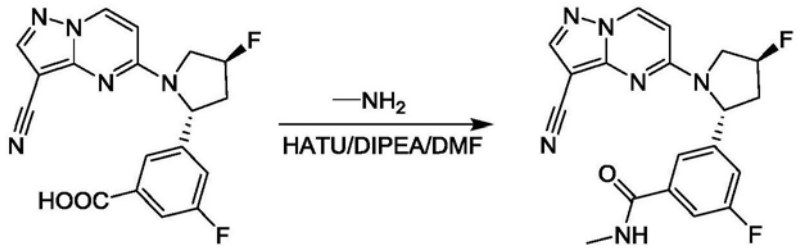
[0215] 步骤4:3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟苯甲酸

[0216] 


[0217] 向3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟苯甲酸甲酯(530.00mg,1.38mmol,1.00当量)于MeOH/$H_2O$(20.00mL,v:v=3:1)中的混合物中

添加NaOH(110.40mg,2.76mmol,2.00当量)。将混合物在20℃下搅拌16小时。浓缩混合物以去除MeOH。向水层中添加HCl(2M)直至pH低于7。然后用EtOAc(3mL*3)萃取水层。将所得有机层经$Na_2SO_4$干燥并浓缩,以得到呈白色固体的3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟苯甲酸(400.00mg,1.08mmol,产率:78.48%)。

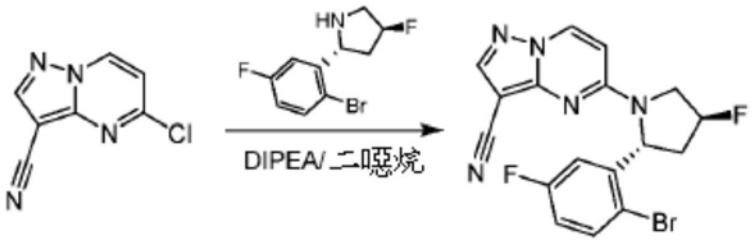
[0218] 步骤5:3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟-N-甲基苯甲酰胺

[0219] 


[0220] 向3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟苯甲酸(80.00mg,216.61umol,1.00当量)于DMF(2.00mL)中的混合物中添加DIPEA(83.99mg,649.84umol,113.49uL,3.00当量)、HATU(98.84mg,259.94umol,1.20当量)和甲胺(17.55mg,259.93umol,1.20当量,HCl)。将混合物在20℃下搅拌1小时。LCMS显示反应完成。然后浓缩混合物以得到粗制产物。通过制备型HPLC(TFA)纯化该粗制产物,以得到呈棕色油状的3-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-5-氟-N-甲基苯甲酰胺(50.70mg,102.14umol,产率:47.15%,TFA)。

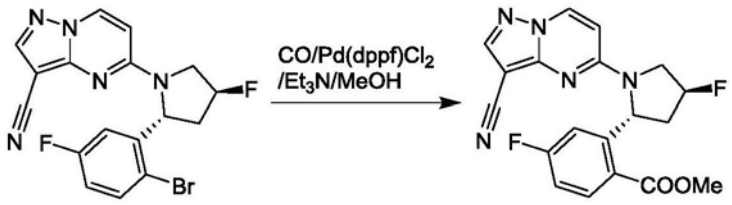
[0221] 实施例10:2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酰胺(化合物22)

[0222] 步骤1:5-((2R,4S)-2-(2-溴-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈

[0223] 

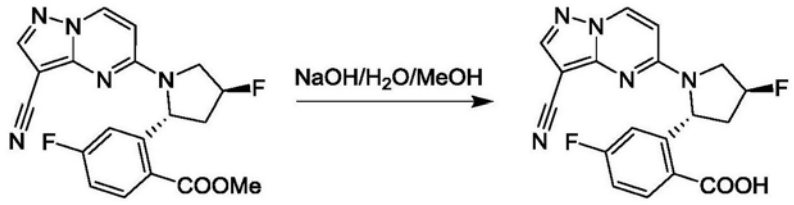

[0224] 将5-氯吡唑并[1,5-a]嘧啶-3-甲腈(500.00mg,2.33mmol,1.00当量,HCl)、(2R,4S)-2-(2-溴-5-氟-苯基)-4-氟-吡咯烷(694.17mg,2.33mmol,1.00当量,HCl)、DIPEA(751.26mg,5.81mmol,1.02mL,2.50当量)于二噁烷(8.00mL)中的混合物在80℃下搅拌16小时。TLC(PE:EtOAc=3:1)显示反应完成。向混合物中添加$H_2O$(10mL),且然后用EtOAc(10mL*3)萃取混合物。将合并的有机层经$Na_2SO_4$干燥,在真空中浓缩以得到呈黄色油状的5-((2R,4S)-2-(2-溴-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(1.00g,粗制物)。

[0225] 步骤2:2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酸甲酯

[0226] 

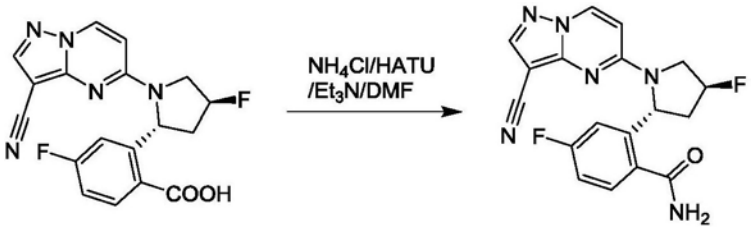

[0227] 将5-((2R,4S)-2-(2-溴-5-氟苯基)-4-氟吡咯烷-1-基)吡唑并[1,5-a]嘧啶-3-甲腈(900.00mg,2.23mmol,1.00当量)、$Pd(dppf)Cl_2$(326.34mg,446.00umol,0.20当量)、$Et_3N$(676.96mg,6.69mmol,927.34uL,3.00当量)于MeOH(10.00mL)中的混合物脱气并用CO吹扫3次。然后将混合物在70℃下在CO(50psi)气氛下搅拌120小时。LCMS显示大多数起始材料被消耗。然后过滤混合物,并在真空下浓缩滤液,以得到呈黄色固体的2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酸甲酯(700.00mg,粗制物)。

[0228] 步骤3:2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酸

[0229] 


[0230] 将2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酸甲酯(700.00mg,1.83mmol,1.00当量)、NaOH(146.08mg,3.65mmol,2.00当量)于MeOH(5.00mL)和$H_2O$(5.00mL)中的混合物在25℃下搅拌16小时。LCMS显示反应完成。在真空下去除MeOH并且然后将稀HCl(1M)添加至混合物中直至pH=6,从而使得形成黄色沉淀物。收集沉淀物并在真空下干燥,以得到呈黄色固体的2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酸(280.00mg,758.15umol,产量:41.43%)。

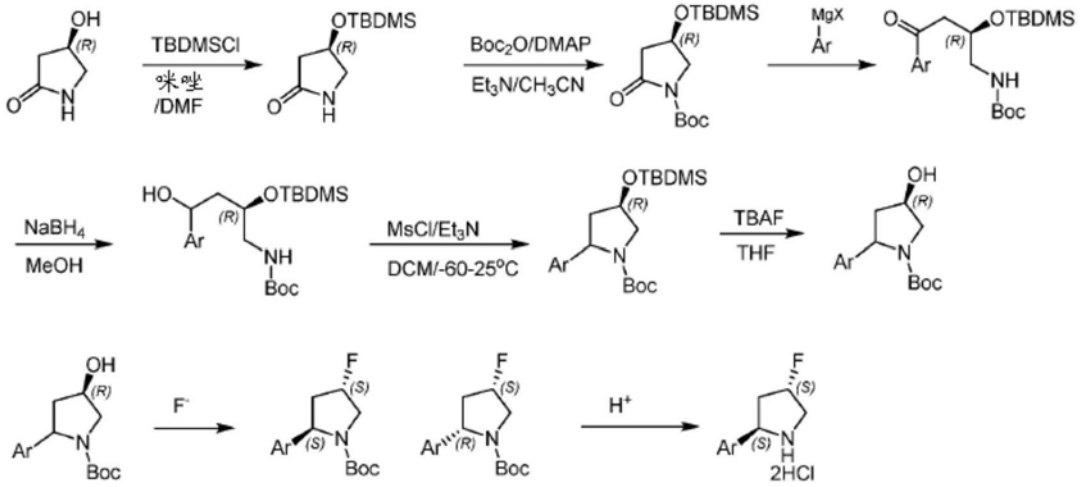
[0231] 步骤4:2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酰胺

[0232] 


[0233] 将2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酸(100.00mg,270.77umol,1.00当量)、$NH_4Cl$(43.45mg,812.31umol,28.40uL,3.00当量)、HATU(113.25mg,297.85umol,1.10当量)和$Et_3N$(82.20mg,812.31umol,112.60uL,3.00当量)于DMF(2.00mL)中的混合物在25℃下搅拌16小时。LCMS显示反应完成。然后在真空下浓缩混合物,并通过制备型HPLC(TFA)纯化,以产生呈黄色油状的2-((2R,4S)-1-(3-氰基吡唑并[1,5-a]嘧啶-5-基)-4-氟吡咯烷-2-基)-4-氟苯甲酰胺(26.70mg,72.49umol,产率:26.77%)。

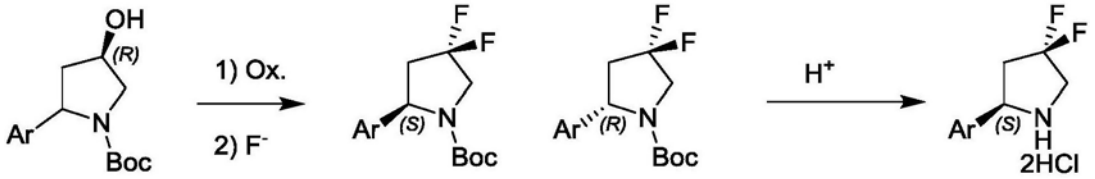
[0234] 实施例11:中间体的合成

[0235] 4-氟-2-芳基吡咯烷

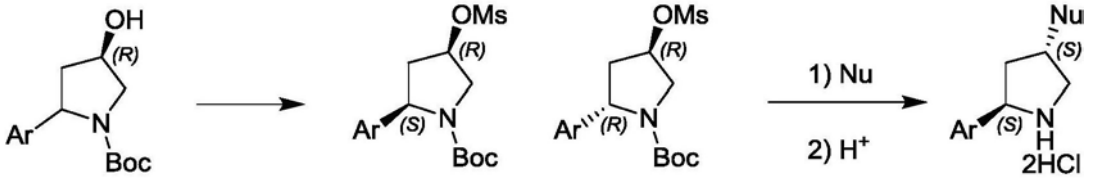
[0236] 


[0237] 4-氟-2-芳基吡咯烷的一般合成如上文所显示。用硅烷基团(例如TBS)保护(R)-4-羟基吡咯烷-2-酮,同时用适合的保护基团(例如Boc)保护内酰胺。亲核格氏试剂(Grignard reagent)打开内酰胺以得到二保护的4-氨基-3-羟基-1-苯基丁-1-酮。用还原剂(例如硼氢化钠)将该酮还原成仲醇。该醇通过(例如)形成甲磺酸酯而转化为离去基团引起环闭合,得到二保护的4-氟-2-羟基吡咯烷。用氟化物源或酸进行醇去保护,随后与亲核氟(例如DAST或BAST)发生反应,得到氟吡咯烷,可在酸性条件下用(例如)TBAF对该氟吡咯烷进行去保护,以得到所需的4-氟-2-芳基吡咯烷。

[0238] (R)-4,4-二氟-2-苯基吡咯烷

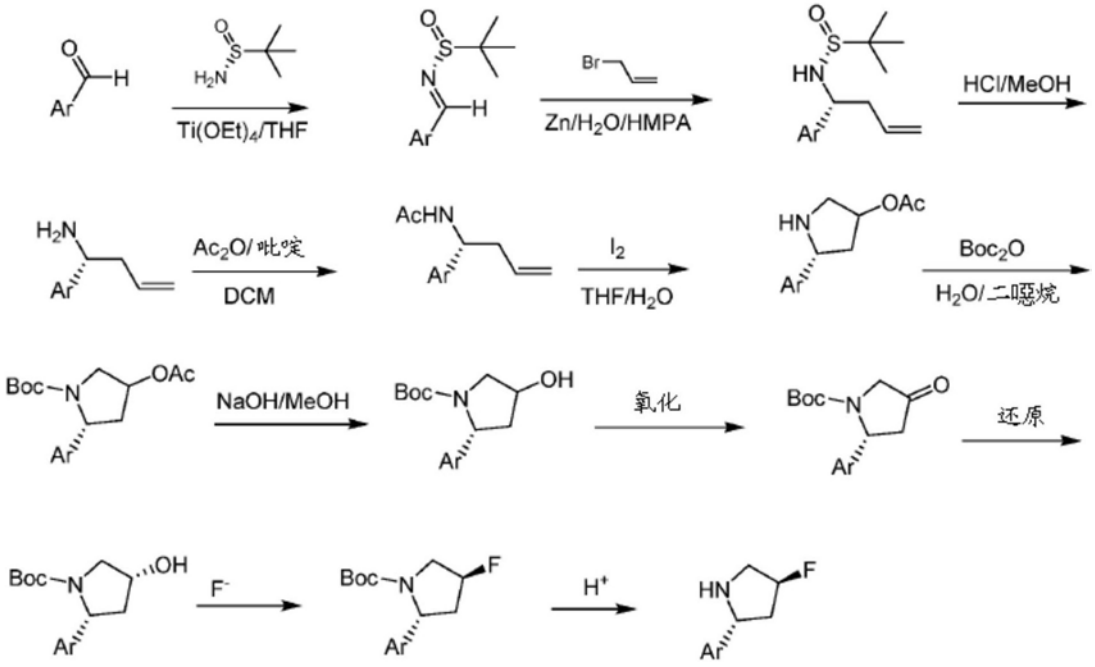
[0239] 


[0240] 如上文所显示由(4R)-4-羟基-2-苯基吡咯烷-1-羧酸叔丁酯通过以下方式来制备(R)-4,4-二氟-2-苯基吡咯烷:用氧化试剂(例如TEMPO或戴斯-马丁(Dess-Martin)过碘烷)将仲醇氧化为酮,随后用例如DAST的试剂进行氟化。Boc基团的酸性去保护得到所需的芳基吡咯烷。

[0241] 

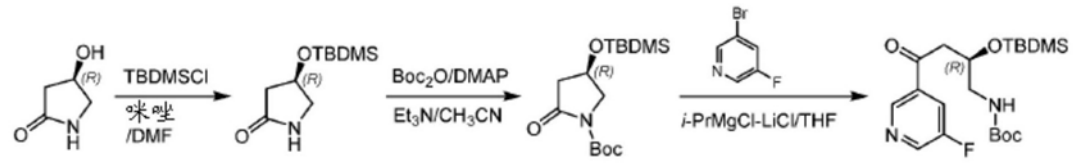

[0242] 还可通过仲甲磺酸酯的亲核置换获得4-取代的2-芳基吡咯烷,所述仲甲磺酸酯可通过(4R)-4-羟基-2-苯基吡咯烷-1-羧酸叔丁酯的甲磺酰化来产生。Boc基团的酸性去保护得到所需的芳基吡咯烷。

[0243]

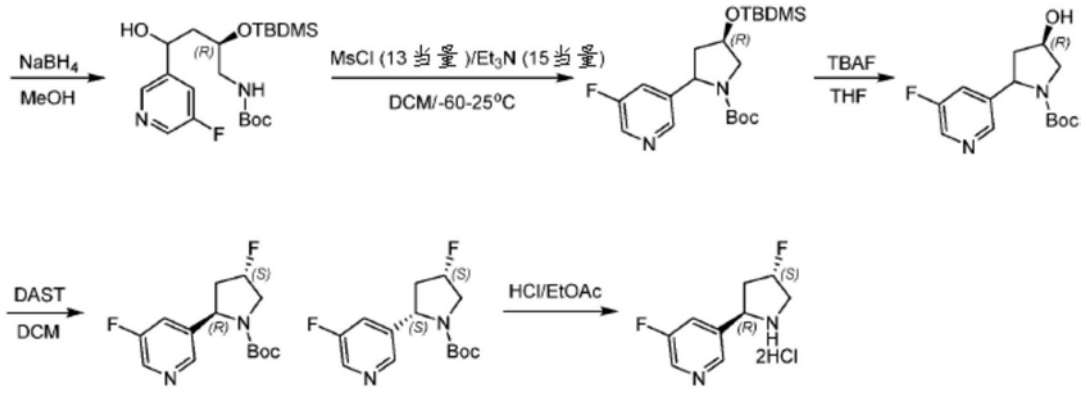



[0244] 用于制备4-氟-2-芳基吡咯烷的另一方法涉及自苯甲醛形成亚磺酰胺，所述亚磺酰胺与烯丙基亲核剂(例如烯丙基锌或烯丙基格氏试剂)立体选择性地反应。在酸性条件转化为游离胺，随后用碘进行乙酰化和闭环，得到2-芳基吡咯烷。用例如Boc的基团保护胺，对乙酸盐进行去保护，并用例如TEMPO或戴斯-马丁过碘烷的试剂进行氧化得到酮，可用硼氢化钠将该酮选择性地还原为仲醇。相继进行氟化和胺去保护，得到所需的芳基吡咯烷。

[0245] 3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶

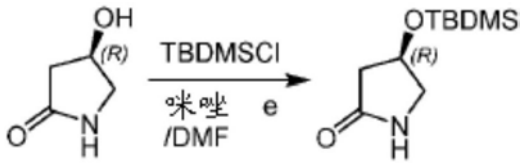



[0246]



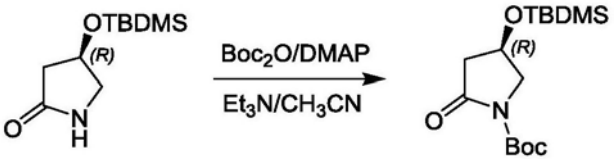

[0247] 步骤1：(R)-4-((叔丁基二甲基甲硅烷基)氧基)吡咯烷-2-酮

[0248]



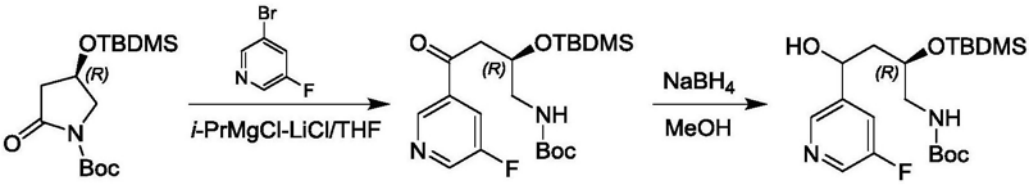
[0249] 在0℃下向(R)-4-羟基吡咯烷-2-酮(9.0g,89.1mmol)于DMF(50mL)中的混合物中一次性添加咪唑(9.09g,134mmol)和TBDMSCl(14.1g,93.6mmol)。将反应混合物在25℃下搅拌3小时。TLC(DCM/MeOH＝10/1,$R_f$＝0.8)显示反应完成,然后添加水(200mL),并通过过滤收集所得沉淀并在真空中干燥,以得到呈白色固体的(R)-4-((叔丁基二甲基甲硅烷基)氧基)吡咯烷-2-酮(15.5g,产量:80.7%)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 5.90(br.s,1H),4.55-4.53(m,1H),3.60-3.56(m,1H),3.24-3.21(m,1H),2.56-2.50(m,1H),2.28-2.23(m,1H),0.87-0.85(m,9H),0.06-0.00(m,6H)。

[0250] 步骤2:(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧代吡咯烷-1-羧酸叔丁酯

[0251] 


[0252] 在0℃下向(R)-4-((叔丁基二甲基甲硅烷基)氧基)吡咯烷-2-酮(15.5g,72.0mmol)于$CH_3CN$(150mL)中的混合物中一次性添加$Et_3N$(8.72g,86.4mmol)、DMAP(4.39g,36mmol)和$Boc_2O$(20.4g,93.7mmol)。将反应混合物在25℃下搅拌10小时。TLC(PE/EtOAc＝3/1)显示反应完成,然后添加水(600mL),并通过过滤收集所得沉淀物,并在真空中干燥,以得到呈粉色固体的(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧代吡咯烷-1-羧酸叔丁酯(19.2g,产量:84.6%)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 4.33-4.30(m,1H),3.81-3.77(m,1H),3.56-3.54(m,1H),2.67-2.61(m,1H),2.41-2.37(m,1H),1.46(s,9H),0.80(s,9H),0.00(s,6H)。

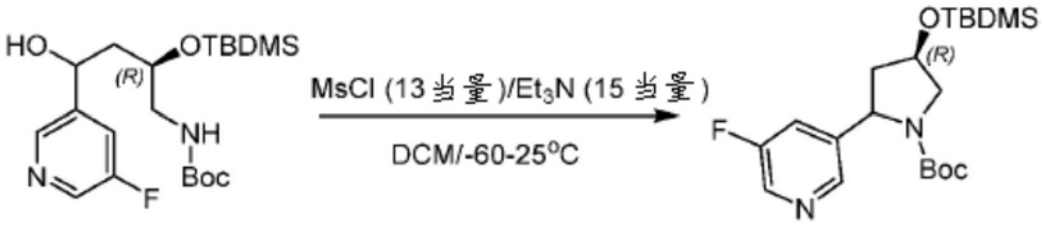
[0253] 步骤3:((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯

[0254] 


[0255] 在0℃下经30分钟向3-溴-5-氟-吡啶(3.35g,19.02mmol,1.20当量)于THF(40.00mL)中的混合物中逐滴添加i-PrMgCl-LiCl(1.3M,17.56mL,1.44当量)(放热)。添加后,经1小时使温度升高至25℃并在25℃下搅拌30分钟。TLC(PE/EtOAc＝10/1)显示产生新斑点,这指示成功地制备了Mg试剂。然后在-78℃下经30分钟将于THF(50mL)中的(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧代吡咯烷-1-羧酸叔丁酯(5.00g,15.85mmol,1.00当量)逐滴添加至溶液中。经1小时使混合物升温至25℃,然后在25℃下搅拌16小时。TLC(PE/EtOAc＝3/1)显示起始材料完全消耗,并且检测到所需的产物(R)-(2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-氧代丁基)氨基甲酸叔丁酯。在0℃下通过添加MeOH(50mL)来淬灭反应混合物。在0℃下添加$NaBH_4$(1.20g,31.70mmol,2.00当量),然后将混合物在25℃下搅拌4小时。TLC(PE/EtOAc＝2/1)和LCMS显示反应完成。通过$NH_4Cl$水溶液(400mL)淬灭合并的反应混合物(4个平行反应)并用EtOAc(600mL*3)萃取。将合并的有机物经$Na_2SO_4$干燥并在真空中浓缩,并通过HPLC纯化残余物以得到呈黄色油状的((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯(1.24g,产

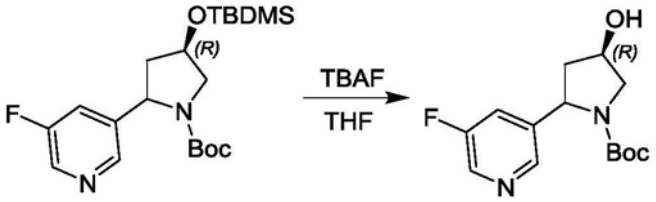
率:18.91%)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 8.26-8.22(m,2H),7.37(d,1H,J=8.8Hz),4.95-4.88(m,2H),4.69(br.s,1H),4.00-3.98(m,2H),3.23-3.10(m,2H),1.73(br.s,2H),1.32(s,9H),0.80-0.79(m,9H),0.00(s,6H)。

[0256] 步骤4:(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0257] 

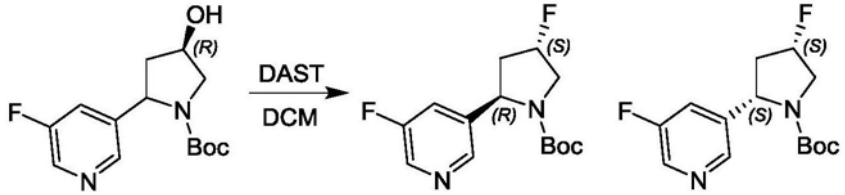

[0258] 在-60℃下经0.5小时向((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯(8.70g,20.98mmol,1.00当量)和$Et_3N$(31.84g,314.70mmol,15.00当量)于DCM(500.00mL)中的混合物中逐滴添加MsCl(31.24g,272.74mmol,13.00当量)。然后将混合物在-60℃下搅拌1小时,并使反应混合物升温至25℃并搅拌18小时。LCMS显示起始材料完全消耗。然后用$H_2O$(200mL*3)洗涤混合物,并用DCM(200mL*4)萃取水相。将合并的有机层经$Na_2SO_4$干燥并在真空中浓缩,以得到呈黑色/呈棕色油状的粗制产物(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(8.30g,粗制物),其不经纯化即直接使用。

[0259] 步骤5:(4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0260] 


[0261] 在25℃下向(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(8.30g,20.93mmol,1.00当量)于THF(250.00mL)中的混合物中添加TBAF(9.43g,41.86mmol,2.00当量)。将混合物在25℃下搅拌16小时。TLC(PE/EtOAc=1/1)显示反应完成后,浓缩混合物并将残余物溶解于EtOAc(600mL)中,用水(200mL*5)洗涤,经$Na_2SO_4$干燥,并浓缩。通过HPLC纯化该粗制产物,以得到呈棕黑色油状的(4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(4.70g,16.65mmol,产率:79.54%)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 8.37-8.33(m,2H),7.48(br.s,1H),5.09-4.89(m,1H),4.56-4.54(m,1H),3.80-3.65(m,2H),2.63-2.43(m,1H),2.03-1.96(m,1H),1.56-1.20(m,9H)。

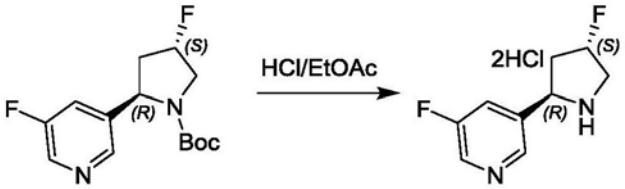
[0262] 步骤6:(2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0263] 


[0264] 在-78℃下经0.5小时向(4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(4.70g,16.65mmol,1.00当量)于DCM(150.00mL)中的混合物中逐滴添加DAST(29.52g,

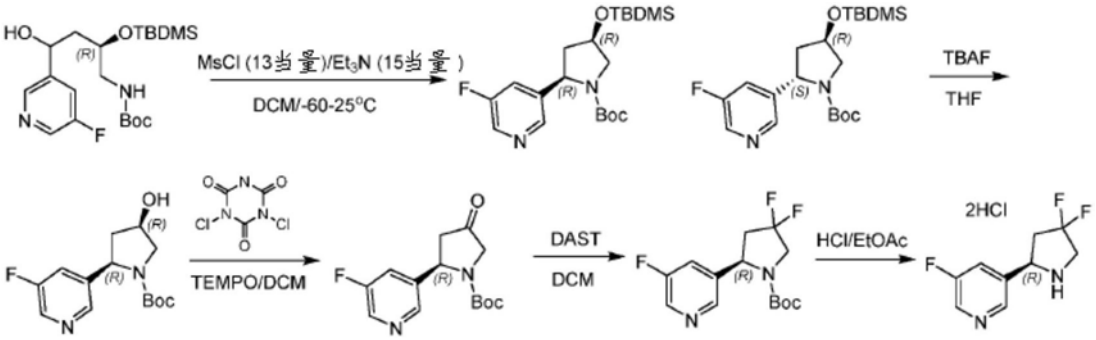
183.15mmol,11.00当量)。将反应混合物在-78℃下搅拌2小时,然后使其升温至25℃并搅拌20小时。TLC(PE/EtOAc=0/1)显示起始材料完全消耗后,使混合物冷却至0℃并通过逐滴添加饱和$NaHCO_3$溶液(100mL)淬灭。分离有机相并经$Na_2SO_4$干燥,浓缩以得到残余物,然后通过硅胶上的柱色谱(PE:EtOAc从10:1、8:1至5:1,然后3:1)纯化以得到呈白色固体的(2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.38g,4.85mmol,产率:29.15%,$R^f$=0.53)和呈黄色油状的(2S,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.36g,4.78mmol,产率:28.73%,$R_f$=0.43)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 8.31-8.27(m,2H),7.20-7.18(m,1H),5.18(d,1H,J=51.6Hz),4.97-4.88(m,1H),4.04-4.00(m,1H),3.64(dd,1H,J=38.8,12.8Hz),2.67(dd,1H,J=15.6,6.8Hz),1.97-1.67(m,1H),1.56-1.12(m,9H)。

[0265] 步骤7:3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶

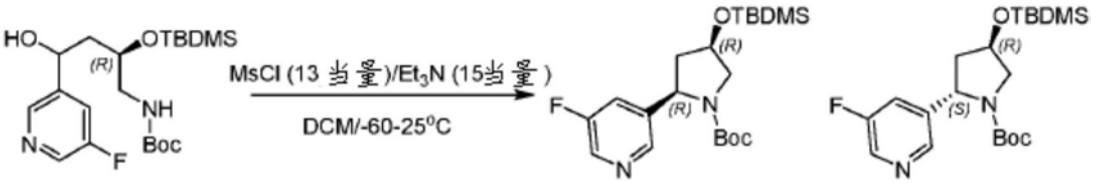
[0266] 


[0267] 在0℃下向(2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.38g,4.85mmol,1.00当量)于EtOAc(10mL)中的混合物中逐滴添加HCl/EtOAc(40.00mL,4M)。使混合物升温至25℃并搅拌3小时。TLC(PE:EtOAc=1:1)显示反应完成后,蒸发溶剂以得到呈棕色固体的3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶(1.25g,4.86mmol,产率:100.00%)。$^1$H-NMR(400MHz,$CD_3OD$)δppm 8.84-8.81(m,2H),8.31(d,1H,J=9.2Hz),5.62(dt,1H,J=52.0,2.4Hz),5.23-5.18(m,1H),4.00-3.95(m,1H),3.88-3.71(m,1H),2.67(td,1H,J=16.0,6.0Hz),1.69-1.59(m,1H)。

[0268] (R)-3-(4,4-二氟吡咯烷-2-基)-5-氟吡啶

[0269] 

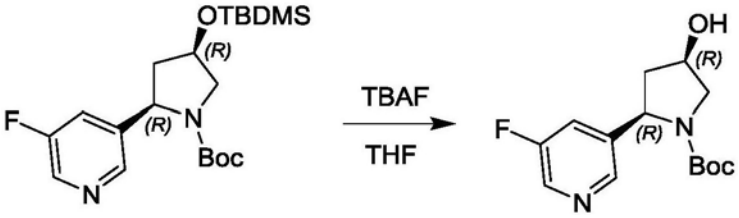

[0270] 步骤1:(2R,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0271] 


[0272] 在-60℃下经30分钟向((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯(6.80g,16.40mmol)和$Et_3N$(24.89g,246.00mmol)于DCM(500.00mL)中的混合物中逐滴添加MsCl(24.42g,213.20mmol)。将混合物在-60℃下搅

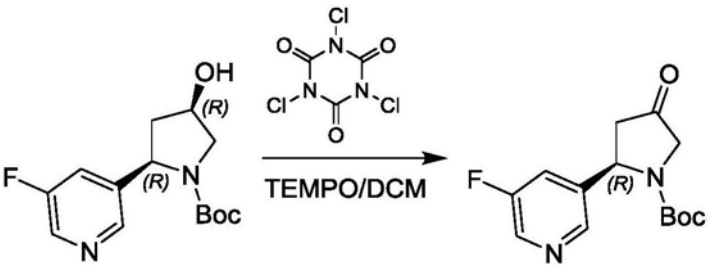
拌1小时。使反应混合物升温至25℃并再搅拌18小时。用$H_2O$(200mL*3)洗涤混合物。用DCM(200mL*4)萃取水相。将合并的有机层经$Na_2SO_4$干燥并在真空中浓缩。通过硅胶色谱(PE:EtOAc＝50/1,20/1,10/1)纯化残余物,以得到呈棕色油状的(2S,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(2.70g,产率:41.52%)和(2R,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(2.40g,产率:36.89%)。1H-NMR(400MHz,CDCl3)δppm 8.40(br.s,2H),7.56-7.45(m,1H),5.11-4.94(m,2H),4.53(br.s,1H),3.85-3.79(m,1H),3.66-3.53(m,1H),2.62-2.58(m,1H),2.04-2.01(m,1H),1.56(s,3H),1.32(s,6H),0.99-0.88(m,9H),0.18-0.00(m,6H)。

[0273] 步骤2:(2R,4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0274] 

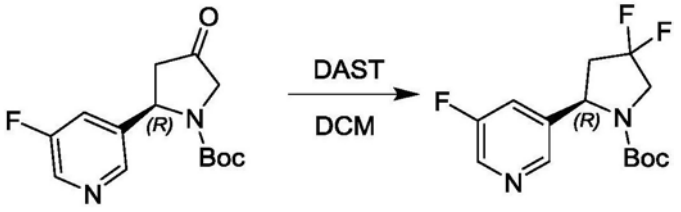

[0275] 在25℃下向(2R,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(2.40g,6.05mmol)于THF(60.00mL)中的混合物中一次性添加TBAF(3.16g,12.10mmol)。在50℃下在减压下浓缩混合物。将残余物添加至水(20mL)中。用乙酸乙酯(30mL*3)萃取水相。用饱和盐水(20mL*2)洗涤合并的有机相,经$Na_2SO_4$干燥,过滤并在真空中浓缩。通过硅胶色谱(PE:EtOAc＝20/1、10/1、1/3)纯化残余物以得到呈黄色固体的(2R,4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.30g,产率:76.11%)。1H-NMR(400MHz,CDCl3)δppm 8.26(d,2H,J＝12.8Hz),7.39(br.s,1H),4.95-4.81(m,1H),4.48-4.47(m,1H),3.73(br.s,1H),3.56-3.53(m,1H),2.55(br.s,1H),1.97-1.98(m,1H),1.65-1.16(m,9H)。

[0276] 步骤3:(R)-2-(5-氟吡啶-3-基)-4-氧代吡咯烷-1-羧酸叔丁酯

[0277] 

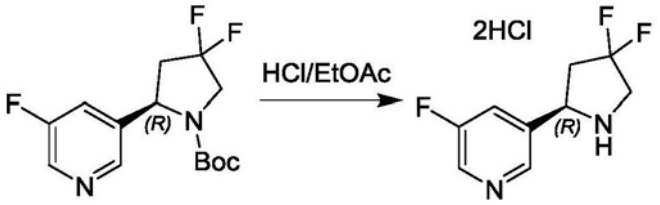

[0278] 在-10℃下向(2R,4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.30g,4.60mmol)和三氯异氰尿酸(1.10g,4.60mmol)的混合物中添加TEMPO(72.41mg,460.49umol)。将混合物在-10℃下搅拌15分钟,然后升温至25℃并搅拌1小时。TLC(EtOAc)显示反应完成。用$NaHCO_3$(20mL*2)洗涤有机相,经$Na_2SO_4$干燥,过滤并在真空中浓缩。通过硅胶色谱(石油醚/乙酸乙酯＝50/1,10/1)纯化残余物,以得到呈棕色油状的(R)-2-(5-氟吡啶-3-基)-4-氧代吡咯烷-1-羧酸叔丁酯(1.10g,产率:85.32%)。

[0279] 步骤4:(R)-4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0280] 

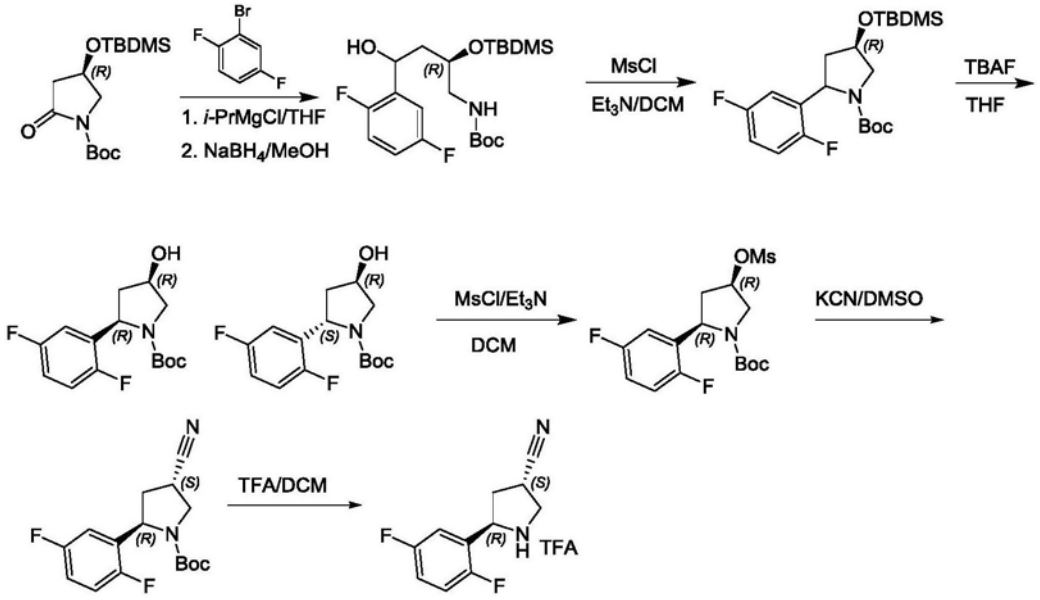

[0281] 在-70℃和$N_2$下向(R)-2-(5-氟吡啶-3-基)-4-氧代吡咯烷-1-羧酸叔丁酯(1.00g,3.57mmol)于DCM(100.00mL)中的混合物中逐滴添加DAST(14.39g,89.25mmol)。将混合物在-70℃下搅拌30分钟。然后将混合物在25℃下搅拌16小时。在0℃下通过饱和$NaHCO_3$水溶液缓慢淬灭反应混合物并用DCM(50mL*4)萃取水相。用饱和盐水(30mL)洗涤合并的有机相,经$Na_2SO_4$干燥,过滤并在真空中浓缩。通过硅胶色谱(石油醚/乙酸乙酯=100/1,30/1)纯化残余物,以得到呈棕色油状的(R)-4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.00g,产率:92.66%)。1H-NMR(400MHz,CDCl3)δppm 8.40(s,1H),8.34(s,1H),7.30-7.21(m,1H),5.06(br.s,1H),4.14-3.85(m,2H),2.91-2.84(m,1H),2.39-2.32(m,1H),1.43-1.14(m,9H)。

[0282] 步骤5:(R)-3-(4,4-二氟吡咯烷-2-基)-5-氟吡啶

[0283] 

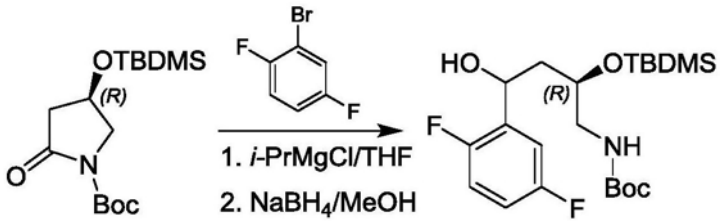

[0284] 将(R)-4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.00g,3.31mmol)于HCl/EtOAc(50.00mL,4M)中的混合物在25℃下搅拌2小时。在减压和30℃下浓缩混合物,以得到双HCl盐形式的呈白色固体的(R)-3-(4,4-二氟吡咯烷-2-基)-5-氟吡啶(840.00mg,产率:92.25%)。1H-NMR(400MHz,MeOD)δppm 8.68-8.63(m,1H),7.97(d,1H,J=9.2Hz),5.26-5.21(m,1H),4.03-3.90(m,2H),3.13-2.92(m,2H)。

[0285] (3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-甲腈

[0286] 

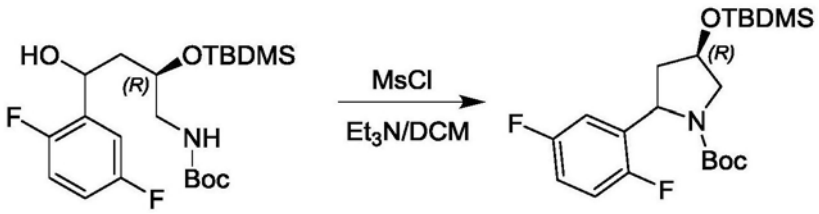

[0287] 步骤1:((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(2,5-二氟苯基)-4-羟基丁

基)氨基甲酸叔丁酯

[0288] 

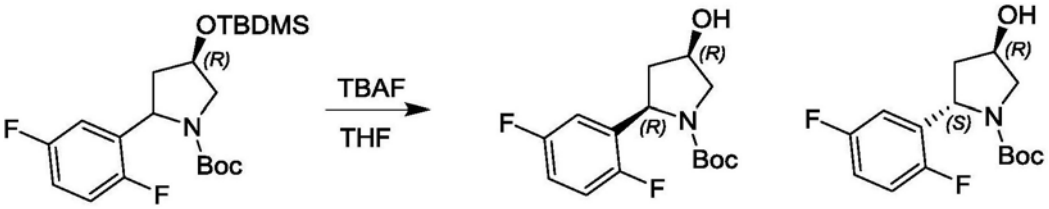

[0289] 在0℃和$N_2$下向2-溴-1,4-二氟-苯(3.01g,15.60mmol,1.20当量)于THF(15mL)中的溶液中逐滴添加异丙基氯化镁络合物(2.27g,15.60mmol,1.20当量)。将反应在15℃下搅拌1小时以制备(2,5-二氟苯基)溴化镁(23mL)。在0℃下经30分钟向(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧代吡咯烷-1-羧酸叔丁酯(4.10g,13.00mmol,1.00当量)于THF(50mL)中的溶液中逐滴添加(2,5-二氟苯基)溴化镁(23mL)。将反应混合物在0℃下搅拌1小时。在0℃下将甲醇(20mL)和$NaBH_4$(738mg,19.50mmol,1.50当量)相继添加至混合物中。将混合物在0℃下搅拌1小时,然后倒入10%$NH_4Cl$水溶液中。用EtOAc(20mL*2)萃取混合物,用盐水洗涤合并的有机层,经$Na_2SO_4$干燥,过滤并浓缩。通过中压液相色谱(MPLC)纯化该粗制产物,以得到((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(2,5-二氟苯基)-4-羟基丁基)氨基甲酸叔丁酯(2.22g,5.14mmol,39.6%产率)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 7.17-7.15(m,1H),6.86-6.79(m,2H),5.11-5.06(m,1H),4.70(br.s,1H),4.02-3.98(m,1H),3.69(br.s,0.5H),3.46(br.s,0.5H),3.33-3.14(m,2H),1.80-1.69(m,2H),1.35(s,9H),0.84-0.82(9H,m),0.04-0.03(6H,m)。

[0290] 步骤2:(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯

[0291] 


[0292] 在-60℃和$N_2$下向((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(2,5-二氟苯基)-4-羟基丁基)氨基甲酸叔丁酯(13.40g,31.05mmol,1.00当量)和$Et_3N$(9.43g,93.14mmol,3.00当量)于DCM(50mL)中的溶液中逐滴添加甲烷磺酰氯(5.33g,46.57mmol,1.50当量)。将混合物在-60℃下搅拌2小时并在15℃下搅拌16小时。LCMS显示起始材料完全消耗。用DCM(30mL*2)萃取反应混合物并用盐水(50mL)洗涤合并的有机物,经$Na_2SO_4$干燥并过滤,浓缩,以得到(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(12.00g,26.11mmol,产率:84.10%,90%纯度),其不经进一步纯化即直接使用。

[0293] 步骤3:(2R,4R)-2-(2,5-二氟苯基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0294] 


[0295] 在15℃下向(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(2,5-二氟苯基)吡咯烷-

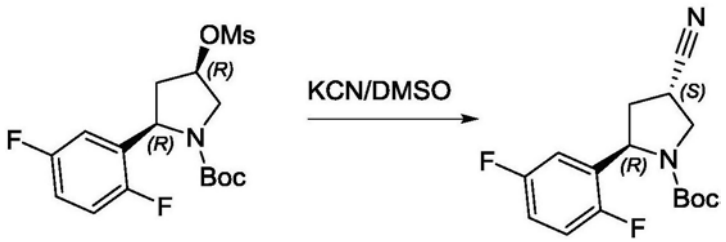
1-羧酸叔丁酯(4.50g,10.88mmol,1.00当量)于THF(30mL)中的溶液中添加TBAF/THF(1M,14.15mL,1.30当量)。将混合物在15℃下搅拌16小时。TLC(PE:EtOAc＝3:1)显示起始材料完全消耗。通过$H_2O$(50mL)淬灭反应混合物,用EtOAc(30mL*2)萃取,并用盐水(10mL)洗涤合并的有机物,经$Na_2SO_4$干燥,过滤并在真空中浓缩。通过中性制备型HPLC纯化残余物以得到呈白色固体的(2R,4R)-2-(2,5-二氟苯基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.00g,3.34mmol,产率:30.70%)。$^1$H-NMR(400MHz,$CDCl_3$)δppm 7.04-6.80(m,3H),5.10-5.00(m,1H),4.43(s,1H),3.75(br.s,1H),3.53-3.49(m,1H),2.53(br.s,1H),1.93-1.90(m,1H),1.40-1.16(m,9H)。

[0296] 步骤4:(2R,4R)-2-(2,5-二氟苯基)-4-((甲基磺酰基)氧基)吡咯烷-1-羧酸叔丁酯

[0297] 

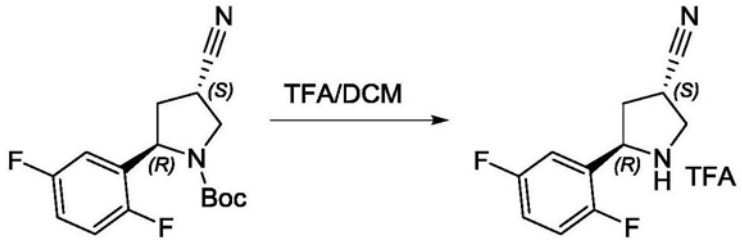

[0298] 在0℃下向(2R,4R)-2-(2,5-二氟苯基)-4-羟基吡咯烷-1-羧酸叔丁酯(3.00g,10.02mmol,1.00当量)和$Et_3N$(2.03g,20.04mmol,2.00当量)于DCM(80.00mL)中的混合物中逐滴添加MsCl(1.61g,14.03mmol,1.40当量)。将混合物在18℃下搅拌2小时。通过$H_2O$(30mL)淬灭混合物。通过DCM(50mL*3)萃取水相。将合并的有机层经$Na_2SO_4$干燥并在减压下浓缩,获得呈棕色固体的(2R,4R)-2-(2,5-二氟苯基)-4-((甲基磺酰基)氧基)吡咯烷-1-羧酸叔丁酯(3.60g,9.54mmol,产率:95.20%)。

[0299] 步骤5:(2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯

[0300] 

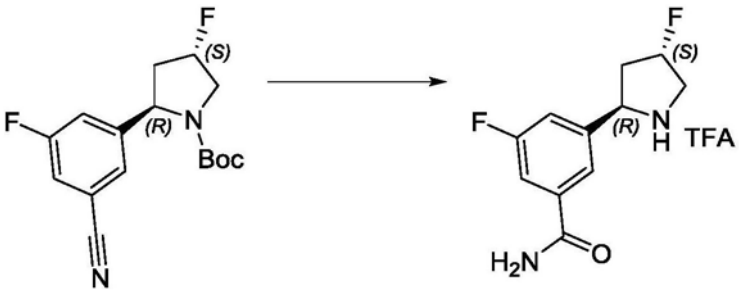

[0301] 向(2R,4R)-2-(2,5-二氟苯基)-4-((甲基磺酰基)氧基)吡咯烷-1-羧酸叔丁酯(3.60g,9.54mmol,1.00当量)于DMSO(20.00mL)中的混合物中一次性添加KCN(745.49mg,11.45mmol,1.20当量)。将混合物在90℃下搅拌3小时。将80mL H2O添加至混合物中,并通过EtOAc(80mL*4)萃取混合物。在减压下浓缩合并的有机层。通过硅胶色谱(PE/EtOAc＝40:1,30:1,10:1)纯化残余物,获得呈浅绿色液体的(2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(1.60g,5.19mmol,产率:54.40%)。

[0302] 步骤6:(3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-甲腈

[0303] 

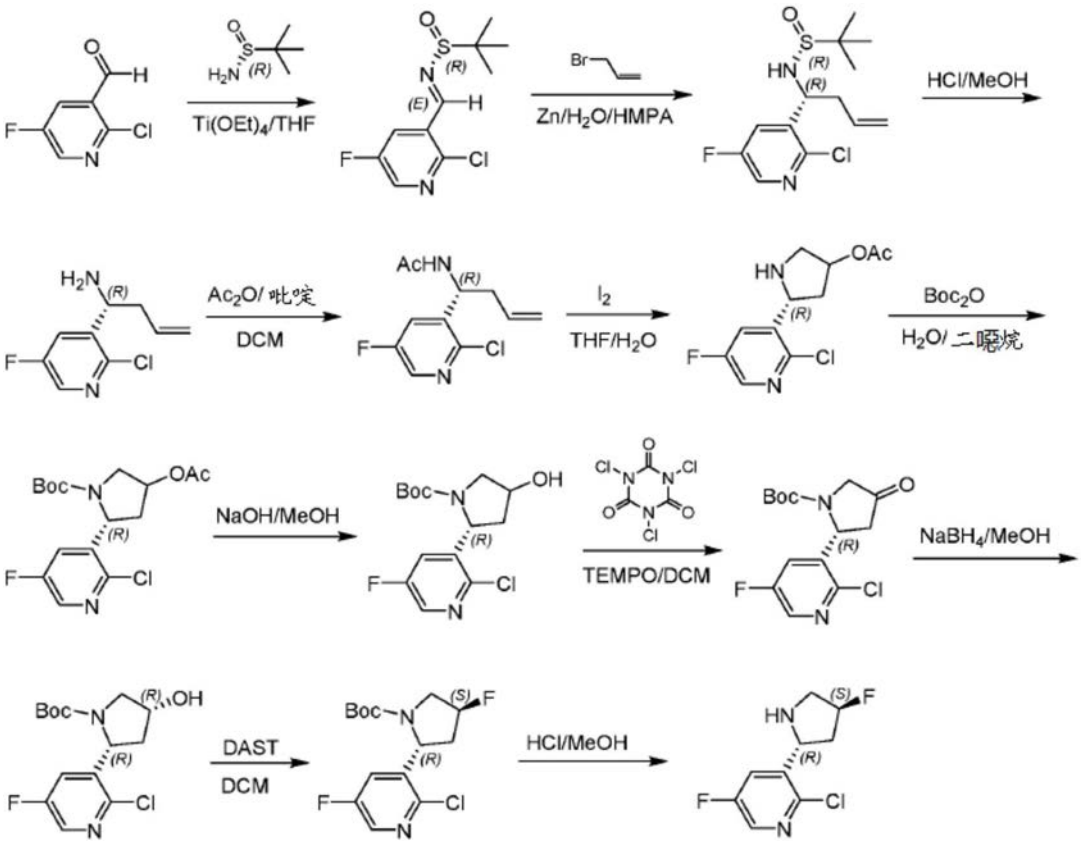
[0304] 将(2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(800.00mg,2.59mmol,1.00当量)于TFA(4.00mL)/DCM(20.00mL)中的混合物在18℃下搅拌3小时。在$N_2$下干燥混合物。获得浅呈黄色固体的(3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-甲腈(780.00mg,2.42mmol,产率:93.44%)。

[0305] 3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酰胺

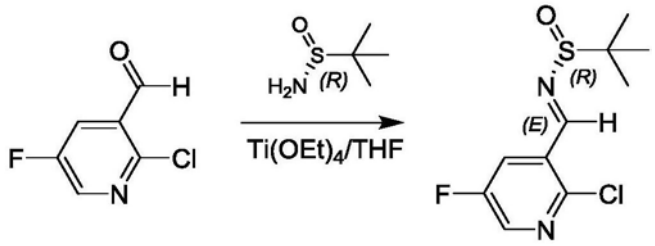
[0306] 


[0307] 将3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲腈(0.050g,0.240mmol)(如WO 2012/034095中制备)吸收于TFA(0.800ml,10.38mmol)和$H_2SO_4$(0.200ml,3.75mmol)中并在室温下搅拌过夜。用冰水(3ml)稀释反应混合物并通过过滤分离固体,并且直接使用。

[0308] 2-氯-5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)吡啶

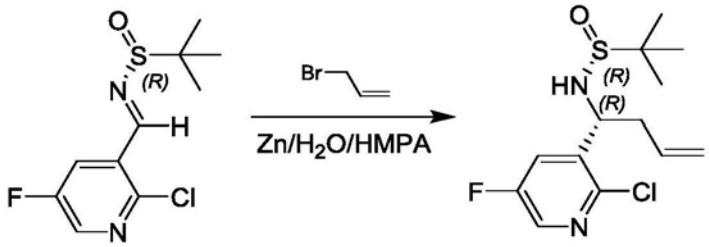
[0309] 


[0310] 步骤1:(S,Z)-N-((2-氯-5-氟吡啶-3-基)亚甲基)-2-甲基丙烷-2-亚磺酰胺

[0311] 

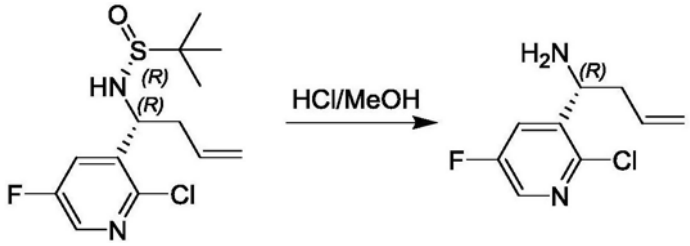

[0312] 在0℃下将2-氯-5-氟烟碱醛(20g,125mmol)吸收于THF(150ml)中。添加(R)-2-甲基丙烷-2-亚磺酰胺(16.71g,138mmol),随后逐滴添加钛酸四丁酯(22.88ml,150mmol)。搅拌反应混合物同时升温至RT。3小时后,使反应混合物冷却至0℃,并添加150ml盐水并搅拌20分钟。借助硅藻土(Celite)过滤混合物。分离水层并丢弃。将有机层经$Na_2SO_4$干燥并去除溶剂,以得到(S,Z)-N-((2-氯-5-氟吡啶-3-基)亚甲基)-2-甲基丙烷-2-亚磺酰胺(32g,122mmol,97%产率),其不经进一步纯化便使用。LCMS:263M+H。

[0313] 步骤2:(R)-N-((R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)-2-甲基丙烷-2-亚磺酰胺

[0314] 

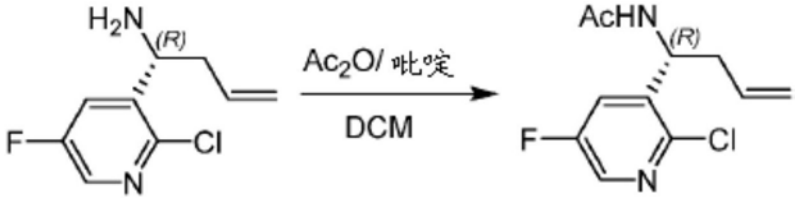

[0315] 将(R,E)-N-((2-氯-5-氟吡啶-3-基)亚甲基)-2-甲基丙烷-2-亚磺酰胺(32.9g,125mmol)溶解于HMPA(100ml)中并冷却至0℃。在0℃下添加锌(16.37g,250mmol)、烯丙基溴(21.67ml,250mmol)和水(2.256ml,125mmol),并使反应混合物升温至RT过夜。LCMS显示完全转化为所需的产物。在RT下添加100ml水并搅拌30分钟。相继添加30mlMBTE和60ml 10%柠檬酸,并将反应混合物搅拌30分钟。借助硅藻土过滤混合物并用MTBE洗涤。用10%柠檬酸、水和盐水洗涤有机层。在真空下去除溶剂以得到呈橙色油状的(R)-N-((R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)-2-甲基丙烷-2-亚磺酰胺(14.5g,47.6mmol,38.0%产率)。LCMS:305M+H。

[0316] 步骤3:(R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-胺盐酸盐

[0317] 

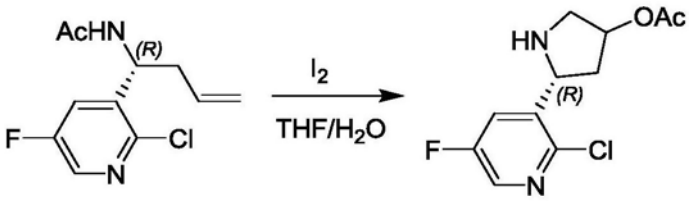

[0318] 将(R)-N-((R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)-2-甲基丙烷-2-亚磺酰胺(7.5g,24.61mmol)吸收于10ml MeOH中。添加HCl(4M于二噁烷中)(30.8ml,123mmol)并在RT下搅拌1小时。在真空下去除溶剂并在DCM中稀释残余物并用饱和NaHCO3水溶液洗涤。分离各层并用$Na_2SO_4$干燥有机层并在真空下去除溶剂。回收呈固体的(R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-胺盐酸盐(5.83g,24.59mmol,100%产率)。LCMS:201M+H。

[0319] 步骤4:(R)-N-(1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)乙酰胺

[0320] 

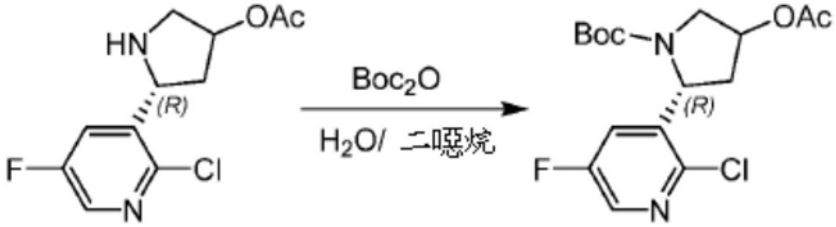

[0321] 在0℃下向于DCM(70.3ml)中的(R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-胺●HCl(5.83g,24.59mmol)中添加TEA(4.11ml,29.5mmol)和乙酸酐(2.320ml,24.59mmol)。将混合物搅拌2小时。将反应混合物倒入饱和$NaHCO_3$水溶液中并用DCM萃取。用盐水洗涤有机层,经$MgSO_4$干燥,并在减压下蒸发。回收(R)-N-(1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)乙酰胺(5.97g,24.60mmol,100%产率)并且不经进一步纯化便使用。LCMS:243M+H。

[0322] 步骤5:(5R)-乙酸5-(2-氯-5-氟吡啶-3-基)吡咯烷-3-基酯

[0323] 

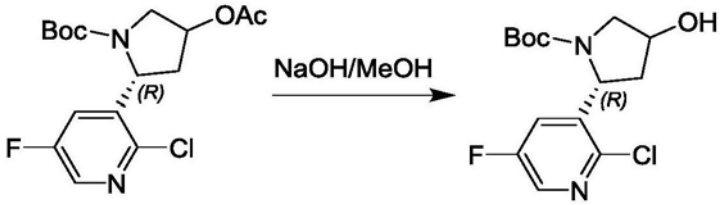

[0324] 将(R)-N-(1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)乙酰胺(5.97g,24.60mmol)吸收于THF(56.2ml)和水(14.06ml)中,随后添加$I_2$(18.73g,73.8mmol)并在RT下搅拌过夜。用饱和$NaHCO_3$和$Na_2S_2O_3$溶液稀释粗制反应物并用EtOAc萃取两次。用饱和$NaHCO_3$水溶液碱化水层并用EtOAc萃取,以获得浅呈黄色油状的(5R)-乙酸5-(2-氯-5-氟吡啶-3-基)吡咯烷-3-基酯(5.9g,22.81mmol,93%产率)。LCMS:259M+H。

[0325] 步骤6:(2R)-4-乙酰氧基-2-(2-氯-5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0326] 


[0327] 向(5R)-乙酸5-(2-氯-5-氟吡啶-3-基)吡咯烷-3-基酯(5.9g,22.81mmol)于二噁烷(76ml)和水(76ml)中的溶液中添加BOC酐(7.94ml,34.2mmol),随后小心添加2N NaOH(7ml)以实现约9的pH。将反应混合物在RT下搅拌1小时。用水稀释反应混合物并用EtOAc萃取三次。将有机层经$Na_2SO_4$干燥并在真空下去除溶剂,以得到(2R)-4-乙酰氧基-2-(2-氯-5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(3.5g,9.75mmol,42.8%产率),其不经进一步纯化便使用。LCMS:359M+H。

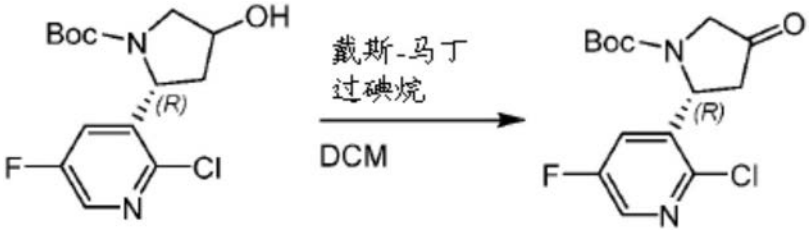
[0328] 步骤7:(2R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0329] 


[0330] 将(2R)-4-乙酰氧基-2-(2-氯-5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(3.5g,

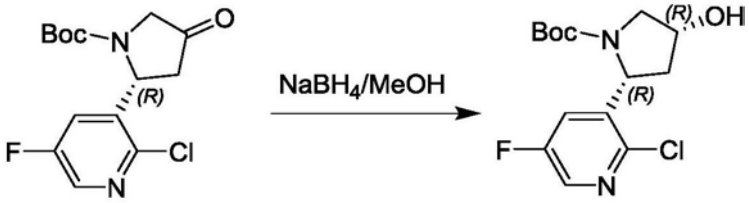
9.75mmol)吸收于MeOH(48.8ml)中,随后添加2M NaOH(5.37ml,10.73mmol)并将反应混合物在RT下搅拌2小时。在真空下去除溶剂并用1N HCl中和水层,并用EtOAc萃取三次。将合并的有机层经$Na_2SO_4$干燥。在真空下去除溶剂并经由硅胶色谱(0-70%Hex/EtOAc)纯化残余物,以得到(2R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(2.1g,6.63mmol,68.0%产率)。LCMS:317M+H。

[0331] 步骤8:(R)-2-(2-氯-5-氟吡啶-3-基)-4-氧代吡咯烷-1-羧酸叔丁酯

[0332] 

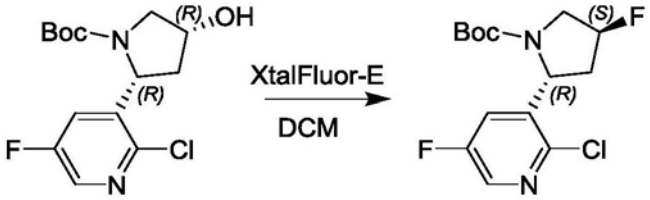

[0333] 将(2R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(2.1g,6.63mmol)吸收于DCM(66.3ml)中,并相继添加$NaHCO_3$(0.557g,6.63mmol)和戴斯-马丁过碘烷(8.44g,19.89mmol)。将反应混合物搅拌过夜。相继添加水(0.119ml,6.63mmol)和戴斯-马丁过碘烷(8.44g,19.89mmol)并搅拌18小时。用饱和$NaHCO_3$水溶液将pH调节至约7并用DCM×3萃取。合并有机层,经$Na_2SO_4$干燥并在真空下去除溶剂。通过急速色谱(0-70%Hex/EtOAc)纯化残余物,以得到(R)-2-(2-氯-5-氟吡啶-3-基)-4-氧代吡咯烷-1-羧酸叔丁酯(1.6g,5.08mmol,77%产率)。LCMS:315M+H。

[0334] 步骤9:(2R,4R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0335] 


[0336] 将(R)-2-(2-氯-5-氟吡啶-3-基)-4-氧代吡咯烷-1-羧酸叔丁酯(1.6g,5.08mmol)悬浮于乙醇(33.9ml)中,并冷却至0℃。逐滴添加$NaBH_4$(0.096g,2.54mmol)并在0℃下搅拌45分钟。用饱和$NH_4Cl$缓慢淬灭反应物并使其升温至RT,并用DCM×3萃取溶液。合并有机层并经$Na_2SO_4$干燥。通过急速色谱(0-70%Hex/EtOAc)纯化残余物,以得到(2R,4R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.446g,4.57mmol,90%产率)。LCMS:317M+H。

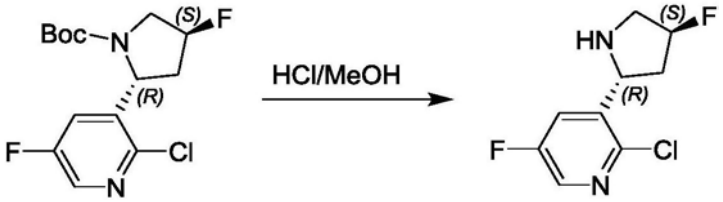
[0337] 步骤10:(2R,4S)-2-(2-氯-5-氟吡啶-3-基)-4-氟吡咯烷-1-羧酸叔丁酯

[0338] 


[0339] 将(2R,4R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.0g,3.16mmol)吸收于DCM(25ml)中,并冷却至-78℃。添加TEA-HF(1.098ml,9.47mmol)并搅拌10分钟。添加XtalFluor-E(1.446g,6.31mmol)并且在10分钟后,将反应混合物转移至冰浴并使其升温至0℃。2小时后,用DCM稀释反应混合物并用饱和$NaHCO_3$水溶液淬灭。分离有机层,

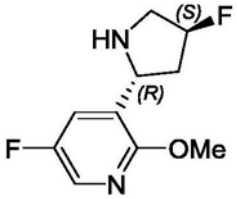
并在真空下去除溶剂。通过ISCO(0-50％Hex/EtOAc;12g柱)纯化残余物,以得到呈白色固体的(2R,4S)-2-(2-氯-5-氟吡啶-3-基)-4-氟吡咯烷-1-羧酸叔丁酯(0.805g,2.53mmol,80％产率)。LCMS:319M+H。

[0340] 步骤11:2-氯-5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)吡啶盐酸盐

[0341] 


[0342] 将(2R,4S)-2-(2-氯-5-氟吡啶-3-基)-4-氟吡咯烷-1-羧酸叔丁酯(0.805g,2.53mmol,80％产率)吸收于EtOAc(5ml)中并添加4N HCl/二噁烷(3ml)。将反应混合物在RT下搅拌1小时。滤出沉淀物,用乙醚洗涤,并在高真空下干燥过夜,以得到灰呈白色固体的2-氯-5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)吡啶盐酸盐(0.612g,2.399mmol,76％产率)。LCMS:219M+H。

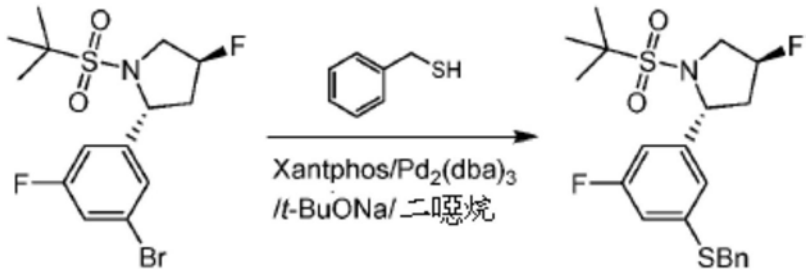
[0343] 5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)-2-甲氧基吡啶

[0344] 


[0345] 5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)-2-甲氧基吡啶是以与3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酰胺相同的方式、用5-氟-2-甲氧基烟碱醛取代2-氯-5-氟烟碱醛来制备。

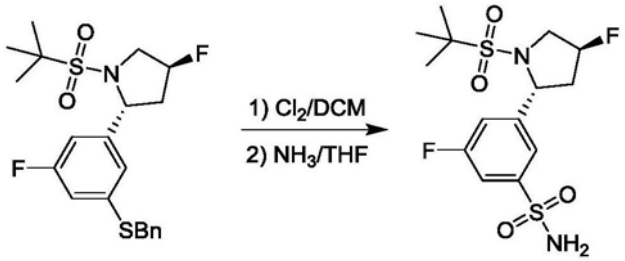
[0346] 3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯磺酰胺

[0347] 步骤1:(2R,4S)-2-(3-(苄硫基)-5-氟苯基)-1-(叔丁基磺酰基)-4-氟吡咯烷

[0348] 

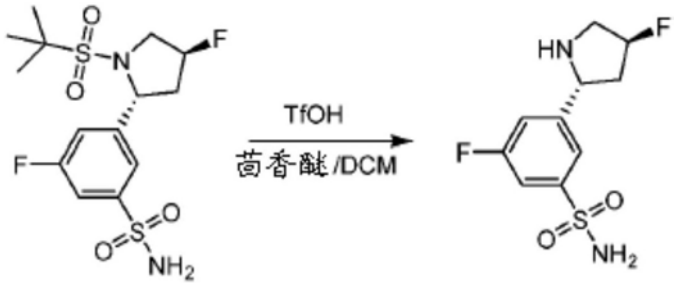

[0349] 向(2R,4S)-2-(3-溴-5-氟苯基)-1-(叔丁基磺酰基)-4-氟吡咯烷(1.00g,2.62mmol,1.00当量)于二噁烷(3.00mL)中的混合物中添加t-BuONa(502.80mg,5.23mmol,2.00当量)、苯基甲硫醇(649.82mg,5.23mmol,613.04uL,2.00当量)、Xantphos(151.37mg,261.60umol,0.10当量)和$Pd_2(dba)_3$(239.55mg,261.60umol,0.10当量)。添加后,将混合物在80℃下在$N_2$下搅拌16小时。浓缩混合物以得到粗制产物。通过硅胶上的柱色谱(PE:EtOAc=20:1-8:1)纯化混合物,以得到呈红色油状的(2R,4S)-2-(3-(苄硫基)-5-氟苯基)-1-(叔丁基磺酰基)-4-氟吡咯烷(700.00mg,1.64mmol,产率:62.78％)。

[0350] 步骤2:3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯磺酰胺

[0351] 


[0352] 在0℃下经6分钟将稳定的$Cl_2$气体流鼓泡穿过(2R,4S)-2-(3-(苄硫基)-5-氟苯基)-1-(叔丁基磺酰基)-4-氟吡咯烷(700.00mg,1.64mmol,1.00当量)于DCM(16.00mL)/AcOH(8.00mL)/$H_2O$(4.00mL)中的混合物。通过用$N_2$气吹扫6分钟使反应混合物消散。然后用过量$NH_3.H_2O$处理所得双-磺酰氯直到水相的pH为9至10,并使其升温至25℃并搅拌16小时。LCMS显示反应完成。用DCM(20mL*3)萃取混合物,浓缩有机层以得到呈黄色油状的3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯磺酰胺(600.00mg,粗制物)。

[0353] 步骤3:3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯磺酰胺

[0354] 


[0355] 在-40℃下向TfOH(706.35mg,4.71mmol,415.50uL,3.00当量)于DCM(20.00mL)中的混合物中添加茴香醚(254.48mg,2.36mmol,254.48uL,1.50当量),然后在-40℃下经0.1小时将3-((2R,4S)-1-(叔丁基磺酰基)-4-氟吡咯烷-2-基)-5-氟苯磺酰胺(600.00mg,1.57mmol,1.00当量)于DCM(10.00mL)中的溶液逐滴添加至混合物中。添加后,使混合物升温至25℃并在25℃下搅拌1小时。TLC(PE:EtOAc=1:1)显示起始材料完全消耗。将混合物添加至饱和$K_2CO_3$水溶液(100mL)中并搅拌0.1小时。用DCM(100mL*2)萃取混合物。浓缩水层以得到粗制产物。用DCM(10mL*3)洗涤混合物,浓缩有机层以得到呈黄色油状的3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯磺酰胺(300.00mg,粗制物)。

[0356] 下文还显示了针对本文所公开的化合物获得的NMR和LC MS数据。

[0357]

| 化合物编号 | $^1$H NMR | MS (M+1) |
|---|---|---|
| 1 | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.55 (br.s, 1H), 8.44 (d, 1H, J = 2.4 Hz), 8.10 (s, 1H), 7.83 (br.s, 1H), 6.69 (br.s, 1H), 6.24 (br.s, 1H), 5.55-5.43 (m, 2H), 4.25-4.16 (m, 2H), 2.95 (br.s, 1H), 2.40-2.26 (m, 1H) | 327 |
| 2 | $^1$H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 48.6 Hz, 1H), 8.33 (d, J = 37.6 Hz, 1H), 7.16 (d, J = 50.9 Hz, 3H), 6.47 (d, J = 238.1 Hz, 1H), 5.74 – 5.24 (m, 2H), 4.26 (d, J = 123.1 Hz, 2H), 2.80 (s, 1H), 2.27 (d, J = 40.7 Hz, 1H) | 344 |
| 3 | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.57-8.53 (m, 3H), 8.12 (br.s, 1H), 7.91 (s, 1H), 6.56 (br.s, 1H), 5.70 (br.s, 1H), 4.46-4.41 (m, 1H), 4.38-4.24 (m, 1H), 3.25-3.11 (m, 1H), 2.69-2.58 (m, 1H) | 345 |
| 4 | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.84 (d, 1H, J = 7.6 Hz), 8.66 (s, 1H), 8.49 (s, 1H), 8.11 (s, 1H), 8.00 (br.s, 1H), 5.60-5.57 (m, 1H), 5.49 (d, 1H, J = 52.4 Hz), 4.49-4.30 (m, 2H), 2.93-2.84 (m, 1H), 2.36-2.22 (m, 1H) | 345 |
| 5 | $^1$H-NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (br.s, 1H), 8.10 (s, 1H), 7.14-7.12 (m, 1H), 7.02 (br.s, 1.5H), 6.73 (br.s, 1.5H), 4.32 (br.s, 2H), 3.35 (br.s, 1H), 2.89 (br.s, 1.0H), 2.53 (br.s, 2H) | 350 |
| 6 | $^1$H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 63.8 Hz, 1H), 8.33 (d, J = 36.7 Hz, 1H), 7.73 (d, J = 39.9 Hz, 2H), 6.46 (d, J = 249.9 Hz, 1H), 5.50 (d, J = 56.3 Hz, 1H), 5.34 (t, 1H), 4.54 - 4.04 (m, 3H), 2.98 - 2.66 (m, 1H), 2.21 (d, J = 42.5 Hz, 1H) | 351 |
| 7 | $^1$H NMR (400 MHz, DMSO-d6) δ ppm 8.73 (dd, J = 59.6, 7.8 Hz, 1H), 8.32 (d, J = 41.5 Hz, 1H), 8.05 (d, J = 42.4 Hz, 1H), 7.65 (m, 1H), 6.76-6.13 (m, 1H), 5.64 – 5.24 (m, 2H), 4.42-4.15 (m, 2H), 3.92 (s, 3H), 2.94 – 2.65 (m, 1H), 2.25 (dt, J = 40.8, 10.7 Hz, 1H) | 357 |
| 8 | $^1$H NMR (400 MHz, DMSO-d6) δ ppm 8.73 (dd, J = 36.6, 7.7 Hz, 1H), 8.32 (d, J = 30.5 Hz, 1H), 7.90 (d, J = 38.4 Hz, 1H), 7.72 – 7.50 (m, 1H), 6.73-6.25 (m, 1H), 5.50 (dd, J = 53.0, 21.0 Hz, 1H), 5.36 – 5.12 (m, 1H), 4.37 (dd, J = 21.7, 13.8 Hz, 1H), 4.21 – 3.95 (m, 1H), 3.41 (d, 3H), 2.86 – 2.54 (m, 1H), 2.29 (m, 1H) | 357 |
| 9 | $^1$H NMR (400 MHz, 甲醇-d4) δ 8.45 (s, 1H), 8.14 (s, 1H), 7.25 (d, J = 1.6 Hz, 1H), 7.09 (dt, J = 9.3, 1.9 Hz, 1H), 6.79 – 6.51 (m, 1H), 6.19 (s, 1H), 5.57 – 5.17 (m, 2H), 4.14 (d, J = 36.3 Hz, 2H), 2.92 (s, 1H), 2.24 (dddd, J = 40.9, 14.6, 9.4, 3.7 Hz, 1H) | 360 |
| 10 | $^1$H NMR (400 MHz, 甲醇-d4) δ 8.57 (s, 1H), 8.26 – 8.04 (m, 2H), 7.61 (dd, J = 8.9, 2.8 Hz, 1H), 6.71 (d, J = | 361 |

[0358]

| | | |
|---|---|---|
| | 7.5 Hz, 1H), 5.68 – 5.36 (m, 2H), 4.20 (d, J = 36.4 Hz, 2H), 2.38 – 2.14 (m, 2H) | |
| **11** | $^1$H NMR (400 MHz, 甲醇-d4) δ 8.42 (s, 1H), 8.13 (s, 1H), 7.69 (t, J = 1.7 Hz, 1H), 7.51 (s, 1H), 7.34 (dt, J = 9.2, 2.0 Hz, 1H), 6.69 (s, 1H), 6.20 (s, 1H), 5.51 (d, J = 13.9 Hz, 1H), 5.40 (s, 1H), 4.18 (d, J = 36.7 Hz, 1H), 2.95 (s, 1H), 2.27 (dddd, J = 40.8, 13.9, 9.3, 3.7 Hz, 1H) | 369 |
| **12** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.81 (d, 1H, J = 7.2 Hz), 8.12 (s, 1H), 7.66 (s, 1H), 7.54 (d, 1H, J = 9.2 Hz), 7.40 (d, 1H, J = 7.6 Hz), 5.52-5.39 (m, 2H), 4.47-4.29 (m, 2H), 2.91-2.81 (m, 1H), 2.29-2.12 (m, 1H) | 369 |
| **13** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.54-8.43 (m, 1H), 8.10 (br.s, 1H), 6.96-6.77 (m, 3H), 5.51-5.38 (m, 2H), 4.05 (br.s, 5H), 2.83 (br.s, 1H), 2.20-2.03 (m, 1H) | 374 |
| **14** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.35 (br.s, 1H), 8.11 (s, 1H), 7.28 (s, 1H), 7.10 (d, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 8.8 Hz), 6.17 (br.s, 1H), 5.42 (d, 1H, J = 52.4 Hz), 5.23 (br.s, 1H), 4.16-4.08 (m, 1H), 2.91 (br.s, 1H), 2.31-2.17 (m, 1H), 1.47 (d, 6H, J = 3.6 Hz). | 384 |
| **15** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.76 (d, 1H, J = 7.2 Hz), 8.09 (s, 1H), 7.69 (s, 1H), 7.44 (d, 1H, J = 9.2 Hz), 7.36 (d, 1H, J = 8.4 Hz), 5.55-5.39 (m, 2H), 4.45-4.33 (m, 2H), 2.90-2.81 (m, 1H), 2.30-2.16 (m, 1H) | 387 |
| **16** | $^1$H-NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (br.s, 1H), 7.98 (s, 2H), 7.92 (d, 1H, J = 6.8 Hz), 7.02 (d, 1H, J = 6.4 Hz), 6.39 (br.s, 1H), 5.55-5.36 (m, 4H), 4.20-4.03 (m, 2H), 2.93 (br.s, 1H), 2.29-2.15 (m, 1H). | 405 |
| **17** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.49 (br.s, 1H), 8.08 (br.s, 1H), 7.36 (s, 1H), 7.08 (d, 2H, J = 8.4 Hz), 6.67 (br.s, 1H), 5.52 (br.s, 2H), 5.46 (d, 1H, J = 52.0 Hz), 4.17 (br.s, 1H), 4.09 (br.s, 1H), 4.87 (br.s, 1H), 2.32-2.16 (m, 1H) | 410 |
| **18** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.37 (br.s, 1H), 8.10 (br.s, 1H), 7.66 (s, 1H), 7.46 (br.s, 1H), 7.30 (br.s, 1H), 6.66 (br.s, 0.5H), 6.17 (br.s, 0.5H), 5.51-5.38 (m, 2H), 4.53 (br.s, 1H), 4.20-4.13 (m, 1H), 3.68-3.65 (m, 2H), 3.46-3.45 (m, 2H), 2.98-2.92 (m, 1H), 2.31-2.22 (m, 1H). | 413 |
| **19** | $^1$H-NMR (400 MHz, $CD_3OD$) δ ppm 8.39 (br.s, 1H), 8.12 (br.s, 1H), 7.65 (s, 1H), 7.47 (br.s, 1H), 7.32 (d, 1H, J = 8.8 Hz), 6.68 (br.s, 0.5H), 6.19 (br.s, 0.5H), 5.52-5.39 (m, 2H), 4.62 (br.s, 1H), 4.23-4.14 (m, 2H), 3.21 (d, 2H, J =6.8 Hz), 2.95 (br.s, 1H), 2.36-2.20 (m, 1H), 1.10-1.07 (m, 1H), 0.50 (d, 2H, J = 8.0 Hz), 0.26 (d, 2H, J = 4.4 Hz). | 423 |

[0359]

| | | |
|---|---|---|
| **20** | $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.38 (br.s, 1H), 8.11 (br.s, 1H), 7.62 (s, 1H), 7.43 (br.s, 1H), 7.31 (d, 1H, $J$ = 9.2 Hz), 6.67-6.62 (m, 0.5H), 6.18 (br.s, 0.5H), 5.45 (d, 1H, $J$ = 52.8 Hz), 5.38 (br.s, 1H), 4.60 (br.s, 1H), 4.21-4.13 (m, 1H), 3.36 (br.s, 1H), 2.88 (s, 3H), 2.34-2.18 (m, 1H). | 383.1 |
| **21** | $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.41 (br.s, 1H), 8.09 (br.s, 1H), 7.20 (s, 2H), 7.05 (br.s, 1H), 6.66 (br.s, 0.5H), 6.18 (br.s, 0.5H), 5.43 (d, 1H, $J$ = 52.4 Hz), 5.36 (br.s, 1H), 4.54 (br.s, 0.5H), 4.19-4.05 (m, 1.5H), 3.08-2.88 (m, 7H), 2.32-2.18 (m, 1H). | 397.1 |
| **22** | $^1$H-NMR (400 MHz, $CD_3OD$) $\delta$ ppm 8.51-8.33 (m, 1H), 8.13-8.04 (m, 1H), 7.55 (br.s, 1H), 7.09-7.00 (m, 2H), 6.67-6.28 (m, 1H), 5.63-5.59 (m, 1H), 5.44 (d, 1H, $J$ = 52.8 Hz), 4.58-4.27 (m, 1H), 4.16-3.97 (m, 1H), 2.97 (br.s, 1H), 2.41-2.24 (m, 1H). | 369.0 |

[0360] 1mM ATP下的NTRK1野生型测定

[0361] 在384孔板的每一孔中,在25℃下在存在或不存在所给药浓度系列的化合物(1%DMSO最终浓度)时,在总共12.5μL缓冲液(100mM HEPES pH 7.5,0.015%Brij 35,10mM $MgCl_2$,1mM DTT)(含有1-2μM CSKtide(Tuft's University或Anaspec;FITC-AHA-KKKKDDIYFFFG-NH2)和1mM ATP)中将1nM至1.5nM的野生型NTRK1酶(BPS Bioscience;40280)培育60分钟。通过添加70μL终止缓冲液(100mM HEPES pH 7.5,0.015%Brij 35,35mM EDTA和0.2%涂布试剂3(Caliper Lifesciences))来终止反应。然后在Caliper EZReader 2上读取板(方案设定:-1.7psi,上游电压-500,下游电压-3000,后样品缓冲(post sample sip)35s)。将数据归一化为0%和100%抑制对照,并使用4参数拟合在CORE LIMS中计算$IC_{50}$。

[0362] NTRK野生型和G595R突变细胞测定方案

[0363] 含有TPM3-NTRK1融合蛋白的KM12野生型结肠癌细胞系从国家癌症研究所(NCI)获得。先前已显示该细胞系的生长和存活依赖于源自NTRK融合蛋白的NTRK活性。KM12Cliff(G595R)细胞系是通过用DNA甲基化剂诱变野生型KM12系并且随后选择对长期暴露于高浓度的已知NTRK抑制剂(克唑替尼)具有抗性的克隆来产生。首先将细胞在完全培养基(10%FBS和1%pen/strep)中以1000个细胞/孔平铺于384孔板中并在37℃下培育过夜。然后使用Bravo液体处置系统用不同浓度的测试物品对细胞进行给药。浓度范围为从25uM降至9.5pM(4倍稀释,总共10个浓度)。每一板中每一化合物是一式两份运行。每一板上包括DMSO和星状孢菌素(staurosporine)(25uM)作为生长抑制的阴性和阳性对照。在给药后72小时,使用CellTiter-Glo(Promega)使测定板显色并在Envision酶标仪上读取所得发光。使用4参数曲线拟合算法计算$IC_{50}$测定值。

[0364] 下表总结了上述生物测定的结果。以下指定用于指示活性:A<10.00nM;B=10.01-100.0nM;C=100.01-1000.0nM;和D>1000.1nM。

[0365]

| 化合物编号 | NTRK1 $IC_{50}$ (nM) | KM12 $IC_{50}$ (nM) | G595R-KM12 $IC_{50}$ (nM) |
|---|---|---|---|
| 1 | A | A | B |
| 2 | A | A | A |
| 3 | B | B | C |
| 4 | A | A | A |
| 5 | B | B | C |
| 6 | A | A | A |
| 7 | A | A | A |
| 8 | B | B | C |
| 9 | A | A | A |
| 10 | A | A | A |
| 11 | A | A | B |
| 12 | A | A | A |
| 13 | A | A | A |
| 14 | B | B | C |
| 15 | A | B | B |
| 16 | A | B | B |
| 17 | A | A | A |
| 18 | B | B | B |
| 19 | A | B | B |
| 20 | B | B | B |
| 21 | B | B | C |
| 22 | B | B | C |

[0366] 以引用方式并入

[0367] 本文所提及的所有公布和专利都以引用的方式整体并入本文中，如同每一个别出版物或专利具体且个别地指示以引用方式并入一样。

[0368] 等效案

[0369] 本领域技术人员仅使用常规实验即可识别或能够确定本文所述的本发明的具体实施方案的许多等效案。所述等效案意在被所附权利要求涵盖。