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(54) Title: SYNTHESIS OF COMPOUNDS THAT MODULATE USE-DEPENDENT VOLTAGE-GATED SODIUM CHANNELS

(57) Abstract: The disclosure provides processes for preparing spiro derivatives, in particular (2R,5S)-7-methyl-2-[4-methyl-6-[4-(trifluoromethyl)-phenyl]pyrimidin-2-yl]-1,7- diazaspiro[4.4]nonan-6-one, as well as intermediates for use in said processes.

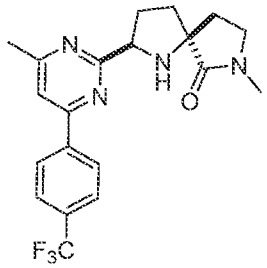
SYNTHESIS OF COMPOUNDS THAT MODULATE USE-DEPENDENT VOLTAGE-GATED SODIUM CHANNELS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/126,873, filed December 17, 2020, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

(2R,5S)-7-Methyl-2-[4-methyl-6-[4-(trifluoromethyl)-phenyl]pyrimidin-2-yl]-1,7-diazaspiro[4.4]nonan-6-one:

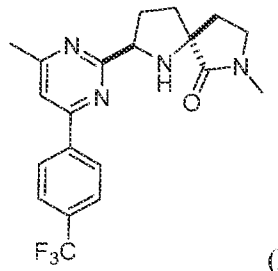


is described in Int. Pub. No. WO 2013/175205 as having utility in the treatment of diseases and conditions mediated by modulation of use-dependent voltage-gated sodium channels. Certain synthetic methods to prepare (2R,5S)-7-methyl-2-[4-methyl-6-[4-(trifluoromethyl)-phenyl]pyrimidin-2-yl]-1,7-diazaspiro[4.4]nonan-6-one are described in Int. Pub. Nos. WO 2013/175205 & WO 2019/075073. The contents of each of these patents are incorporated by reference in their entirety.

However, there is a need for the development of alternative processes for the preparation of such spiro derivatives, which are capable of practical application to large scale manufacture.

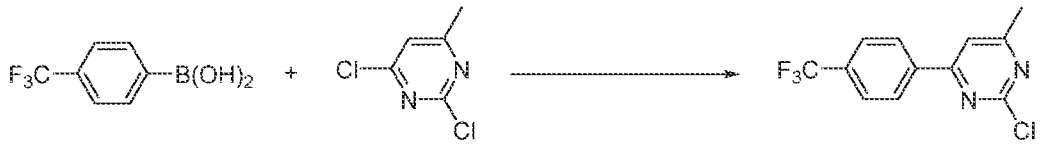
SUMMARY OF THE INVENTION

The present invention provides processes for preparing a compound of formula (I)



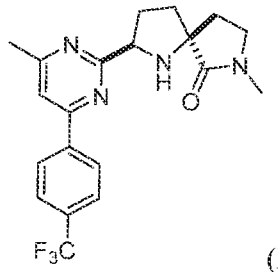
(I),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (II) with a compound of formula (III), in the presence of a metal compound, a phosphine that comprises an alkyl group, and a base, thereby producing a compound of formula (IV):



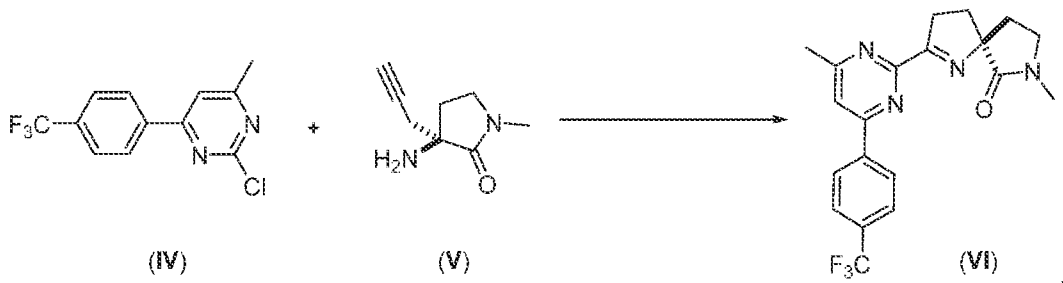
(II) (III) (IV)

The present invention further provides processes for preparing a compound of formula (I)



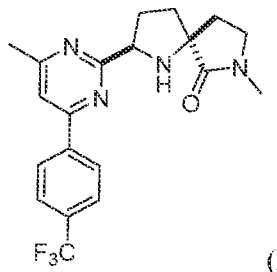
(I),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (IV) with a compound of formula (V) or a salt thereof, in the presence of a palladium compound and a copper salt and a base, thereby producing a compound of formula (VI):



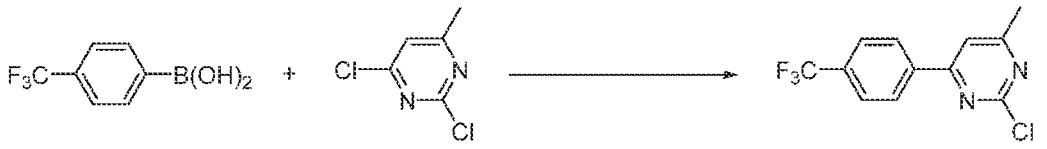
(IV) (V) (VI)

The present invention further provides processes for preparing a compound of formula (I)



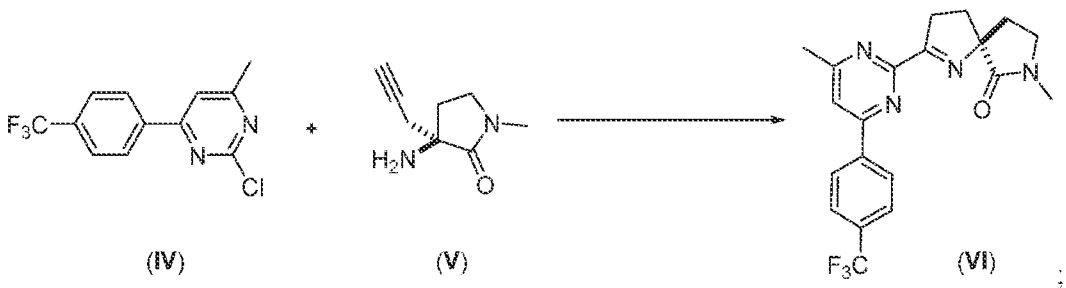
(I),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (**II**) with a compound of formula (**III**) in the presence of a metal compound, a phosphine that comprises an alkyl group, and a base, thereby producing a compound of formula (**IV**):



(II) (III) (IV) ;

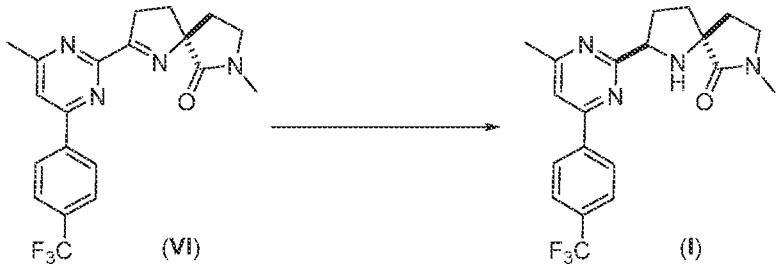
reacting a compound of formula (**IV**) with a compound of formula (**V**) or a salt thereof in the presence of a palladium compound, a copper salt and a base, thereby producing a compound of formula (**VI**):



(IV) (V) (VI) ;

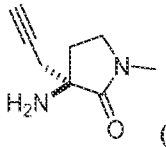
and

reducing the compound of formula (**VI**), thereby producing the compound of formula (**I**), or a pharmaceutically acceptable salt thereof



(VI) (I)

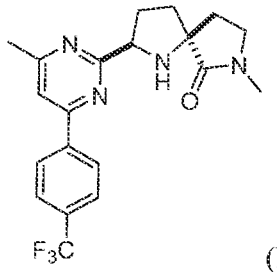
The present invention further provides the compound of formula (**V**),



(V),

or a salt thereof.

The present invention further provides processes for preparing a compound of formula (**I**)

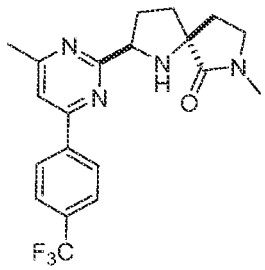


(I),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (**VII**) with an azide compound and an amine in the presence of *t*-butanol, thereby producing a compound of formula (**VIII**):

(VII) (VIII)

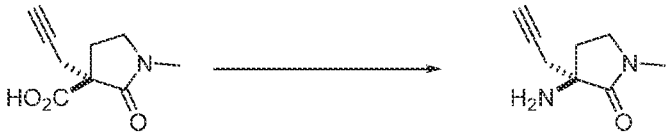
The present invention further provides processes for purification of the compound of formula (**I**),



,

or a pharmaceutically acceptable salt thereof.

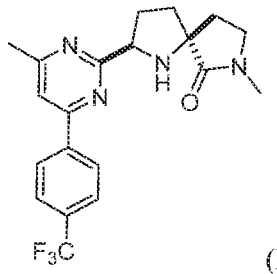
The present invention further provides processes for preparing a compound of formula **V**, comprising reacting a compound of formula (**VII**) with an azide compound and an amine followed by treatment with a base:



(VII) (V)

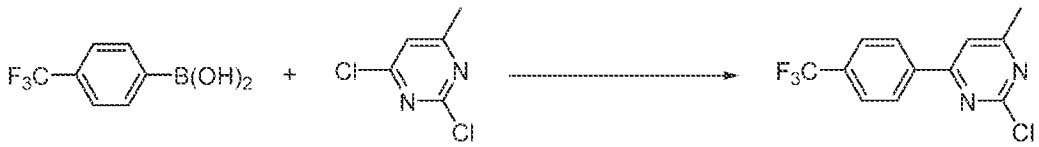
DETAILED DESCRIPTION OF THE INVENTION

In certain aspects, the present disclosure provides processes for preparing a compound of formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (**II**) with a compound of formula (**III**) in the presence of a metal compound, a phosphine that comprises an alkyl group, and a base, thereby producing a compound of formula (**IV**):



(**II**) (**III**) (**IV**)

In certain embodiments, the metal compound is a palladium compound,, such as palladium acetate.

In certain embodiments, the phosphine that comprises an alkyl group is *tert*-butyldiphenylphosphine.

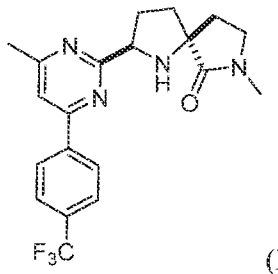
In certain embodiments, the base is diisopropylethylamine.

In certain embodiments, the compound of formula (**II**) is reacted with the compound of formula (**III**) in the presence of a solvent, such as isopropanol.

In certain embodiments, the chemical yield of the compound of formula (**IV**) is at least about 65% or at least about 70%.

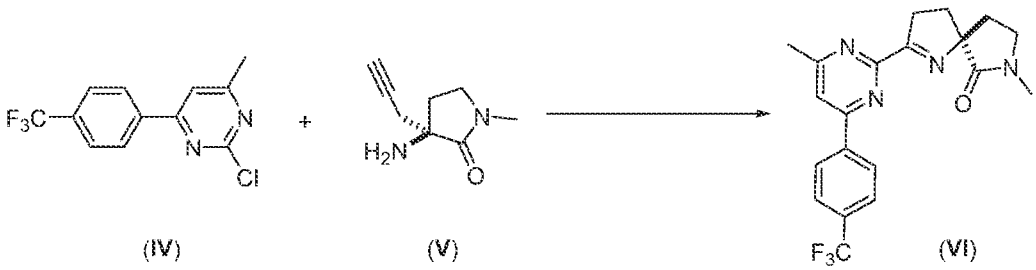
In certain embodiments, the compound of formula (**II**) is reacted with the compound of formula (**III**) at a scale of at least 5 kg of the compound of formula (**II**) and at least 5 kg of the compound of formula (**III**). In certain embodiments, the compound of formula (**II**) is reacted with the compound of formula (**III**) at a scale of at least 20 kg of the compound of formula (**II**) and at least 20 kg of the compound of formula (**III**). In certain embodiments, the compound of formula (**II**) is reacted with the compound of formula (**III**) at a scale of at least 50 kg of the compound of formula (**II**) and at least 50 kg of the compound of formula (**III**).

In certain aspects, the present disclosure provides processes for preparing a compound of formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (**IV**) with a compound of formula (**V**) or a salt thereof (such as a trifluoroacetate or hydrochloride salt), in the presence of a palladium compound, a metal salt and a base, thereby producing a compound of formula (**VI**):



(**IV**) (**V**) (**VI**)

wherein the metal salt is not a silver salt.

In certain embodiments, the compound of formula (**V**) is a trifluoroacetate salt. In certain embodiments, the compound of formula (**V**) is a hydrochloride salt. In certain embodiments, the compound of formula (**V**) is a not a salt (i.e., a free base).

In certain embodiments, the palladium compound is $PdCl_2$(dppf)-CH_2Cl_2 or $PdCl_2$(DPEphos).

In certain embodiments, the metal salt is a copper salt, such as copper (I) iodide.

In certain embodiments, the base is an organic base, such as diisopropylamine.

In certain embodiments, the base is an inorganic base, such as potassium carbonate.

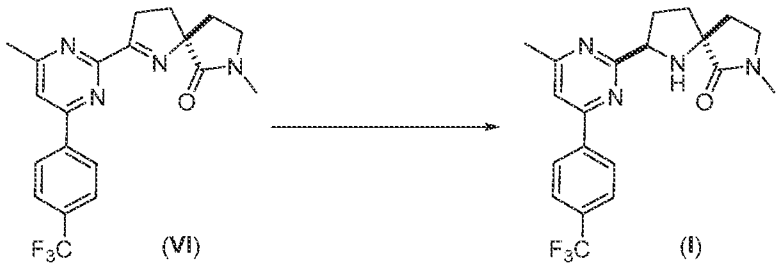
In certain embodiments, the compound of formula (**IV**) is reacted with the compound of formula (**V**) in the presence of a solvent. In certain embodiments, the solvent comprises isopropyl acetate or acetonitrile.

In certain embodiments, the chemical yield of the compound of formula (**VI**) is at least about 65%; at least about 70%; or at least about 75%.

In certain embodiments, the compound of formula (**IV**) is reacted with the compound of formula (**V**) at a scale of at least 5 kg of the compound of formula (**IV**) and at least 5 kg of

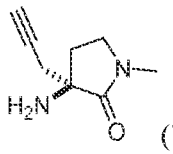
the compound of formula (V). In certain embodiments, the compound of formula (IV) is reacted with the compound of formula (V) at a scale of at least 20 kg of the compound of formula (IV) and at least 20 kg of the compound of formula (V). In certain embodiments, the compound of formula (IV) is reacted with the compound of formula (V) at a scale of at least 50 kg of the compound of formula (IV) and at least 50 kg of the compound of formula (V).

In certain aspects, the process further comprises reducing the compound of formula (VI), thereby producing the compound of formula (I), or a pharmaceutically acceptable salt thereof:



In certain embodiments, the compound of formula (VI) is reduced to the compound of formula (I), or a pharmaceutically acceptable salt thereof in the presence of a boron compound. In certain embodiments, the boron compound is a borane, such as borane-tert-butyl amine complex.

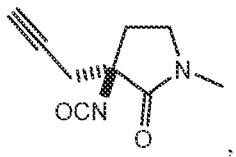
In certain aspects, the present disclosure provides a compound of formula (V) or a salt thereof:



(V),

In certain embodiments, the compound of formula (V) is a trifluoroacetate salt. In certain embodiments, the compound of formula (V) is a hydrochloride salt. In other embodiments, the compound of formula (V) is a not a salt (i.e., a free base).

In certain aspects, the present disclosure provides a compound represented by the following structure:



,

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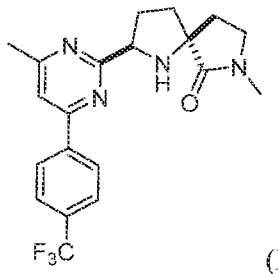
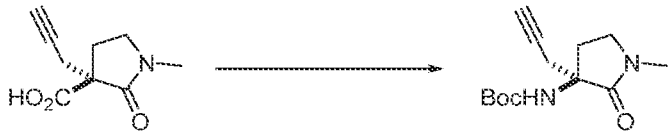
In certain aspects, the present disclosure provides processes for preparing a compound of formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, comprising converting a compound of formula (**VII**) to a compound of formula (**VIII**) in the presence of an azide compound and an amine in the presence of t-butanol:



(**VII**) (**VIII**)

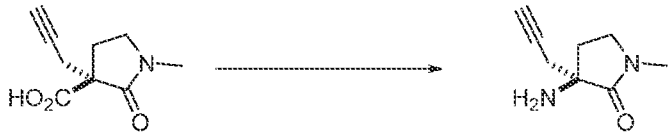
In certain embodiments, the azide compound is diphenylphosphoryl azide.

In certain embodiments, the amine is N-methylmorpholine.

In certain embodiments, the conversion of the compound of formula (**VII**) to the compound of formula (**VIII**) is carried out in the presence of a solvent. In certain embodiments, the solvent comprises toluene.

In certain embodiments, the reaction is performed in a continuous flow process. In certain aspects, the reaction is performed in a batch process.

In certain aspects, the present disclosure provides processes for preparing a compound of formula (**V**), comprising reacting a compound of formula (**VII**) with an azide compound and an amine followed by treatment with a base:



(**VII**) (**V**)

In certain embodiments, the azide compound is diphenylphosphoryl azide.

In certain embodiments, the amine is N-methylmorpholine.

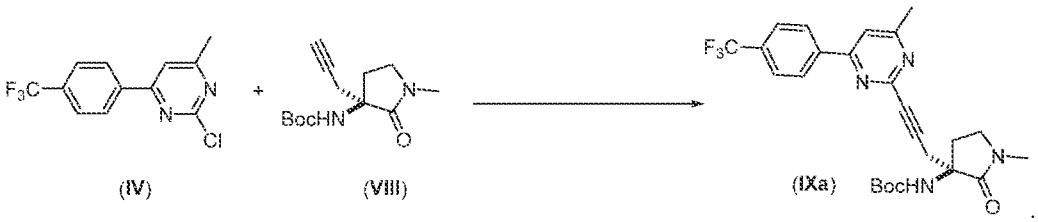
In certain embodiments, the reaction is performed in a batch process.

In certain embodiments, the conversion of the compound of formula (**VII**) to the compound of formula (**V**) is carried out in the presence of a solvent. In certain embodiments, the solvent comprises toluene.

In certain embodiments, the base is aqueous sodium hydroxide.

In certain embodiments, the conversion of the compound of formula (**VII**) to the compound of formula (**VIII**) is performed at a scale of at least 5 kg of the compound of formula (**VII**). In certain embodiments, the conversion of the compound of formula (**VII**) to the compound of formula (**VIII**) is performed at a scale of at least 20 kg of the compound of formula (**VII**). In certain embodiments, the conversion of the compound of formula (**VII**) to the compound of formula (**VIII**) is performed at a scale of at least 50 kg of the compound of formula (**VII**).

In certain embodiments, the process further comprises reacting a compound of formula (**IV**) with the compound of formula (**VIII**) in the presence of a palladium compound, a copper salt and a base, thereby producing a compound of formula (**IXa**) or a salt thereof:



(**IV**) (**VIII**) (**IXa**)

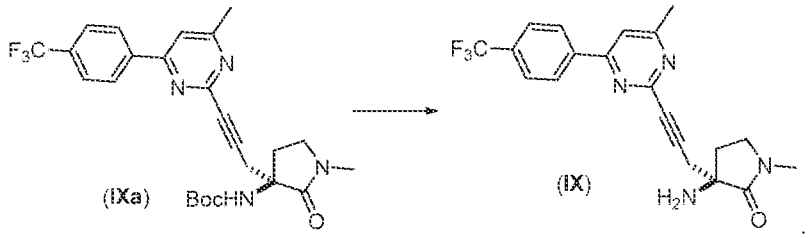
In certain embodiments, the palladium compound is $PdCl_2$(DPEphos).

In certain embodiments, the copper salt is copper (I) iodide.

In certain embodiments, the base is an amine. In certain embodiments, the amine is diisopropylamine.

In certain embodiments, the compound of formula (**IV**) is reacted with the compound of formula (**VIII**) in the presence of a solvent. In certain embodiments, the solvent comprises isopropyl acetate.

In certain embodiments, the process further comprising reacting the compound of formula (**IXa**) with an acid, thereby producing a compound of formula (**IX**) or a salt thereof:



(**IXa**) (**IX**)

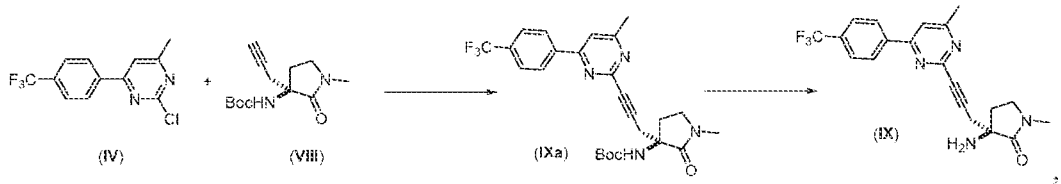
In certain embodiments, the compound of formula (**IXa**) is reacted with the acid in the presence of a solvent. In certain embodiments, the solvent comprises acetonitrile.

In certain embodiments, the acid is methanesulfonic acid.

In certain embodiments, the process further comprising

i) reacting a compound of formula (**IV**) with the compound of formula (**VIII**) in the presence of a palladium compound, a copper salt and a base, thereby producing a compound of formula (**IXa**) or a salt thereof; and

ii) reacting a compound of formula (**IXa**) with an acid, thereby producing a compound of formula (**IX**) or a salt thereof



wherein the compound of formula (**IXa**) is not isolated.

In certain embodiments, the palladium catalyst is $PdCl_2$(DPEphos).

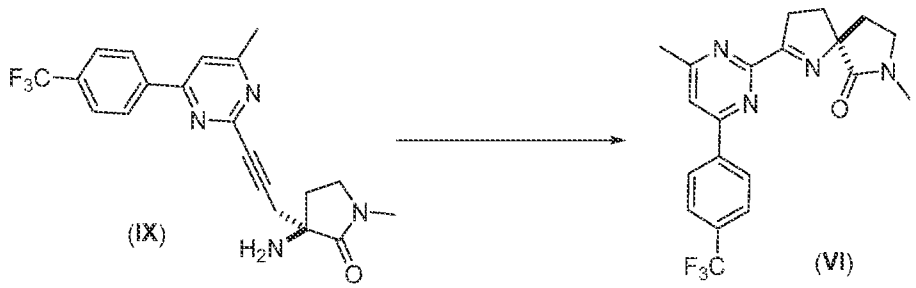
In certain embodiments, the copper salt is copper(I) iodide.

In certain embodiments, the base is diisopropylamine.

In certain embodiments, the compound of formula (**IV**) is reacted with the compound of formula (**VIII**) in the presence of a solvent. In certain embodiments, the solvent comprises isopropyl acetate.

In certain embodiments, the compound of formula (**IXa**) is reacted with the acid in the presence of a solvent. In certain embodiments, the solvent comprises isopropyl acetate and acetonitrile.

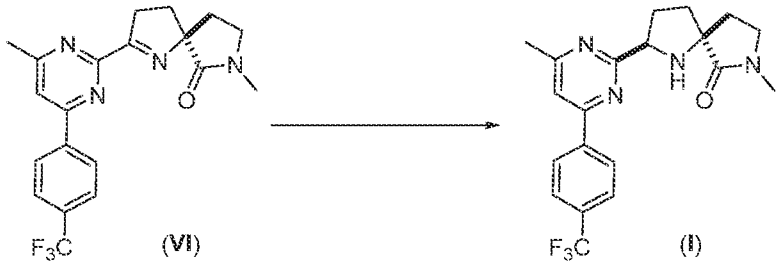
In certain embodiments, the process further comprises performing a cyclization reaction of the compound of formula (**IX**), or a salt thereof, in the presence of a metal salt to produce a compound of formula (**VI**):



In certain embodiments, the metal salt is a copper salt, such as copper (I) iodide. In certain embodiments, the metal salt is not a silver salt.

In certain embodiments, the compound of formula (**IX**) is a salicylate salt.

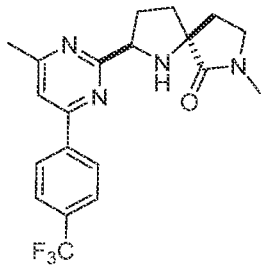
In certain embodiments, the process further comprises reducing the compound of formula (**VI**), thereby producing the compound of formula (**I**), or a pharmaceutically acceptable salt thereof:



(**VI**) (**I**)

In certain embodiments, the compound of formula (**VI**) is reduced to the compound of formula (**I**), or a pharmaceutically acceptable salt thereof in the presence of a boron compound. In certain embodiments, the boron compound is a borane. In certain embodiments, the borane is borane-tert-butyl amine complex.

In certain aspects, the present disclosure provides processes for the purification of a compound of formula (**I**):



or a pharmaceutically acceptable salt thereof, comprising recrystallizing the compound of formula (**I**) or a pharmaceutically acceptable salt thereof in a solvent.

In certain embodiments, the compound of formula (**I**) is a hydrogen sulfate salt.

In certain embodiments, the solvent comprises water and acetone.

In certain embodiments, the solvent further comprises methyl *t*-butyl ether.

In certain embodiments, the yield of the process is at least about 80%.

In certain embodiments, the process provides the compound of formula (**I**) with a purity of at least about 99%; of at least about 99.5%; or at least about 99.9%.

In certain embodiments, the purification of a compound of formula (**I**) is performed at a scale of at least 5 kg of the compound of formula (**I**). In certain embodiments, the purification of a compound of formula (**I**) is performed at a scale of at least 20 kg of the

compound of formula (I). In certain embodiments, the purification of a compound of formula (I) is performed at a scale of at least 50 kg of the compound of formula (I).

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the

art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, nitro, silyl, acyl, acyloxy, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OCO-CH_2-O-alkyl, -OP(O)(O-alkyl)$_2$ or $-CH_2$-OP(O)(O-alkyl)$_2$. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited to C_1-C_{10} straight-chain alkyl groups or C_1-C_{10} branched-chain alkyl groups. Preferably, the "alkyl" group refers to C_1-C_6 straight-chain alkyl groups or C_1-C_6 branched-chain alkyl groups. Most preferably, the "alkyl" group refers to C_1-C_4 straight-chain alkyl groups or C_1-C_4 branched-chain alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The "alkyl" group may be optionally substituted.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "alkyl" refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_{1-30} for straight chains, C_{3-30} for branched chains), and more preferably 20 or fewer.

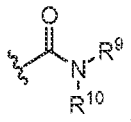
Moreover, the term "alkyl" as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

The term "C_{x-y}" or "C_x-C_y", when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. C_0alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. A C_{1-6}alkyl group, for example, contains from one to six carbon atoms in the chain.

The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

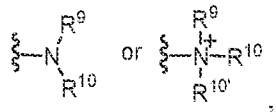
The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

The term "amide", as used herein, refers to a group



wherein R^9 and R^{10} each independently represent a hydrogen or hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



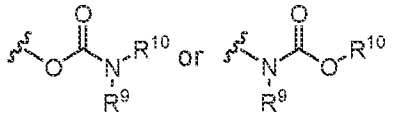
wherein R^9, R^{10}, and $R^{10'}$ each independently represent a hydrogen or a hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term "carbamate" is art-recognized and refers to a group



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbonate" is art-recognized and refers to a group $-OCO_2-$.

The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

The term "ester", as used herein, refers to a group $-C(O)OR^9$ wherein R^9 represents a hydrocarbyl group.

The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more

preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and even trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

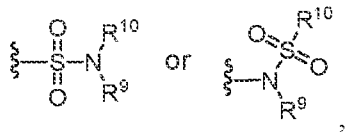
The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms "polycyclyl", "polycycle", and "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term "sulfate" is art-recognized and refers to the group $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl.

The term "sulfoxide" is art-recognized and refers to the group–S(O)-.

The term "sulfonate" is art-recognized and refers to the group SO_3H, or a pharmaceutically acceptable salt thereof.

The term "sulfone" is art-recognized and refers to the group $-S(O)_2-$.

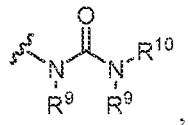
The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term "thioalkyl", as used herein, refers to an alkyl group substituted with a thiol group.

The term "thioester", as used herein, refers to a group $-C(O)SR^9$ or $-SC(O)R^9$ wherein R^9 represents a hydrocarbyl.

The term "thioether", as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by the general formula



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl.

The term "modulate" as used herein includes the inhibition or suppression of a function or activity (such as cell proliferation) as well as the enhancement of a function or activity.

The phrase "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Salt" is used herein to refer to an acid addition salt or a basic addition salt.

Many of the compounds useful in the methods and compositions of this disclosure have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The disclosure contemplates all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds, salts, prodrugs or mixtures thereof (including all possible mixtures of stereoisomers). See, e.g., WO 01/062726.

Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the disclosure includes both mixture and separate individual isomers.

Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present disclosure.

EXAMPLES

In order that the invention described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Exemplary Materials and Methods

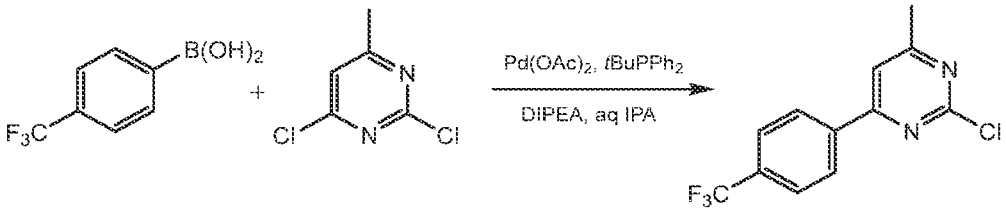
Unless otherwise stated, reactions were performed in jacketed glass-lined reactors under a nitrogen atmosphere. All solvents and reagents were used as received from commercial sources, unless otherwise noted. Reaction temperatures above 23 °C refer to jacket temperatures. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AV-500, DRX-500, and AV-400 MHz spectrometers, with ^{13}C NMR spectroscopic operating frequencies of 125, 125, and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual protonated solvent: $CDCl_3$ signal (δ = 7.26 for ^{1}H NMR; δ = 77.2 for ^{13}C NMR), C_6D_6 signal (δ = 7.16 for ^{1}H NMR; δ = 128.1 for ^{13}C NMR), DMSO-d_6 (δ = 2.50 for ^{1}H NMR; δ = 39.5 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, coupling constants (Hz), and number of hydrogen atoms. Data for ^{13}C NMR spectra are reported in terms of chemical shift. The following abbreviations are used to describe the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; m = multiplet; br = broad. Melting points (MP) are uncorrected and were recorded using an Electrothermal® capillary melting point apparatus. IR spectra were recorded on a Jasco FTIR-4100 spectrometer with an ATR attachment; the selected signals are reported in cm^{-1}. HRMS (DART) was performed using a Thermo Fisher Scientific Exactive Plus spectrometer equipped with an IonSense ID-CUBE DART source. X-ray crystallographic data were collected using a Bruker SMART CCD-based diffractometer equipped with a low-temperature apparatus operated at 100 K.

Abbreviations:

Abbreviations: ACN, acetonitrile; BOC, tert-butoxycarbonyl; CPME, cyclopentyl methyl ether; DCM, dichloromethane; DIPA, diisopropylamine; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DPPA, diphenylphosphoryl azide; DPEphos, bis[(2-diphenylphosphino)phenyl] ether; dppf, 1,1'-bis(diphenylphosphino)ferrocene; MsOH, methanesulfonic acid; MTBE, methyl tert-butyl

ether; NMM, N-methylmorpholine; IPA, isopropanol; IPAc, isopropyl acetate; LDA, lithium diisopropylamide; phen, phenanthroline; Tf, triflate; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

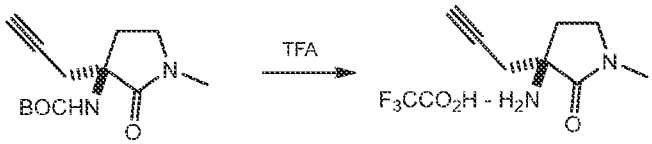
Example 1: Preparation of 2-chloro-4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidine



A reactor was charged with (4-(trifluoromethyl)phenyl)boronic acid (70 g), 2,4-dichloro-6-methylpyrimidine (66.1 g) and isopropanol (330 g), and the contents of the reactor were cooled to about 10 °C. With good stirring, DIPEA (143 g) and water (210 g) were charged, the contents of the reactor were aged at 10 °C for 15 – 30 min followed by sparging with nitrogen for 30 – 60 min. Under an inert atmosphere of nitrogen, $Pd(OAc)_2$ (828 mg) and *tert*-butyldiphenylphosphine (1.8 g) were charged and the reaction was aged for 15 – 20 h while monitoring its progress by HPLC (completion: 100(% area boronic area / (% area boronic acid + % area product) $\leq$ 50). The contents of the reactor were warmed to about 25 °C, aged for about 24 h, slowly warmed to about 55 °C and aged for 10 – 20 h while continuing to monitor reaction progress by HPLC (completion: 100(% area boronic area / (% area boronic acid + % area product) $\leq$ 1.5). Upon completion, the contents of the reactor were cooled to about 10 °C, water (1052 g) was charged and the reaction mixture was aged for 5 – 10 h. Solids were isolated by filtration, washed with water (140 g) and dried to constant weight *in vacuo* at about 50 °C. A reactor was charged with the dried solids and methylcyclohexane (168 g) and with good stirring the contents of the reactor were heated to about 50 °C, aged for 2 – 8 h, cooled to about 0 °C and aged for 5 – 10 h. Solids were isolated by filtration, washed with the mother liquor, twice washed with methylcyclohexane (56 g per wash) and dried to constant weight *in vacuo* at 55 °C to give 74.1 g (74%) of the title product; 99.2 % area purity.

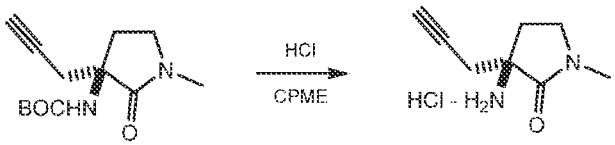
Example 2: Preparation of (S)-3-amino-1-methyl-3-(prop-2-yn-1-yl)pyrrolidin-2-one

Procedure A



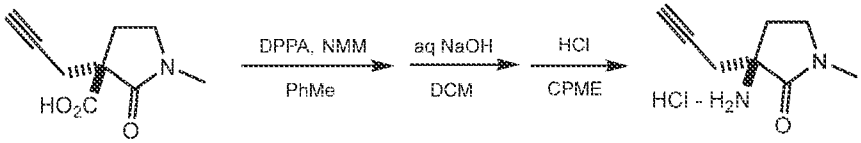
Into a reactor containing TFA (100 mL) cooled to 0 – 5 °C was charged *tert*-butyl (*S*)-(1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidin-3-yl)carbamate (50.0 g) in portions over about 1 h with good stirring. Following the charge, the contents of the reactor were warmed to 25 °C and aged for about 1 h. Following addition of toluene (34.8 g) the solution was concentrated *in vacuo* to about 50 mL and re-concentrated three times from toluene (43.5 g per concentration) to give a viscous oil. After charging MTBE (148 g) and aging at ambient temperature with good stirring, solids were isolated by filtration, washed twice with MTBE (74 g per wash) and dried to constant weight *in vacuo* at 40 °C to give 49.62 g (94%) of the title compound as its TFA salt.

Procedure B



Into a reactor containing 3M HCl in cyclopentyl methyl ether (89.5 g) was charged *tert*-butyl (*S*)-(1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidin-3-yl)carbamate (25.0 g) in portions. Following the charge, the contents of the reactor were maintained at 30 – 40 °C; the progress of the reaction was monitored by HPLC. Upon completion, the contents of the reactor were cooled to 20 - 25 °C. Solids were isolated by filtration, twice washed with CPME (43 g per wash) and dried to constant weight *in vacuo* at 40 °C to give 18.0 g (96%) of the title compound as its HCl salt.

Procedure C



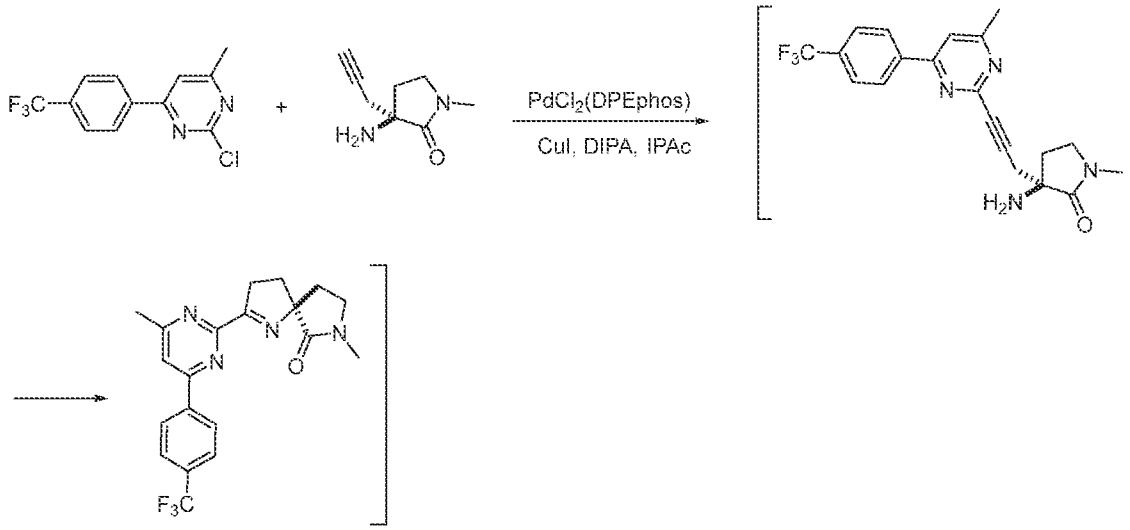
Under an inert atmosphere of nitrogen, a reactor was charged with (*S*)-1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylic acid (50.0 g activity), *N*-methylmorpholine (29.0 g) and anhydrous toluene (564 g). With good stirring, the contents of the reactor were heated to 77 – 80 °C and DPPA (78.3 g) was added over about 30 min; the charging line was rinsed forward into the reactor using toluene (43.3 g). The progress of the reaction was monitored

by GC. After about 3 h, the contents of the reactor were cooled to 20 – 25 °C and quenched into cold (0 – 5 °C) 2.5M aqueous NaOH solution (233 mL) over about 20 min. The mixture was aged for about 30 min, warmed to 20 – 25 °C and aged for about 15 h. Solids were removed by filtration, and the phases were separated. To the lower aqueous phase was added NaCl (250 g) with good stirring. The solution was cooled to 0 – 5 °C and was aged for about 1 h. Solids were removed by filtration, washed with cold (0 – 5 °C) dichloromethane (333 g) and the phases were separated. The upper aqueous layer was twice extracted with dichloromethane (333 g per extraction) and the combined extracts were concentrated *in vacuo* to an oil, which was re-concentrated from dichloromethane (333 g). The oil was re-dissolved in dichloromethane (333 g), aged for about 1 h at 20 – 25 °C. Solids were removed by filtration, washed twice with dichloromethane (167 g per wash) and the combined filtrate and washes were concentrated *in vacuo* to an oil (36.9 g), determined by internal standard ^{1}H NMR analysis to contain 32.47 g (77%) of the free base form of the title product.

With good stirring, the oil was re-dissolved in dichloromethane (492 g), the solution was cooled to 8 – 12 °C, 3M HCl in cyclopentyl methyl ether (95.8 g) was added over about 15 min and the slurry was aged for about 1 h. Solids were isolated by filtration, washed with dichloromethane (246 g), twice slurry washed with acetonitrile (146 g per wash) and dried to constant weight at ambient temperature to give 37.3 g (70% assay corrected yield) of the title compound as its HCl salt.

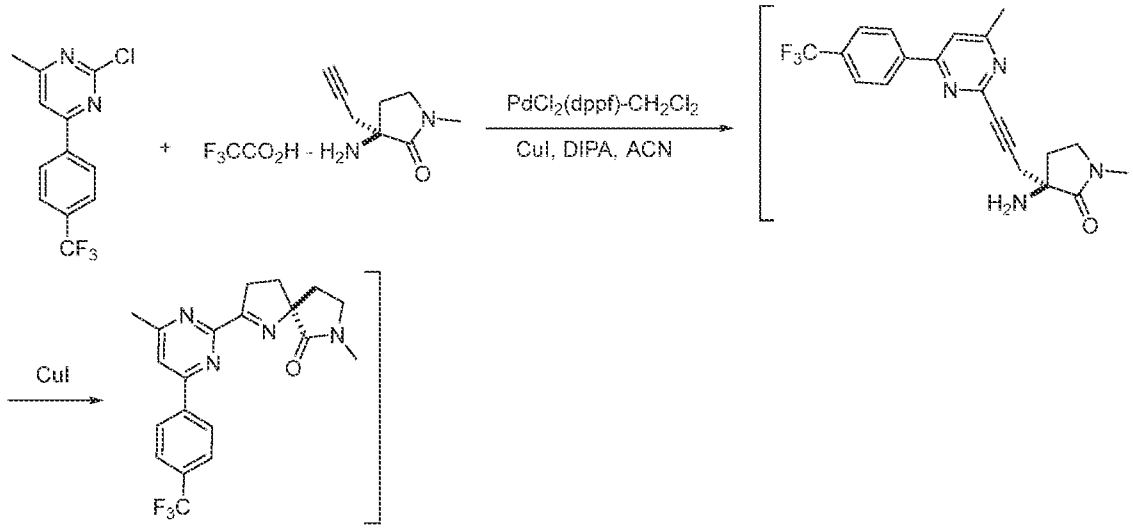
Example 3: Preparation of (S)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]non-1-en-6-one

Procedure A



A reactor was charged with (*S*)-3-amino-1-methyl-3-(prop-2-yn-1-yl)pyrrolidin-2-one (2.0 g), 2-chloro-4-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine (3.58 g), diisopropylamine (1.46 g), dichloro[bis[2-(diphenylphosphino)phenyl]ether]palladium (II) (24 mg), CuI (12.5 mg) and isopropyl acetate (8.7 g). After sparging the solution with nitrogen, the contents of the reactor were heated to 75 – 80 °C; the progress of the reaction was monitored by UPLC. After about 48 h, 77 % area of the title product was present in the solution.

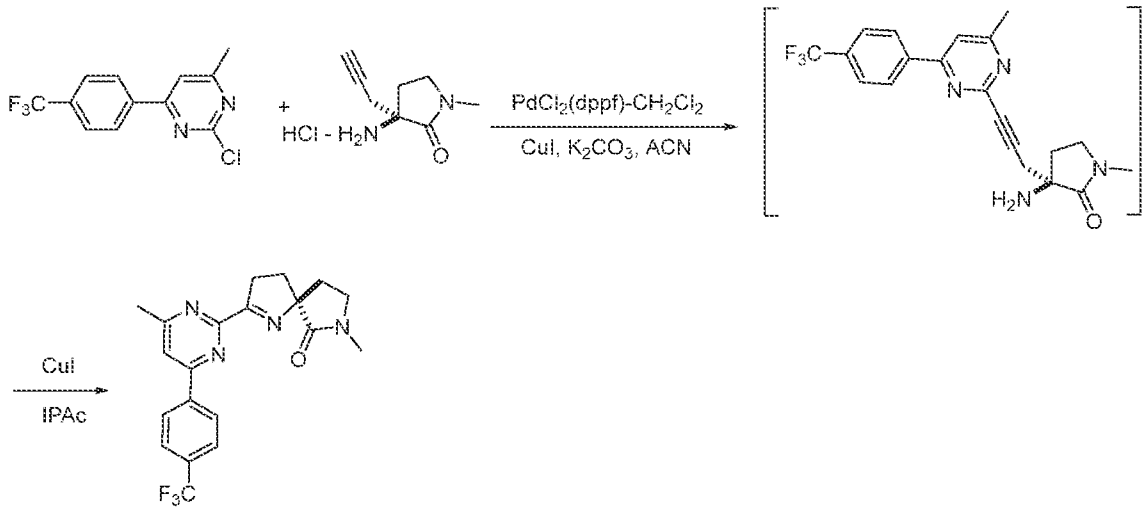
Procedure B



A reactor was charged with (*S*)-3-amino-1-methyl-3-(prop-2-yn-1-yl)pyrrolidin-2-one trifluoroacetic acid salt (1:1; 11.0 g), 2-chloro-4-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine (10.0 g), diisopropylamine (9.36 g) and acetonitrile (23.7 g). With good stirring at ambient temperature, the mixture was sparged with nitrogen for about 3 min. After charging $PdCl_2(dppf) \cdot CH_2Cl_2$ (152 mg) and CuI (70 mg) and nitrogen

sparging for an additional 3 min, the contents of the reactor were heated to about 80 °C; the progress of the reaction was monitored by UPLC. After about 3.5 h, the Sonogashira coupling reaction was complete; additional CuI (0.97 g) was charged. The hydroamination portion of the reaction was continued at 80 °C; reaction progress was monitored by UPLC. After about 20 h, 85.3 % area of the title product was present in solution. The contents of the reactor were cooled to 25 °C and split into two equal portions for separate downstream processing experiments.

Procedure C

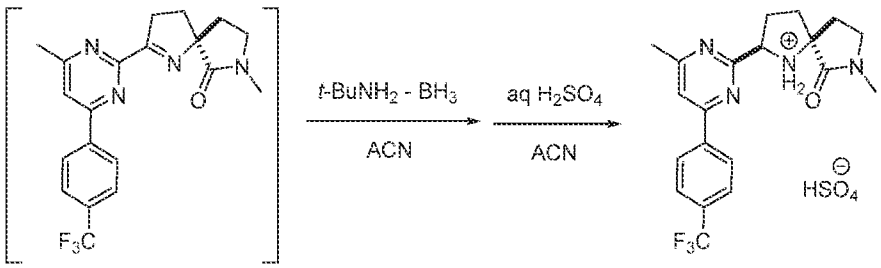


A reactor was charged with (*S*)-3-amino-1-methyl-3-(prop-2-yn-1-yl)pyrrolidin-2-one hydrochloride salt (1:1; 7.47 g), 2-chloro-4-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine (10.0 g), potassium carbonate (12.67 g) and acetonitrile (23.7 g). With good stirring at ambient temperature, the mixture was sparged with nitrogen for about 10 min. After charging $PdCl_2(dppf) - CH_2Cl_2$ (150 mg) and CuI (70 mg) and nitrogen sparging for an additional 10 min, the contents of the reactor were heated to about 78 °C; the progress of the reaction was monitored by UPLC. After about 8 h, the contents of the reactor were cooled to 20 °C and isopropyl acetate (52.2 g) was charged. The organic layer was treated with water (60 g) for about 10 min, and the layers were separated. The organic solution was treated twice for about 15 min (50 mL per treatment) with an aqueous solution prepared from NaCl (60 g), concentrated NH_4OH solution (20 mL), L-cysteine (2 g) and water (200 mL). Following the layer separation, the organic phase was washed with brine (50 mL), concentrated to about 30 mL *in vacuo* and re-concentrated twice from isopropyl acetate (43.5 g per concentration) to a volume of about 30 mL each time. Solids were removed by filtration and washed with isopropyl acetate (8.7 g). By internal standard ^1H NMR analysis,

the solution contained 13.85 g (97%) of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one. Following additions of CuI (70 mg) and isopropyl acetate (16.5 g) and sparging the solution with nitrogen for about 10 min with good stirring, the contents of the reactor were heated to about 75 °C; the progress of the reaction was monitored by UPLC. After about 24 h, the contents of the reactor were cooled to about 40 °C over about 3 h and aged for about 20 h. Solids were isolated by filtration, washed twice with isopropyl acetate (24.4 g per wash) and dried to constant weight *in vacuo* at 40 °C to give 11.0 g (77%) of the title product; purity >99.9 % area.

Example 4: Preparation of (2R,5S)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]nonan-6-one, sulfuric acid salt (1:1)

Procedure A



A reactor was charged with one-half of the product solution (27.63 g) from Example 3 Procedure B (containing 7.12 g of the product (theory)) and acetonitrile (22.1 g). After briefly sparging the solution with nitrogen, a solution of *tert*-butylamine - borane (1.31 g) in acetonitrile (14.2 g) was charged slowly over about 5 min; the progress of the reaction, performed at 25 °C, was monitored by UPLC. After about 5 h, the contents of the reactor were cooled to 0 - 5 °C and 5M aqueous HCl solution (28 mL) was slowly charged under a nitrogen sweep. Following the addition, the contents of the reactor were warmed to 25 °C and aged for about 15 min. The contents of the reactor were transferred to a 500 mL Erlenmeyer flask. The reactor was rinsed forward into the flask with acetonitrile (8.4 g). A 50 wt% aqueous K_3PO_4 solution (71 mL) was slowly added with good stirring over about 30 min and the mixture was aged for about 30 min. The layers were separated and the aqueous layer was back-extracted with acetonitrile (11.1 g). The combined organic layers were washed with brine (28 mL) and concentrated *in vacuo* to a volume of about 18 mL (KF = 19.7%). Acetonitrile (25.3 g) was added and the mixture was re-concentrated to about 18 mL. After three repetitions of this re-concentration process (KF <1%), solids were removed by

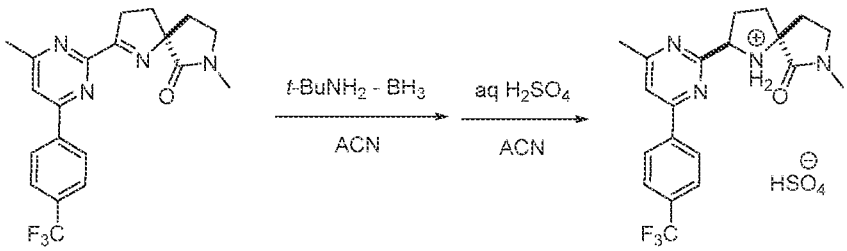
filtration and the filter cake was washed with acetonitrile (5.6 g). The KF of the filtrate (21.93 g) was adjusted to 2.7% by charging water (0.57 g). The solution was warmed to about 50 °C, a 7.5M aqueous solution of H_2SO_4 (2.44 mL) was added dropwise over about 10 min and the resulting slurry was aged at about 50 °C for about 1 h. The slurry was cooled to about 25 °C over 45 min, isopropanol (5.5 g) was charged and the slurry was aged over the weekend. The slurry was cooled to 0-5 °C and aged for about 1 h. Solids were isolated by filtration, washed with cold (0 – 5 °C) acetonitrile - MTBE (1:1 v/v, 14 mL) and cold (0 – 5 °C) MTBE (10.4 g), and dried to constant weight *in vacuo* at 40 °C to yield 3.44 g (39% from 2-chloro-4-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine) of the title product; 98.5 % area purity.

Procedure B

A reactor was charged with one-half of the product solution (27.17 g) from Example 3 Procedure B (containing 7.12 g of the product (theory)). The acetonitrile solution was stirred three times for about 15 min with an aqueous NH_4OH – brine solution (35 mL per treatment; the solution was prepared by adding concentrated NH_4OH solution (10 mL) into brine (100 mL)). The organic solution was stirred twice for about 30 min with an aqueous NH_4OH – brine – L-cysteine solution (35 mL per treatment; the solution was prepared by adding concentrated NH_4OH solution (10 mL) and L-cysteine (1.22 g) into brine (100 mL)). Following the last aqueous treatment, solids precipitated from the acetonitrile solution. The solids were isolated by filtration, washed with water (7 g; 14 g) and partially dried under suction for about 10 min. The solid was dissolved in acetonitrile (39.5 g) and the solution was concentrated *in vacuo* to a volume of about 18 mL (KF = 7.9%). Acetonitrile (25.3 g) was added and the mixture was re-concentrated to about 18 mL. After two repetitions of this re-concentration process (KF <0.1%), the solution was briefly sparged with nitrogen and a solution of *tert*-butylamine - borane (1.35 g) in acetonitrile (14.2 g) was charged slowly over about 15 min; the charging apparatus was rinsed forward into the reactor with acetonitrile (4 g). The progress of the reaction, performed at 25 °C, was monitored by UPLC. After about 2 h, the contents of the reactor were cooled to 0 - 5 °C and 5M aqueous HCl solution (28 mL) was slowly charged over about 15 min under a nitrogen sweep. Following the addition, the contents of the reactor were warmed to 10 °C and aged for about 20 min. The contents of the reactor were cooled to 0 – 5 °C and a 50 wt% aqueous K_3PO_4 solution (71 mL) was slowly added with good stirring over about 15 min. The contents of the reactor were warmed to about 10 °C and aged for about 15 min. The layers were separated and the aqueous layer was

back-extracted with acetonitrile (11.1 g). The combined organic layers were washed with brine (28 mL) and concentrated *in vacuo* to a volume of about 18 mL. Acetonitrile (25.3 g) was added (KF = 7.4%) and the mixture was re-concentrated to about 18 mL. After three repetitions of this re-concentration process (KF <1%; final concentration was to a volume of about 21 mL), solids were removed by filtration and the filter cake was washed with acetonitrile (5.6 g). The KF of the filtrate (21.93 g) was adjusted to 2.6% by charging water (0.67 g). The solution was warmed to about 50 °C, a 7.5M aqueous solution of H_2SO_4 (2.44 mL) was added dropwise over about 10 min and the resulting slurry was aged at about 50 °C for about 1 h. The slurry was cooled to about 25 °C over 45 min, isopropanol (5.5 g) was charged and the slurry was aged overnight. The slurry was cooled to 0 - 5 °C and aged for about 1 h. Solids were isolated by filtration, washed with cold (0 – 5 °C) acetonitrile - MTBE (1:1 v/v, 14 mL) and cold (0 – 5 °C) MTBE (10.4 g) and dried to constant weight *in vacuo* at 40 °C to yield 3.69 g (41% from 2-chloro-4-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine) of the title product; 98 % area purity.

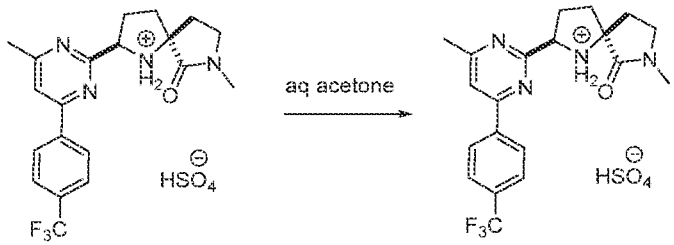
Procedure C



A reactor was charged with (*S*)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]non-1-en-6-one (1175 g) and acetonitrile (6.42 kg). With good stirring, a solution of *tert*-butylamine - borane (215.7 g) in acetonitrile (2.30 kg) was charged over 35 - 40 min; the charging vessel and line was rinsed forward into the reactor with acetonitrile (0.93 kg). The progress of the reaction, performed at 20 °C, was monitored by UPLC. After about 2.75 h, the contents of the reactor were cooled to 10 - 15 °C and 5M aqueous HCl solution (4.7 L) was charged over 30 – 35 min under a nitrogen sweep while maintaining a reaction temperature of ≤ 20 °C. Following the addition, the contents of the reactor were aged for about 45 min. A 50 wt% aqueous K_3PO_4 solution (18.90 kg) was slowly added with good stirring over about 70 min while maintaining a reaction temperature of ≤ 20 °C, and the mixture was aged for about 20 min. The layers were separated and the aqueous layer was back-extracted with acetonitrile (1.84 kg). The combined organic layers were washed with brine (5.63 kg) and the organic layer

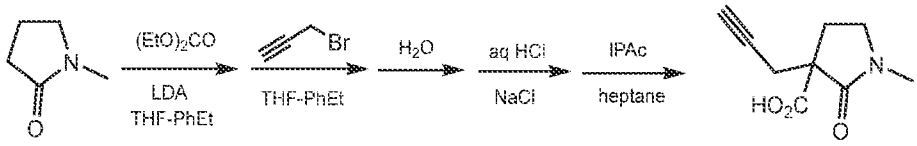
was concentrated *in vacuo* to a volume of 2.9 – 3.0 L. Acetonitrile (4.16 kg) was added and the mixture (KF = 3.1%) was re-concentrated to about 3.0 L. Acetonitrile (4.15 kg) was charged, solids were removed by filtration and the filter cake was washed with acetonitrile (0.92 kg). The KF of the filtrate (7424 g) was adjusted from 0.54% to 2.45% by charging water (150.5 g). The solution was warmed to about 50 °C, a 7.5M aqueous solution of H_2SO_4 (0.57 kg) was added dropwise over about 1 h and the resulting slurry was aged at about 50 °C for about 1 h. The slurry was cooled to about 20 °C over 45 min, isopropanol (0.93 kg) was charged and the slurry was aged for about 12 h. The slurry was cooled to 0-5 °C over about 45 min and aged for about 2.25 h. Solids were isolated by filtration, washed with cold (0 – 5 °C) acetonitrile - MTBE (1:1 v/v, 1.84 kg) and cold (0 – 5 °C) MTBE (1.73 kg) and dried to constant weight *in vacuo* at 40 °C to yield 1065 g (72%) of the title product; 98.9 % area.

Example 5: Recrystallization of (2R,5S)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]nonan-6-one, sulfuric acid salt (1:1)



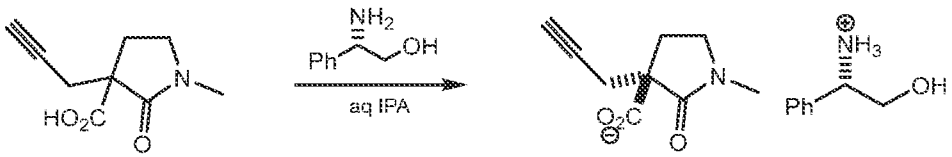
A reactor was charged with (2*R*,5*S*)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]nonan-6-one, sulfuric acid salt (1:1) (524 g), distilled water (0.91 kg) and acetone (1.70 kg) and the mixture was heated to solution at 35 – 37 °C with good stirring. The solution was polish filtered into a second reactor and was reheated to solution at 38 – 40 °C. Over about 3.5 h, acetone (6.38 L) was charged while maintaining a reaction temperature of 38 – 40 °C. The slurry was aged for about 1 h, cooled to about 25 °C over about 1 h, aged for about 18 h, cooled to 0 – 5 °C over about 1 h and aged for about 3 h. Solids were isolated by filtration, twice washed with cold (0 – 5 °C) acetone (0.33 kg per wash) and dried to constant weight *in vacuo* at 50 °C to give 433 g (83%) of the title compound; 99.9 % area.

Example 6: Preparation of 1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylic acid



Under an inert atmosphere of nitrogen, a reactor was charged with NMP (49.6 kg), diethyl carbonate (59.1 kg) and THF (423 kg), and the solution was cooled to 0 – 5 °C with good stirring. A freshly titrated solution of LDA in PhEt (13.07 wt%; 2.0 eq) was added slowly followed by warming the contents of the reactor to 25 °C; the progress of the reaction was monitored by GC. After aging for about 2 h, the slurry was cooled to 0 – 5 °C and a solution of propargyl bromide in toluene (80 wt%, 1.0 equiv, assay corrected (NMR internal standard)) was added slowly followed by warming the contents of the reactor to 25 °C; the progress of the reaction was monitored by HPLC. After about 6 h, an additional charge of propargyl bromide in toluene (80 wt%, 0.03 equiv) was added and the reaction was continued at 25 °C. After an additional 2 h, water (198 kg) was added and the solution was stirred at 25 °C; the progress of the reaction was monitored by HPLC. After about 1.5 h, concentrated HCl solution was added to about pH 0.6, NaCl (25.3 kg) was charged and the contents of the reactor were warmed to 45 °C. After four extractions with isopropyl acetate (129.5 kg per extraction), the combined organic layers were concentrated *in vacuo* to about 350 L, and the resulting solution was cooled to 25 °C. After slowly charging heptane (202 kg), the contents of the reactor were cooled to 0 - 5 °C and aged for about 1 h. Solids were isolated by filtration, washed with isopropyl acetate – heptane (1:6 v/v, 35.3 kg) and dried to constant weight *in vacuo* at 45 °C to yield 69.9 kg (68%, assay corrected) of the title compound. A second crop of 4.9 kg (5%, assay corrected) of the title compound was also obtained for a combined yield of 74.8 kg (73%, assay corrected).

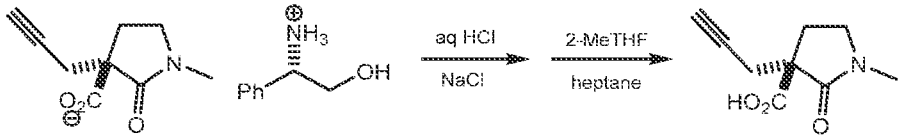
Example 7: Preparation of (S)-2-hydroxy-1-phenylethan-1-aminium (S)-1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylate (1:1)



A reactor was charged with 1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylic acid (75.2 kg activity) and isopropanol (413.3 kg) and the mixture was heated to 50 °C with good stirring. A solution of (*S*)-2-phenylglycinol (57.0 kg) in water (41.9 kg), also heated to 50

°C, was added to the isopropanol solution of the racemic acid, and the reactor and charging line which contained the aqueous solution were rinsed forward with isopropanol (26.0 kg). The resulting solution was aged for about 20 min at 50 °C, slowly cooled to about 41 °C and was seeded (100 g). After aging for about 30 min, the slurry was cooled to 0 – 5 °C and aged for about 4 h. Solids were isolated by filtration, washed twice with isopropanol – MTBE (5/95 v/v, 279.3 kg per wash) and dried to constant weight *in vacuo* at 30 °C to give 57.3 kg (41%) of the title compound; chiral purity: 99.4%.

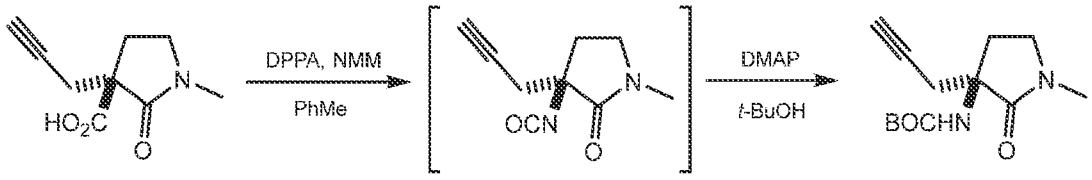
Example 8: Preparation of (S)-1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylic acid



A reactor was charged with (*S*)-2-hydroxy-1-phenylethan-1-aminium (*S*)-1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylate (1:1, 47.2 kg activity) and water (141 kg), and the contents of the reactor were cooled to 0 – 5 °C with good stirring. Concentrated HCl solution (16.48 kg) was added slowly to about pH 1.43, the contents of the reactor were warmed to 20 °C and aged for about 2 h. After charging NaCl (23.6 kg), the solution was heated to about 45 °C and was extracted three times with 2-methylTHF (201.5 kg per extraction). The combined organic extracts were washed with acidic brine (164.3 kg; acidified with concentrated HCl solution (60 g)), dried over anhydrous $MgSO_4$ (4.7 kg) for about 1 h, filtered and the spent filter cake was washed with 2-methylTHF (40.3 kg). The combined filtrate and wash were concentrated *in vacuo* to about 120 L, cooled to 20 – 25 °C and heptane (290.5 kg) was slowly added. The contents of the reactor were cooled to 0 – 5 °C and aged for about 1 h. Solids were isolated by filtration, washed with 2-methylTHF – heptane (1/9 v/v, 66.1 kg) and dried to constant weight *in vacuo* at 45 °C to give 24.36 kg (91%) of the title compound; chiral purity: 100%.

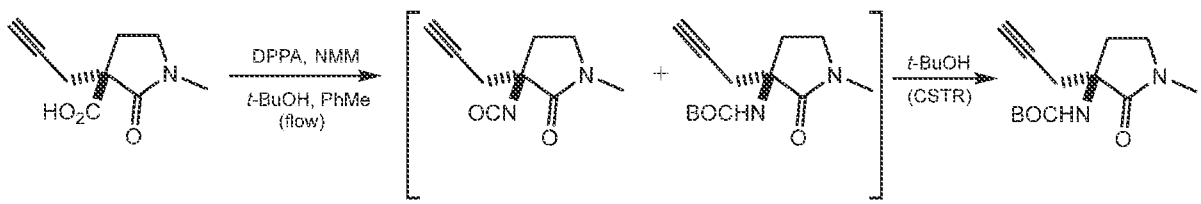
Example 9: Preparation of tert-butyl (S)-(1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidin-3-yl)carbamate

Procedure A: batch process



Under an inert atmosphere of nitrogen a reactor was charged with (*S*)-1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylic acid (750 g), *N*-methylmorpholine (435 g) and toluene (9.14 kg). With good stirring, the contents of the reactor were heated to 77 – 80 °C followed by slow addition of DPPA (1173 g) over about 15 min; the charging vessel and line were rinsed forward into the reactor with toluene (653 g). The progress of the reaction was monitored by GC. After about 5 h, DMAP (222.5 g) and *t*-BuOH (1687 g) were charged, and the reaction was continued at 77 – 80 °C; the progress of the reaction was monitored by GC. After about 15 h, the contents of the reactor were cooled to 20 – 25 °C, basic alumina (2.25 kg) was charged and stirring was continued for about 30 min. Solids were removed by filtration through a pad of basic alumina (3.75 kg); the spent filter cake was washed twice with toluene (2.0 kg per wash). The filtrate was concentrated *in vacuo* to a volume of about 1.5 L and was diluted with dichloromethane (10.0 kg). The organic phase was treated twice for about 15 min with 2M aqueous NH_4OH solution (4.5 L per treatment), treated twice for about 15 min with 1M aqueous HCl solution (7.5 L per treatment) and dried over anhydrous $MgSO_4$ (750 g) for about 1 h. Solids were removed by filtration and washed twice with dichloromethane (2 kg per wash). The filtrate was concentrated *in vacuo* to a volume of about 1.5 L and MTBE – heptane (1:2 v/v, 3.75 L) was added over about 20 min at 20 – 25 °C with good stirring. The slurry was cooled to 0 – 5 °C and was aged for about 2 h. Solids were isolated by filtration, washed twice with heptane (1.0 kg per wash) and dried to constant weight *in vacuo* at 30 °C to give 690 g (66%) of the title compound; 98.0 % area purity.

Procedure B: flow process



Feed 1 Solution: (*S*)-1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-3-carboxylic acid (24.34 kg),

N-methylmorpholine (27.1 kg) and *t*-BuOH (99.6 kg); this feed solution was maintained at 25- 35 °C during the run

Feed 2 Solution: DPPA (46.02 kg) and toluene (218.1 kg); this feed solution was maintained at 5 – 25 °C during the run

Pipe In Series Reactor:

- two units connected in series
- each unit contains 6 pipes, each of about 1 m in length
    - up flow: three 1 inch diameter pipes
    - down flow: three ¼ inch diameter pipes

Flow Rates:

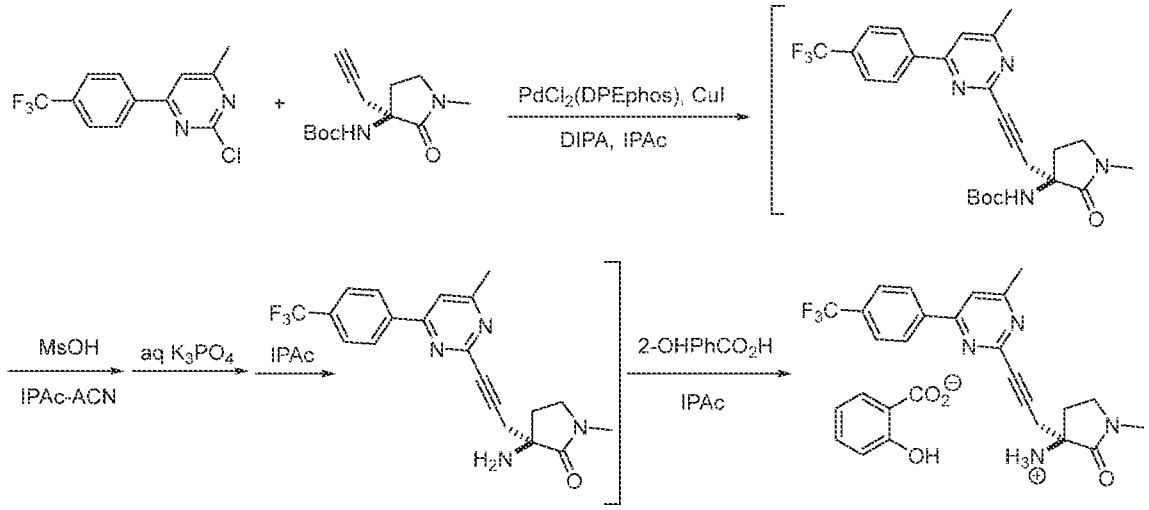
- Feed 1: 44.6 g / min
- Feed 2: 75.3 g / min

Residence Time: 1 h

Reaction Temperature: 80 °C

After reaching steady state, eluent from the flow reactor was collected for about 42 h into a continuously stirred tank reactor which was pre-heated to about 80 °C. Following the collection period, the contents of the reactor were aged at about 80 °C; the progress of the reaction was monitored by HPLC. After about 18 h, the reaction mixture was cooled and with good stirring, was quenched with a solution composed of $NaNO_2$ (9.0 kg), 25% aqueous NaOH (16.28 kg) and water (54.0 kg). After stirring for about 12 h at 20 – 30 °C, the layers were separated and the aqueous layer was back extracted with toluene (285 kg). The combined organic layers were washed four times with 4.5% aqueous $NaHCO_3$ solution (54.4 kg per wash) and with water (22 kg). The organic layer was concentrated *in vacuo* to about 33 L, additional toluene (18.9 kg) was added and the contents of the reactor were heated to about 50 °C, cooled to 20 °C, further cooled to -10 °C and aged for about 2.5 h. Solids were isolated by filtration, washed with heptane (29.9 kg) and dried to constant weight *in vacuo* at 50 °C to yield 17.48 kg (57% based on processed starting material) of the title product; 100 % area; chiral purity: 100%.

Example 10: Preparation of (S)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1)



Part A: a reactor was charged with 2-chloro-4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidine (20.0 kg) and *tert*-butyl (*S*)-(1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidin-3-yl)carbamate (20.1 kg). After three vacuum / nitrogen break cycles, the reactor was charged with isopropyl acetate (44 kg) and the contents of the reactor were stirred at 20 °C. After charging diisopropylamine (8.2 kg) the container and transfer line were rinsed forward into the reactor with isopropyl acetate (4.4 kg). After four vacuum / nitrogen break cycles the reactor was charged with a slurry composed of dichloro[bis[2-(diphenylphosphino)phenyl]ether]palladium (II) (131 g) in isopropyl acetate (1.3 kg) followed by a slurry of CuI (71 g) in isopropyl acetate (1.3 kg). Following each charge, the container and transfer line were rinsed forward into the reactor with isopropyl acetate (0.9 kg per container). The contents of the reactor were warmed to 75 – 80 °C (target: 78 °C); the progress of the reaction was monitored by UPLC. Upon completion, the contents of the reactor were cooled to 18 – 23 °C, aged for about 20 min and filtered. The spent filter cake was washed with isopropyl acetate (34.9 kg); the combined filtrate and wash were stirred for about 15 min to give an isopropyl acetate solution of *tert*-butyl (*S*)-(1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)-2-oxopyrrolidin-3-yl)carbamate.

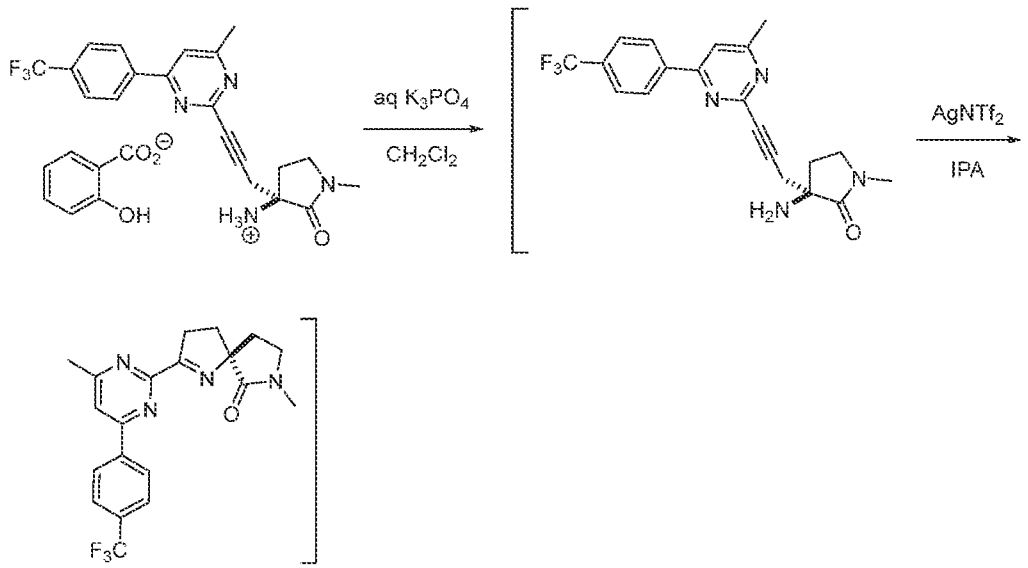
Part B: To the solution prepared in Part A at 20 °C was charged acetonitrile (56.9 kg). With good stirring, methansulfonic acid (21.1 kg) was added over about 15 min while controlling

the reaction temperature at ≤ 26 °C. Following the addition, the container and transfer line were rinsed forward into the reactor with acetonitrile (7.9 kg) and the contents of the reactor were heated to 60 – 70 °C (target: 65 °C); the progress of the reaction was monitored by UPLC. Upon completion, the contents of the reactor were cooled to about 45 °C and purified water (179.3 kg) was charged over about 90 min while maintaining a reaction temperature of 45 – 50 °C. Following the addition, the contents of the reactor were cooled to 18 – 25 °C and aged for about 15 min. The layers were separated and the lower aqueous layer was basified (pH ≥12) with 50 wt% aqueous K_3PO_4 solution (33.60 kg) over about 30 min while maintaining a reaction temperature of 20 – 25 °C. Isopropyl acetate (62.6 kg) was charged and the contents of the reactor were stirred for about 10 min. The layers were separated and the lower aqueous layer was back extracted with isopropyl acetate (41.1 kg). The combined organic layers were concentrated *in vacuo* to a volume of about 108 L. Isopropyl acetate (156.3 kg) was charged and the solution was concentrated *in vacuo* to a volume of about 72 L. Isopropyl acetate (156.3 kg) was charged and the solution was concentrated *in vacuo* to a volume of about 72 L (KF = 0.6 % (limit: ≤1.6%)) to give an isopropyl acetate solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one.

Part C: The solution prepared in Part B was polish filtered. The reactor which contained the solution and the transfer line were rinsed forward with isopropyl acetate (10 kg). The contents of the reactor were warmed to 30 – 40 °C (target: 35 °C) with good stirring. A solution of salicylic acid (12.2 kg) in isopropyl acetate (63.5 kg) was added over about 110 min while maintaining a reaction temperature of 32 – 36 °C. Following the addition the contents of the reactor were aged at 30 – 40 °C (target: 35 °C) for about 3 h, cooled to 24 – 26 °C (target: 25 °C) over about 2 h, cooled to -5 to -15 °C (target: -10 °C) over about 80 min and aged for about 35 min. Solids were isolated by filtration, twice washed with cold (0 – 5 °C) MTBE – ACN (1:1 v/v, 59 L per wash), dried on the filter (jacket temperature: 60 °C) under suction while applying a stream of warm nitrogen (60 °C) for about 14 h followed by further drying on the filter under suction for about 33 h to give 28.9 kg (75%) of the title compound; purity: 97.6 % area; chiral purity: 99.8 % area.

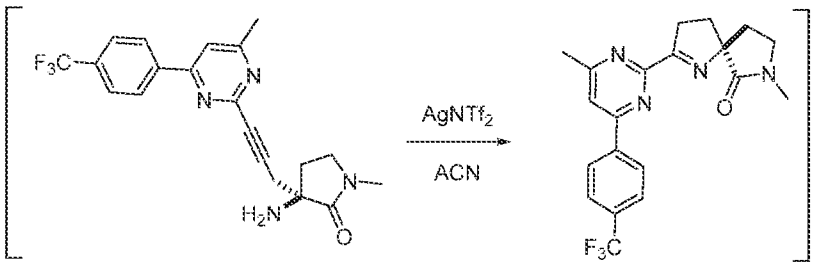
Example 11: Preparation of (S)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]non-1-en-6-one

Description 1



A reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (333 mg) and dichloromethane (2 mL). With good stirring, 20 wt% aqueous K_3PO_4 solution was charged. Following salt dissolution and a pH measurement of the aqueous layer (≥12), the layers were separated and the upper aqueous layer was back extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a viscous, immobile syrup which was dissolved in isopropanol (2 mL). Following addition of $AgNTf_2$ (17 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 24 h. UPLC analysis showed that 94 % area of the title compound was present in the solution.

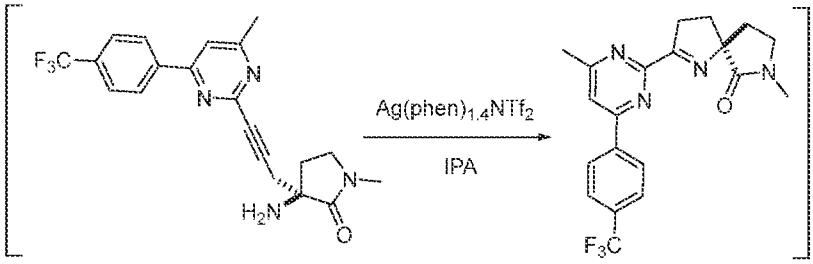
Description 2



A reactor was charged with a solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one (1.57 g) in

acetonitrile (6.4 mL). Following addition of $AgNTf_2$ (110 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 25 h. UPLC analysis showed that 89 % area of the title compound was present in the solution.

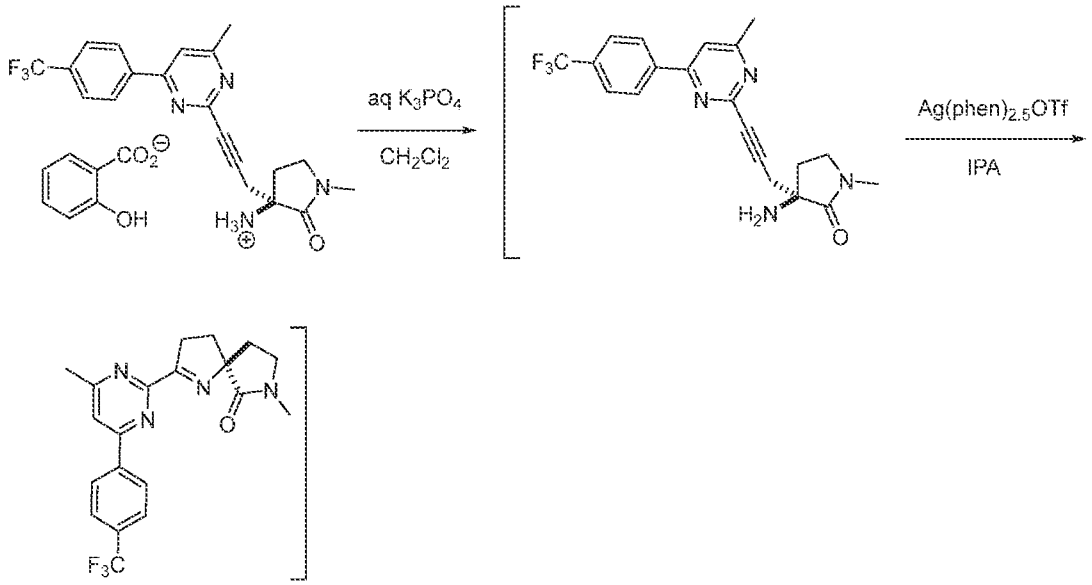
Description 3



Part A: A reactor was charged with 1,10-phenanthroline (465 mg) and MeOH (15 mL). With good stirring at ambient temperature, a solution of $AgNTf_2$ (1.00 g) in water (15 mL) was added. After aging for about 15 min, solids were isolated by filtration, washed with MeOH and dried to constant weight *in vacuo* at ambient temperature to give 920 mg (78%) of $Ag(phen)_{1.4}NTf_2$. ^1H and ^{19}F NMR spectra (d_6-DMSO) using 1,4-difluorobenzene as an internal standard indicated a mol ratio of $AgNTf_2$: 1,10- phenanthroline = 1:1.4.

Part B: A reactor was charged with a solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one (1.10 g) in isopropanol (4.5 mL). Following addition of $Ag(phen)_{1.4}NTf_2$ (161 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 20 h. UPLC analysis showed that 96 % area of the title compound was present in the solution.

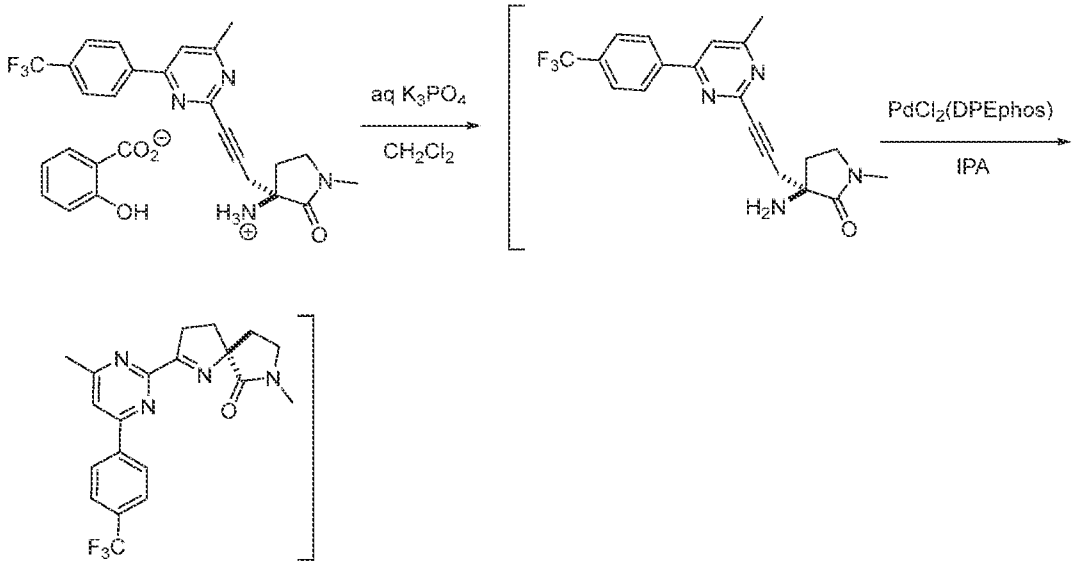
Description 4



Part A: A reactor was charged with 1,10-phenanthroline (2.00 g) and MeOH (70 mL). With good stirring at ambient temperature, a solution of AgOTf (2.85 g) in water (70 mL) was added. After aging for about 15 min, solids were isolated by filtration, washed with MeOH and dried to constant weight *in vacuo* at ambient temperature to give 3.35 g (>100%) of $Ag(phen)_{2.5}OTf$. ^1H and ^{19}F NMR spectra (d_6-DMSO) using 1,4-difluorobenzene as an internal standard indicated a mol ratio of AgOTf : 1,10- phenanthroline = 1:2.5.

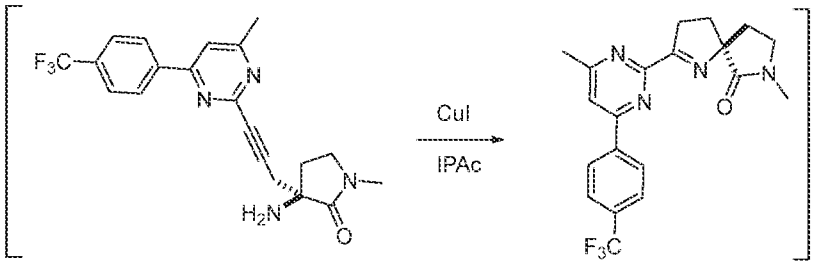
Part B: a reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (6 g) and dichloromethane (60 mL). With good stirring, 20 wt% aqueous K_3PO_4 solution was charged. Following salt dissolution and a pH measurement of the aqueous layer (≥12), the layers were separated and the upper aqueous layer was back extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a viscous, immobile syrup which was dissolved in isopropanol (18 mL). Following addition of $Ag(phen)_{2.5}OTf$ (497 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 20 h. UPLC analysis showed that 95 % area of the title compound was present in the solution.

Description 5



A reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (333 mg) and dichloromethane (2 mL). With good stirring, 20 wt% aqueous K_3PO_4 solution was charged. Following salt dissolution and a pH measurement of the aqueous layer (≥12), the layers were separated and the upper aqueous layer was back extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a viscous, immobile syrup which was dissolved in isopropanol (1 mL). Following addition of dichloro[bis[2-(diphenylphosphino)phenyl]ether]palladium (II) (36 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 40 h. UPLC analysis showed that 56 % area of the title compound was present in the solution.

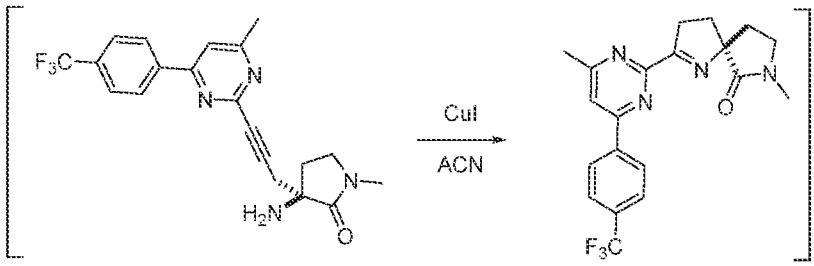
Description 6



A reactor was charged with a solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one (1.0 g) in isopropyl acetate (5.0 mL). Following addition of CuI (20 mg) and three vacuum / nitrogen break

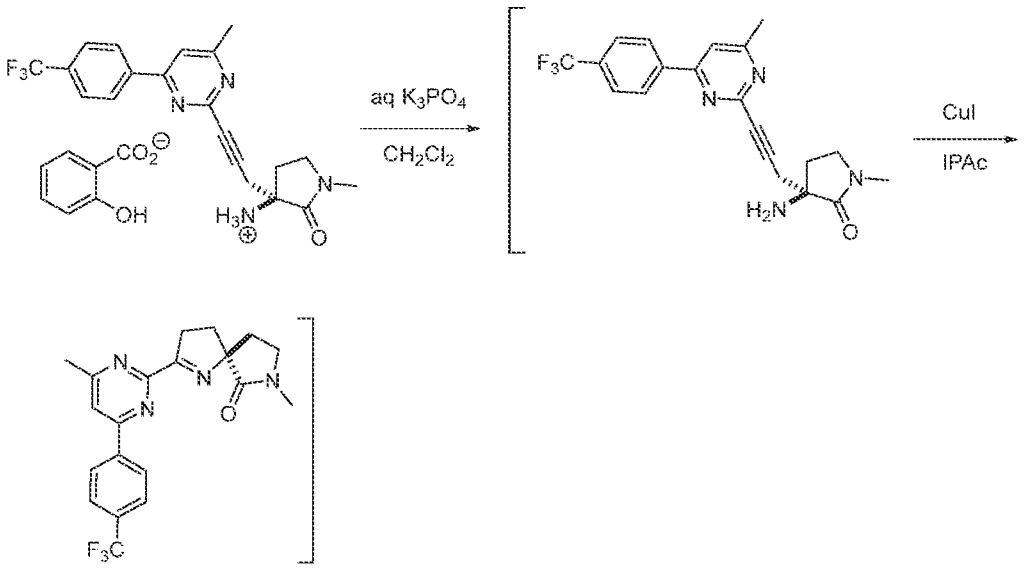
cycles, the resulting solution was heated to about 80 °C and aged for about 7 h. UPLC analysis showed that 90 % area of the title compound was present in the solution.

Description 7



A reactor was charged with a solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one (1.0 g) in acetonitrile (5.0 mL). Following addition of CuI (20 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 7 h. UPLC analysis showed that 68 % area of the title compound was present in the solution.

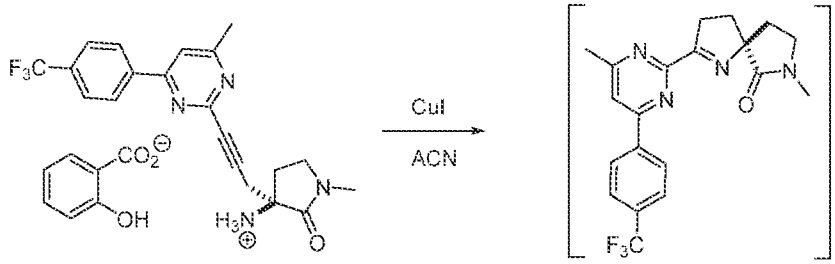
Description 8



A reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (7 g) and dichloromethane (70 mL). With good stirring, 20 wt% aqueous K_3PO_4 solution (39.3 g) was charged. Following salt dissolution and a pH measurement of the aqueous layer (≥12), the layers were separated and the upper aqueous layer was back

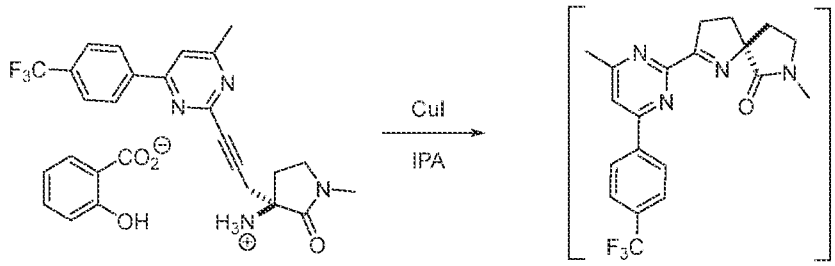
extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a viscous, immobile syrup which was dissolved in isopropyl acetate (42 mL). Following addition of CuI (127 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 3.5 h. UPLC analysis showed that 92 % area of the title compound was present in the solution.

Description 9



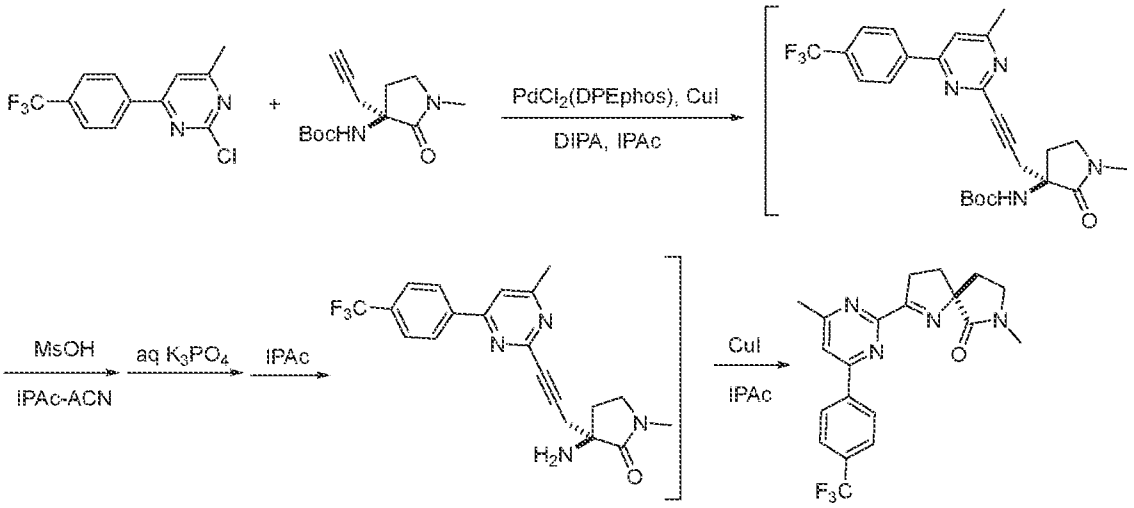
A reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (1.35 g) and acetonitrile (5 mL). Following addition of CuI (20 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 23 h. UPLC analysis showed that 42 % area of the title compound was present in the solution.

Description 10



A reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (13.5 g) and isopropanol (40 mL). Following addition of CuI (489 mg) and three vacuum / nitrogen break cycles, the resulting solution was heated to about 80 °C and aged for about 11 h. UPLC analysis showed that 89 % area of the title compound was present in the solution.

Description 11



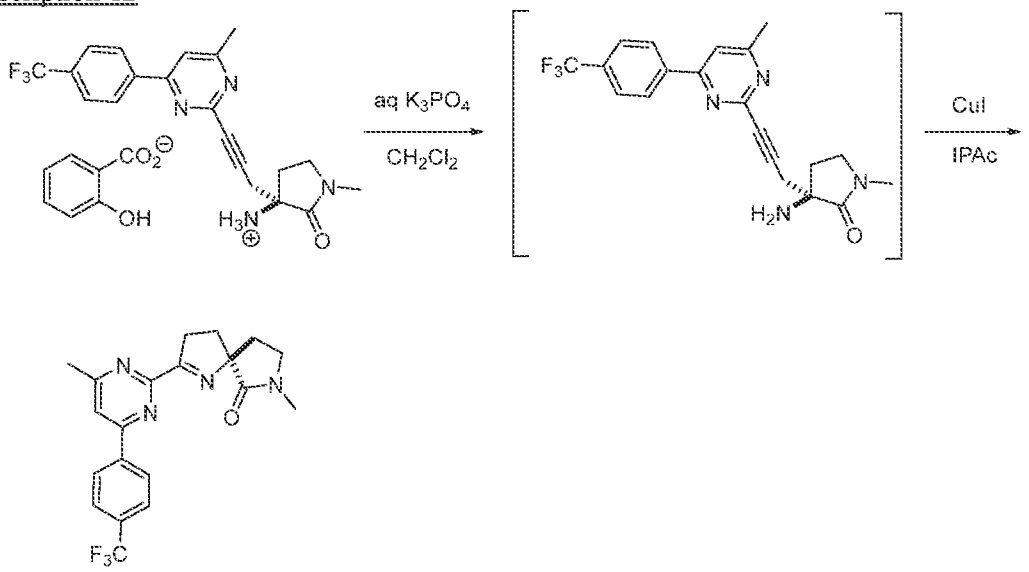
Part A: a reactor was charged with 2-chloro-4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidine (10.0 g) and *tert*-butyl (*S*)-(1-methyl-2-oxo-3-(prop-2-yn-1-yl)pyrrolidin-3-yl)carbamate (9.99 g), diisopropylamine (4.08 g), dichloro[bis[2-(diphenylphosphino)phenyl]ether]palladium (II) (66 mg), CuI (35 mg) and isopropyl acetate (26.1 g). The contents of the reactor were sparged with nitrogen for about 15 min then warmed to 80 °C; the progress of the reaction was monitored by UPLC. Upon completion, the contents of the reactor were cooled to 20 °C and filtered. The spent filter cake was washed twice with isopropyl acetate (8.7 g per wash); the combined filtrate and wash were stirred briefly to give an isopropyl acetate solution of *tert*-butyl (*S*)-(1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)-2-oxopyrrolidin-3-yl)carbamate (58.4 g). By ^{1}H NMR internal standard analysis, the solution contained 13.6 g (76%) of the desired product.

Part B: To the solution prepared in Part A at 20 °C was charged acetonitrile (22.1 g) and methansulfonic acid (6.96 g) and the contents of the reactor were heated to 65 °C; the progress of the reaction was monitored by UPLC. Upon completion, water (70 mL) was charged and the contents of the reactor were cooled to about 20 °C. The layers were separated and the lower aqueous layer was basified (pH $\geq$12) with 50 wt% aqueous K_3PO_4 solution (52 mL). Isopropyl acetate (24.4 g) was charged, the layers were separated and the lower aqueous layer was back extracted with isopropyl acetate (12.2 g). The combined organic layers were concentrated *in vacuo* to a volume of about 30 mL. Isopropyl acetate (60.9 g) was charged and the solution was concentrated *in vacuo* to a volume of about 30

mL; this re-concentration was repeated one time. Solids were removed by filtration and washed with isopropyl acetate (8.7 g) to give an isopropyl acetate solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one (50.7 g). By ^{1}H NMR internal standard analysis, the solution contained 10.9 g (100 %) of the desired product.

Part C: The solution prepared in Part B was sparged with nitrogen for about 15 min. After charging CuI (267 mg), the contents of the reactor were sparged with nitrogen for about 15 min then heated to 75 °C; the progress of the reaction was monitored by UPLC. Upon completion, the contents of the reactor were cooled to 40 °C and aged for about 16 h. Solids were isolated by filtration, washed twice with isopropyl acetate (19.1g per wash) and dried to constant weight *in vacuo* at 40 °C to give 7.4g (68%) of the title compound; purity: 99.9 % area.

Description 12

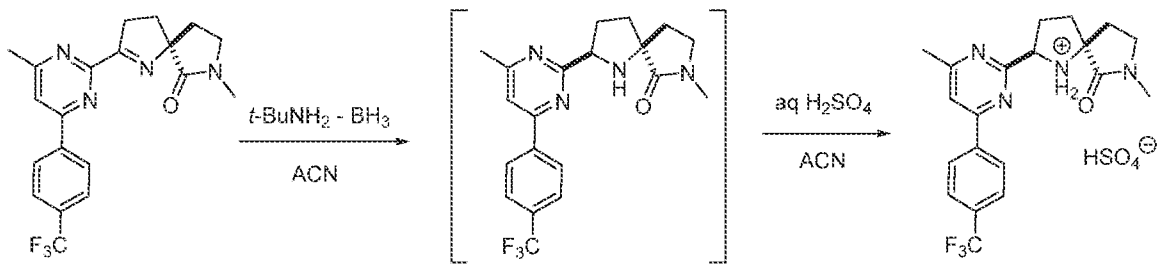


Part A: a reactor was charged with (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one, salicylic acid salt (1:1) (28.55 kg) and dichloromethane (310.0 kg). With good stirring, the reaction temperature was adjusted to 15 – 25 °C (target: 18 °C) and 20 wt% aqueous K_3PO_4 solution (210.85 kg) was charged over about 25 min while maintaining a reaction temperature of ≤30 °C. After aging for about 30 min, the layers were separated and the upper aqueous layer was back extracted with dichloromethane (124.2 kg). The combined organic layers were

concentrated *in vacuo* to a volume of about 70 L, isopropyl acetate (102.15 kg) was charged, the solution was concentrated *in vacuo* to a volume of about 70 L, isopropyl acetate (101.9 kg) was charged and the solution was concentrated *in vacuo* to a volume of about 47 L, isopropyl acetate (103.85 kg) was charged and the solution was concentrated *in vacuo* to a volume of about 47 L (KF ≤1.0%). The solution was polish filtered, and the reactor, polish filter and transfer line were rinsed forward with isopropyl acetate (20.6 kg) to give an isopropyl acetate solution of (*S*)-3-amino-1-methyl-3-(3-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)prop-2-yn-1-yl)pyrrolidin-2-one.

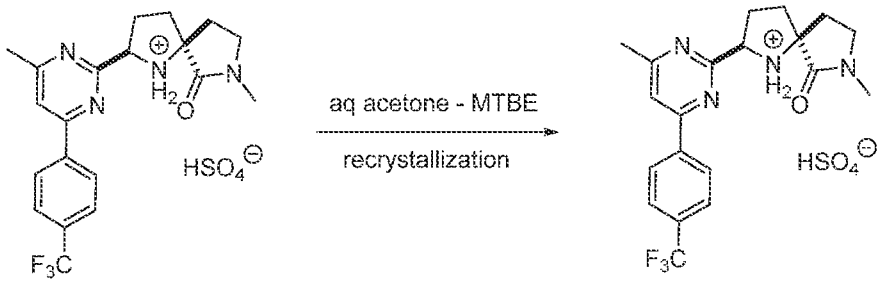
Part B:
The solution prepared in Part A at 15 – 25 °C (target: 20 °C) was subjected to four vacuum / nitrogen break cycles. After charging a slurry of CuI (434 g) in isopropyl acetate (1.0 kg) to the reactor, the container and charging line were rinsed forward into the reactor with isopropyl acetate (0.6 kg). After four vacuum / nitrogen break cycles and sparging the solution with nitrogen for about 30 min, the contents of the reactor were heated to 70 – 80 °C (target: 75 °C); the progress of the reaction was monitored by UPLC. Upon completion, the contents of the reactor were cooled to 37 – 43 °C (target: 40 °C) over about 3.5 h; the progress of the crystallization was monitored by ReactIR. Upon completion, the contents of the reactor were aged at 37 – 40 °C (target: 40 °C) for about 2 h. Solids were isolated by filtration, washed twice with isopropyl acetate (29.8 kg per wash), dried on the filter for about 1 h under a stream of nitrogen, dried on the filter (jacket temperature: 40 °C) while applying a stream of warm nitrogen (40 °C) for about 15 h followed by further drying on the filter under suction for about 15 h to give 13.1 kg (62%) of the title compound; purity: 99.9 % area.

Example 12: Preparation of (2R,5S)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]nonan-6-one, sulfuric acid salt (1:1)



Under an inert atmosphere of nitrogen a reactor was charged with (*S*)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]non-1-en-6-one (13.0 kg) and acetonitrile (71.7 kg) and with good stirring the contents of the reactor were adjusted to 15 – 25 °C (target: 19 °C). A solution of *tert*-butylamine – borane complex (2.4 kg) in acetonitrile (25.7 kg) was charged over 35 – 40 min while maintaining a reaction temperature of ≤20 °C. Following the addition, the vessel and charging line were rinsed forward into the reactor with acetonitrile (10.3 kg); the progress of the reaction was monitored by UPLC. Upon completion, the contents of the reactor were cooled to 10 – 15 °C (target: 12 °C) and 5M aqueous HCl solution (55.55 kg) was added over about 1 h while maintaining a reaction temperature of ≤20 °C. The contents of the reactor were aged for about 30 min. With continued good stirring, 50 wt% aqueous K_3PO_4 solution (209.45 kg) was charged over 75 – 80 min while maintaining a reaction temperature of ≤20 °C. The contents of the reactor were aged for about 20 min. The layers were separated, the lower aqueous layer was back extracted with acetonitrile (20.5 kg) and the combined organic layers were washed with brine (59.7 kg). The combined organic layers were concentrated *in vacuo* to a volume of about 33 L. After charging acetonitrile (46.3 kg), the contents of the reactor were concentrated *in vacuo* to a volume of about 33 L. After charging acetonitrile (46.2 kg), the contents of the reactor were concentrated *in vacuo* to a volume of about 33 L. After charging acetonitrile (46.1 kg) a KF <3% was measured and the contents of the reactor were aged for about 1 h. Following a polish filtration, the reactor, polish filter and transfer line were rinsed forward with acetonitrile (10.2 kg). To the solution (KF 1.2%) was charged water (1.1 kg; final KF 2.3%) and the contents of the reactor were warmed to 48 – 53 °C (target: 50 °C). With good stirring, 7.5M aqueous sulfuric acid solution (6.25 kg) was added over about 1 h, the slurry was aged for about 1 h then cooled to 18 – 23 °C (target: 20 °C) over about 1 h. Isopropanol (10.2 kg) was charged over about 25 min, the slurry was aged for about 12 h, cooled to 0 – 5 °C over about 2.25 h and aged for about 2 h. Solids were isolated by filtration, washed with cold (0 – 5 °C) MTBE – ACN (1:1 v/v, 20 kg), cold (0 – 5 °C) MTBE (19.3 kg), dried on the filter while applying a stream of nitrogen for about 90 min, dried on the filter (jacket temperature: 40 °C) while applying a stream of warm nitrogen (40 °C) for about 12 h followed by further drying on the filter under suction for about 17 h to give 11.95 kg (73%) of the title compound; purity: 98.6 % area.

Example 13: Recrystallization of (2R,5S)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]nonan-6-one, sulfuric acid salt (1:1)



A reactor was charged with (*2R,5S*)-7-methyl-2-(4-methyl-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,7-diazaspiro[4.4]nonan-6-one, sulfuric acid salt (1:1) (11.95 kg), purified water (23.25 kg) and acetone (43.9 kg) and the contents of the reactor were warmed to 35 – 40 °C (target: 39 °C) with good stirring. Following a wash of a polish filter system with a warm aqueous acetone solution (23.45 kg purified water and 43.5 kg acetone; the wash was discarded), the contents of the reactor were polish filtered into a reactor that was pre-heated to 35 – 40 °C (target: 39 °C). To the resulting solution was charged MTBE (210.5 kg) over about 3 h while maintaining a reaction temperature of 35 – 40 °C (target: 39 °C). After aging for about 30 min, the contents of the reactor were cooled to 0 – 5 °C over about 3.5 h and aged for about 30 min. The contents of the reactor were warmed to 38 – 43 °C (target: 40 °C) over about 1.5 h, aged for about 2 h, cooled to 8 – 14 °C (target: 10 °C) over about 4.5 h and aged for about 12 h. Solids were isolated by filtration, washed twice with cold (0 – 5 °C) MTBE – acetone (1:1 v/v, 21.5 kg per wash), dried on the filter while applying a stream of nitrogen for about 1 h, dried on the filter (jacket temperature: 60 °C) while applying a stream of warm nitrogen (60 °C) for about 12 h followed by further drying on the filter under suction for about 33.5 h to give 10.14 kg (85%) of the title compound; purity: 99.9 % area.

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. In case of conflict, the present application, including any definitions herein, will control.

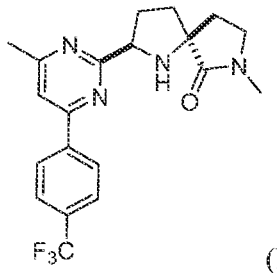
EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

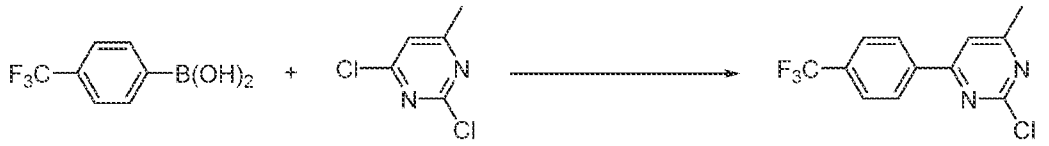
We claim:

1. A process for preparing a compound of formula (**I**)



(**I**),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (**II**) with a compound of formula (**III**), in the presence of a metal compound, a phosphine that comprises an alkyl group, and a base, thereby producing a compound of formula (**IV**):



(**II**) (**III**) (**IV**)

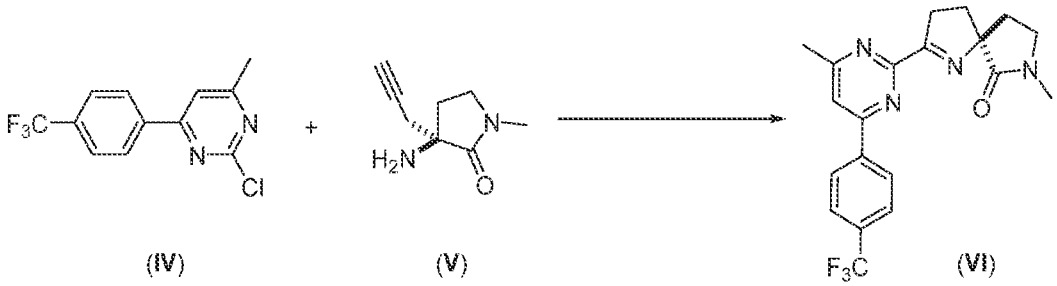
2. The process of claim 1, wherein the metal compound is a palladium compound.

3. The process of claim 2, wherein the palladium compound is palladium(II) acetate.

4. The process of any one of claims 1-3, wherein the phosphine is *tert*-butyldiphenylphosphine.

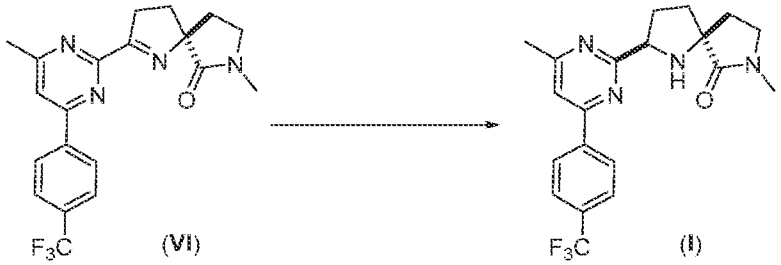
5. The process of claim 4, wherein the base is diisopropylethylamine.

6. The process of any one of the preceding claims, further comprising reacting the compound of formula (**IV**) with a compound of formula (**V**) or a salt thereof in the presence of a palladium compound, a copper salt and a base, thereby producing a compound of formula (**VI**):



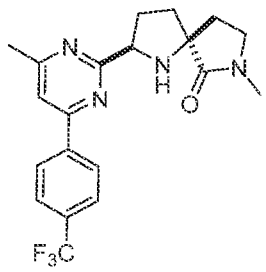
(IV) (V) (VI)

7. The process of any one of the preceding claims, further comprising reducing the compound of formula (**VI**), thereby producing the compound of formula (**I**), or a pharmaceutically acceptable salt thereof



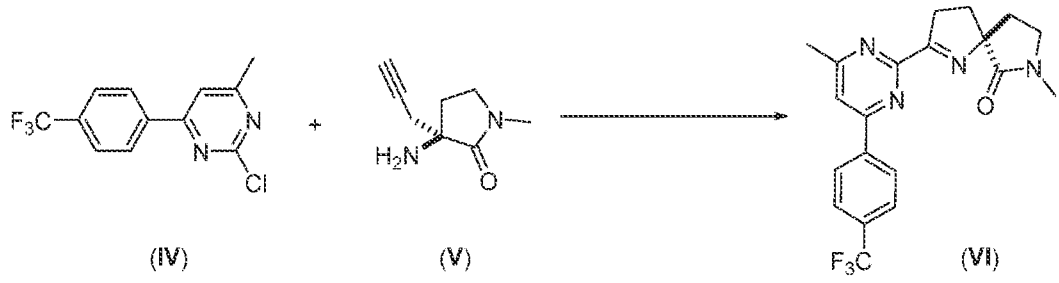
(VI) (I)

8. A process for preparing a compound of formula (**I**)



(I),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (**IV**) with a compound of formula (**V**) or a salt thereof in the presence of a palladium compound, a metal salt and a base, thereby producing a compound of formula (**VI**):



(IV) (V) (VI)

wherein the metal salt is not a silver salt.

9. The process of claim 8, wherein the compound of formula (V) is a trifluoroacetate salt

10. The process of claim 8, wherein the compound of formula (V) is a hydrochloride salt.

11. The process of claim 8, wherein the compound of formula (V) is not a salt.

12. The process of any one of claims 8-11, wherein the palladium compound is $PdCl_2$(dppf)-CH_2Cl_2 or $PdCl_2$(DPEphos).

13. The process of any one of claims 8-12, wherein the metal salt is copper(I) salt (e.g., copper(I) iodide).

14. The process of any one of claims 8-13, wherein the base is an inorganic base, e.g. potassium carbonate.

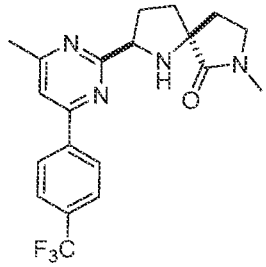
15. The process of any one of claims 8-13, wherein the base is an organic base, e.g. diisopropylamine.

16. The process of any one of claims 8-15, wherein the compound of formula (IV) is reacted with the compound of formula (V) in the presence of a solvent.

17. The process of claim 16, wherein the solvent comprises isopropyl acetate or acetonitrile.

18. The process of any one of claims 8-17, wherein the chemical yield of the compound of formula (VI) is at least about 75%.

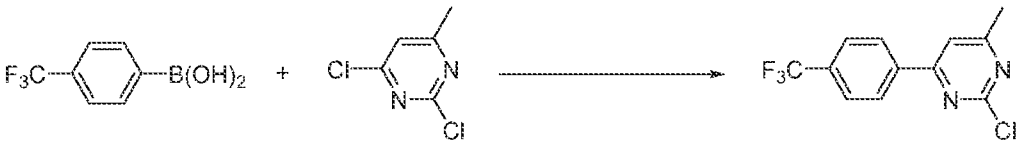
19. A process for preparing a compound of formula (I)



(I),

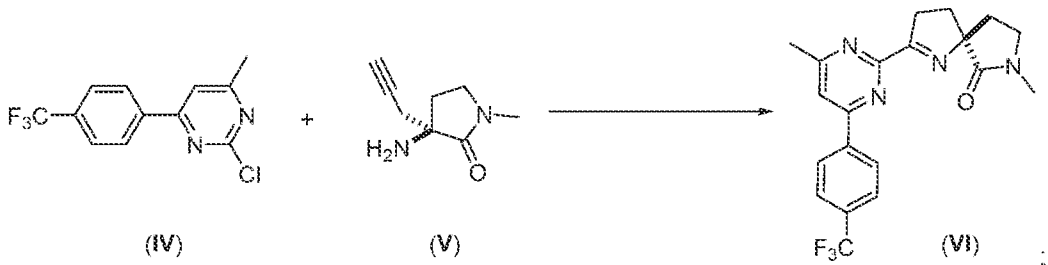
or a pharmaceutically acceptable salt thereof comprising:

reacting a compound of formula (**II**) with a compound of formula (**III**) in the presence of a metal compound, a phosphine that comprises an alkyl group, and a base, thereby producing a compound of formula (**IV**):



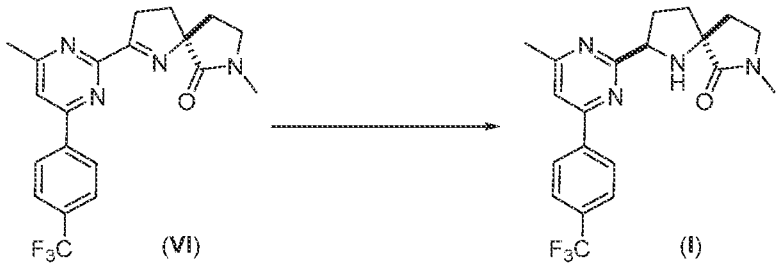
(II) (III) (IV) ;

reacting the compound of formula (**IV**) with a compound of formula (**V**) or a salt thereof in the presence of a palladium compound, a copper salt, and a base, thereby producing a compound of formula (**VI**):



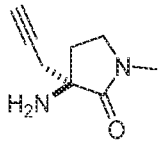
(IV) (V) (VI) ; and

reducing the compound of formula (**VI**), thereby producing the compound of formula (**I**), or a pharmaceutically acceptable salt thereof:



(VI) (I)

20. A compound of formula (**V**),



(V),

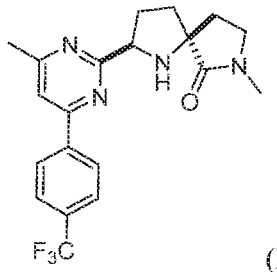
or a salt thereof.

21. The compound of claim 20, wherein the compound of formula (**V**) is a trifluoroacetate salt.

22. The compound of claim 20, wherein the compound of formula (V) is a hydrochloride salt.

23. The compound of claim 20, wherein the compound of formula (V) is not a salt.

24. A process for preparing a compound of formula (I)



(I),

or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula (VII) with an azide compound and an amine in the presence of *t*-butanol, thereby producing a compound of formula (VIII):

(VII) (VIII)

25. The process of claim 24, wherein the azide compound is diphenylphosphoryl azide.

26. The process of claim 24 or 25, wherein the amine is N-methylmorpholine.

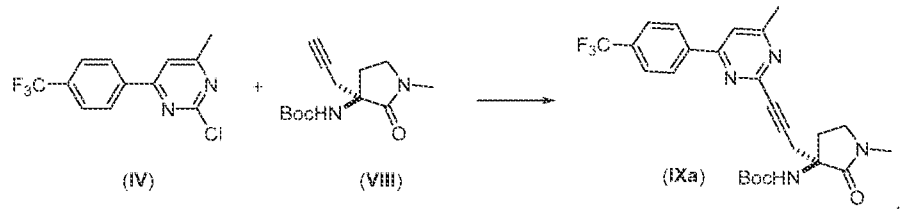
27. The process of any one of claims 24-26, wherein the reaction is performed in a batch process.

28. The process of any one of claims 24-26, wherein the reaction is performed in a continuous flow process.

29. The process of any one of claims 24-28, wherein the reaction is performed in the presence of a solvent.

30. The process of claim 29, wherein the solvent comprises toluene.

31. The process of any one of claims 24-30, further comprising reacting a compound of formula (**IV**) with the compound of formula (**VIII**) in the presence of a palladium compound, a copper salt and a base, thereby producing a compound of formula (**IXa**) or a salt thereof:



32. The process of claim 31, wherein the palladium catalyst is $PdCl_2$(DPEphos).

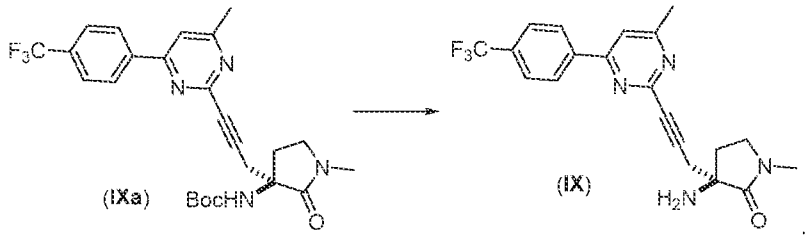
33. The process of claims 31 or 32, wherein the copper salt is copper(I) iodide.

34. The process any one of claims 31-33, wherein the base is diisopropylamine.

35. The process of any one of claims 31-34, wherein the compound of formula (**IV**) is reacted with the compound of formula (**VIII**) in the presence of a solvent.

36. The process of claim 35, wherein the solvent comprises isopropyl acetate.

37. The process of any one of claims 31-36, further comprising reacting the compound of formula (**IXa**) with an acid, thereby producing a compound of formula (**IX**) or a salt thereof:



38. The process of claim 37, wherein the compound of formula (**IXa**) is reacted with the acid in the presence of a solvent.

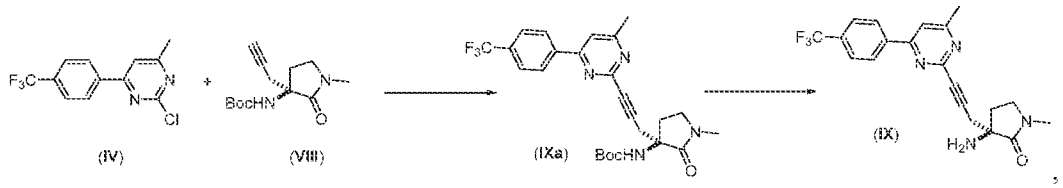
39. The process of claim 38, wherein the solvent comprises acetonitrile.

40. The process of any one of claims 37-39, wherein the acid is methanesulfonic acid.

41. The process of any one of claims 24-30, further comprising

i) reacting a compound of formula (**IV**) with the compound of formula (**VIII**) in the presence of a palladium compound, a copper salt and a base, thereby producing a compound of formula (**IXa**) or a salt thereof; and

ii) reacting a compound of formula (**IXa**) with an acid, thereby producing a compound of formula (**IX**) or a salt thereof



wherein the compound of formula (**IXa**) is not isolated.

42. The process of claim 41, wherein the palladium catalyst is $PdCl_2$(DPEphos).

43. The process of claims 41 or 42, wherein the copper salt is copper(I) iodide.

44. The process any one of claims 41-43, wherein the base is diisopropylamine.

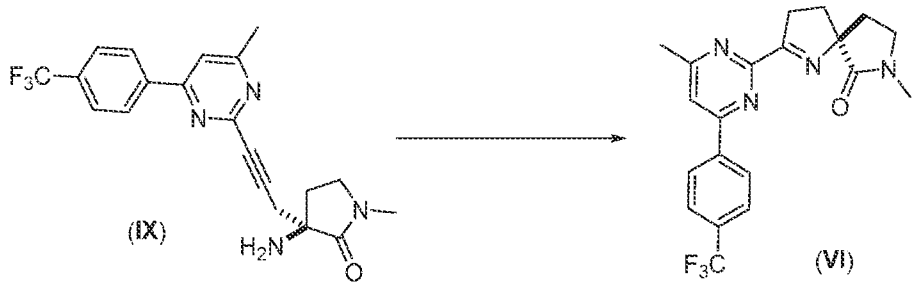
45. The process of any one of claims 41-44, wherein the compound of formula (**IV**) is reacted with the compound of formula (**VIII**) in the presence of a solvent.

46. The process of claim 45, wherein the solvent comprises isopropyl acetate.

47. The process of any one of claims 41-46, wherein the compound of formula (**IXa**) is reacted with the acid in the presence of a solvent.

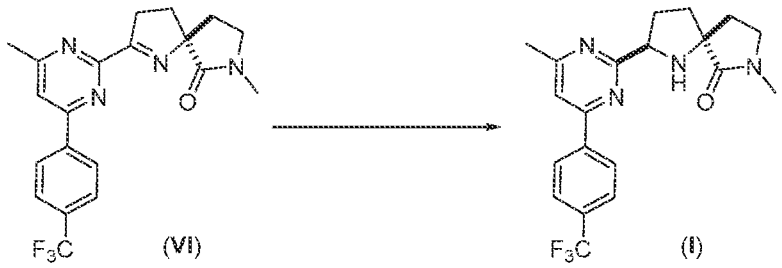
48. The process of claim 47, wherein the solvent comprises isopropyl acetate and acetonitrile.

49. The process of any one of claims 24-48, further comprising performing a cyclization reaction of the compound of formula (**IX**), or a salt thereof in the presence of a metal salt to produce a compound of formula (**VI**):



wherein the metal salt is not a silver salt.

50. The process of any one of claims 24-49, further comprising reducing the compound of formula (**VI**), thereby producing the compound of formula (**I**), or a pharmaceutically acceptable salt thereof

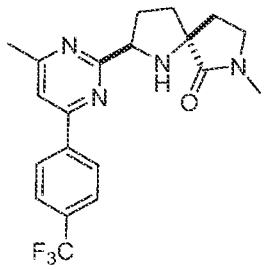


51. The process of claim 50, wherein the compound of formula (**VI**) is reduced to the compound of formula (**I**), or a pharmaceutically acceptable salt thereof in the presence of a boron compound.

52. The process of claim 51, wherein the boron compound is a borane.

53. The process of claim 52, wherein the borane is borane-tert-butyl amine complex.

54. A process for purification of a compound of formula (**I**),



,

or a pharmaceutically acceptable salt thereof, comprising recrystallizing the compound of formula (**I**) or a pharmaceutically acceptable salt thereof in a solvent.

55. The process of claim 54, wherein the compound of formula (I) is a hydrogen sulfate salt.

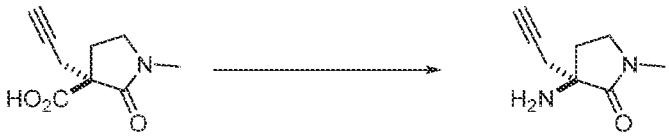
56. The process of claim 54 or 55, wherein the solvent comprises water and acetone.

57. The process of any one of claims 54-56, wherein the solvent further comprises methyl *t*-butyl ether.

58. The process of any one of claims 54-57, wherein the chemical yield of the process is at least about 80%.

59. The process of any one of claims 54-58, wherein the process provides the compound of formula (I) with a purity of at least about 99%.

60. A process for preparing a compound of formula V, comprising reacting a compound of formula (VII) with an azide compound and an amine followed by treatment with a base:



(VII) (V)

61. The process of claim 60, wherein the azide compound is diphenylphosphoryl azide.

62. The process of claim 60 or 61, wherein the amine is N-methylmorpholine.

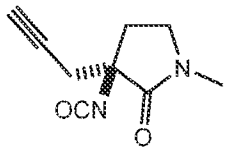
63. The process of any one of claims 60-62, wherein the reaction is performed in a batch process.

64. The process of any one of claims 60-63, wherein the reaction is performed in the presence of a solvent.

65. The process of claim 64, wherein the solvent comprises toluene.

66. The process of any one of claims 60-65, wherein the base is aqueous sodium hydroxide.

67. A compound represented by the following structure:



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/063825

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/10(2022.01)i; ***C07D 207/273***(2022.01)i; ***C07D 207/26***(2022.01)i; ***C07F 5/02***(2022.01)i; ***C07D 239/30***(2022.01)i; ***C07D 209/32***(2022.01)i; ***C07D 209/18***(2022.01)i
CPC:C07D 487/10; C07D 207/273; C07D 207/26; C07F 5/025; C07D 239/30; C07D 209/32; C07D 209/18

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 487/10; C07D 207/273; C07D 207/26; C07F 5/02; C07D 239/30; C07D 209/32; C07D 209/18
CPC:C07D 487/10; C07D 207/273; C07D 207/26; C07F 5/025; C07D 239/30; C07D 209/32; C07D 209/18

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)

Databases consulted: Google Patents, CAPLUS, REGISTRY, Google Scholar Search terms used: BIIB-095; BIIB 095; CAS RN: 1493790-64-9

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 2013175205 A1 (CONVERGENCE PHARMACEUTICALS [GB])28 November 2013 (2013-11-28)	
Y	example 2; page 47, lines 21-22; page 13, scheme 2, step 1; pages 39-40, description 5	1-7,19,21-67
X	page 11, scheme 1, compound VIII [CAS RN:1444535-33-4]	8-18,20
	WO 2013175206 A1 (CONVERGENCE PHARMACEUTICALS [GB])28 November 2013 (2013-11-28)	
Y	page 22, scheme 1	1-7,19,21,22,24-67
X	page 22, scheme 1, compound VIII [CAS RN:1444535-33-4]	8-18,20,23
	WO 2017075056 A1 (GILEAD APOLLO LLC [US])04 May 2017 (2017-05-04)	
Y	page 244, para. [0710], compound 114.4	24-53,60-67
	Palladium-catalyzed Suzuk-Miyaura cross-coupling reactions employing dialkylbiaryl phosphine ligands. Accounts of chemical research, 2008, 41.11: 1461-1473 MARTIN, Ruben; BUCHWALD, Stephen L. (2008/12/07)	
Y	page 1463, figure 2, L2 and L5; page 1464, Table 1; page 1466, table 4	1-7,19-23

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 2022	**10 April 2022**

Name and mailing address of the ISA/IL
Israel Patent Office
Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel
Israel
Telephone No. **972-73-3927144**
Email: **pctoffice@justice.gov.il**

Authorized officer
NAHAMANI Moshe
Telephone No.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/063825

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2013175205 A1	28 November 2013	WO 2013175205 A1	28 November 2013
		AU 2013265001 A1	18 December 2014
		AU 2013265001 B2	01 December 2016
		AU 2017201421 A1	23 March 2017
		AU 2017201421 B2	07 December 2017
		AU 2018201653 A1	29 March 2018
		AU 2018201653 B2	02 May 2019
		BR 112014029280 A2	27 June 2017
		CA 2873956 A1	28 November 2013
		CA 2873956 C	23 March 2021
		CN 104640867 A	20 May 2015
		CN 104640867 B	21 July 2017
		CN 107344942 A	14 November 2017
		CN 107344942 B	25 September 2020
		CY 1118274 T1	28 June 2017
		DK 2861602 T3	28 November 2016
		DK 3106464 T3	23 March 2020
		EA 201492169 A1	30 April 2015
		EA 025579 B1	30 January 2017
		EP 2861594 A1	22 April 2015
		EP 2861594 B1	24 August 2016
		EP 2861602 A1	22 April 2015
		EP 2861602 B1	10 August 2016
		EP 3106464 A1	21 December 2016
		EP 3106464 B1	08 January 2020
		ES 2602193 T3	20 February 2017
		ES 2602308 T3	20 February 2017
		ES 2782088 T3	10 September 2020
		GB 201209015 D0	04 July 2012
		HK 1209423 A1	01 April 2016
		HR P20161349 T1	27 January 2017
		HR P20200580 T1	02 October 2020
		HU E031664 T2	28 July 2017
		HU E049445 T2	28 September 2020
		IL 235805 D0	01 February 2015
		IL 235805 A	29 May 2017
		IL 252033 D0	29 June 2017
		IL 252033 A	31 December 2019
		IL 271330 D0	30 January 2020
		IL 271330 A	28 February 2021
		IL 280595 D0	25 March 2021
		IN 2393MUN2014 A	21 August 2015
		JP 2015517561 A	22 June 2015
		JP 6169687 B2	26 July 2017
		JP 2017206534 A	24 November 2017
		JP 6378404 B2	22 August 2018
		JP 2015517562 A	22 June 2015
		KR 20150023401 A	05 March 2015
		KR 102161101 B1	20 October 2020
		KR 20200113027 A	05 October 2020

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/063825

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		LT	2861602	T	10 November 2016
		LT	3106464	T	10 April 2020
		MX	2014014274	A	17 June 2015
		MX	355303	B	12 April 2018
		PL	2861602	T3	31 May 2017
		PL	3106464	T3	16 November 2020
		PT	2861602	T	14 November 2016
		PT	3106464	T	03 April 2020
		RS	55415	B1	28 April 2017
		RS	60368	B1	31 July 2020
		SG	10201703527W	A	29 June 2017
		SG	11201407755U	A	30 December 2014
		SI	2861602	T1	31 March 2017
		SI	3106464	T1	31 December 2020
		SM	T201600421	B	10 January 2017
		US	2015119404	A1	30 April 2015
		US	9309254	B2	12 April 2016
		US	2015166551	A1	18 June 2015
		US	9376445	B2	28 June 2016
		US	2016263115	A1	15 September 2016
		US	9737536	B2	22 August 2017
		US	2017304303	A1	26 October 2017
		US	10010551	B2	03 July 2018
		US	2018360833	A1	20 December 2018
		US	10485801	B2	26 November 2019
		US	2016184306	A1	30 June 2016
		US	2020289508	A1	17 September 2020
		WO	2013175206	A1	28 November 2013
		ZA	201408253	B	23 December 2015
WO 2013175206 A1	28 November 2013	WO	2013175206	A1	28 November 2013
		AU	2013265001	A1	18 December 2014
		AU	2013265001	B2	01 December 2016
		AU	2017201421	A1	23 March 2017
		AU	2017201421	B2	07 December 2017
		AU	2018201653	A1	29 March 2018
		AU	2018201653	B2	02 May 2019
		BR	112014029280	A2	27 June 2017
		CA	2873956	A1	28 November 2013
		CA	2873956	C	23 March 2021
		CN	104640867	A	20 May 2015
		CN	104640867	B	21 July 2017
		CN	107344942	A	14 November 2017
		CN	107344942	B	25 September 2020
		CY	1118274	T1	28 June 2017
		DK	2861602	T3	28 November 2016
		DK	3106464	T3	23 March 2020
		EA	201492169	A1	30 April 2015
		EA	025579	B1	30 January 2017
		EP	2861594	A1	22 April 2015
		EP	2861594	B1	24 August 2016

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/063825

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		EP	2861602	A1	22 April 2015
		EP	2861602	B1	10 August 2016
		EP	3106464	A1	21 December 2016
		EP	3106464	B1	08 January 2020
		ES	2602193	T3	20 February 2017
		ES	2602308	T3	20 February 2017
		ES	2782088	T3	10 September 2020
		GB	201209015	D0	04 July 2012
		HK	1209423	A1	01 April 2016
		HR	P20161349	T1	27 January 2017
		HR	P20200580	T1	02 October 2020
		HU	E031664	T2	28 July 2017
		HU	E049445	T2	28 September 2020
		IL	235805	D0	01 February 2015
		IL	235805	A	29 May 2017
		IL	252033	D0	29 June 2017
		IL	252033	A	31 December 2019
		IL	271330	D0	30 January 2020
		IL	271330	A	28 February 2021
		IL	280595	D0	25 March 2021
		IN	2393MUN2014	A	21 August 2015
		JP	2015517561	A	22 June 2015
		JP	6169687	B2	26 July 2017
		JP	2017206534	A	24 November 2017
		JP	6378404	B2	22 August 2018
		JP	2015517562	A	22 June 2015
		KR	20150023401	A	05 March 2015
		KR	102161101	B1	20 October 2020
		KR	20200113027	A	05 October 2020
		LT	2861602	T	10 November 2016
		LT	3106464	T	10 April 2020
		MX	2014014274	A	17 June 2015
		MX	355303	B	12 April 2018
		PL	2861602	T3	31 May 2017
		PL	3106464	T3	16 November 2020
		PT	2861602	T	14 November 2016
		PT	3106464	T	03 April 2020
		RS	55415	B1	28 April 2017
		RS	60368	B1	31 July 2020
		SG	10201703527W	A	29 June 2017
		SG	11201407755U	A	30 December 2014
		SI	2861602	T1	31 March 2017
		SI	3106464	T1	31 December 2020
		SM	T201600421	B	10 January 2017
		US	2015119404	A1	30 April 2015
		US	9309254	B2	12 April 2016
		US	2015166551	A1	18 June 2015
		US	9376445	B2	28 June 2016
		US	2016263115	A1	15 September 2016
		US	9737536	B2	22 August 2017

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2021/063825

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		US 2017304303 A1	26 October 2017
		US 10010551 B2	03 July 2018
		US 2018360833 A1	20 December 2018
		US 10485801 B2	26 November 2019
		US 2016184306 A1	30 June 2016
		US 2020289508 A1	17 September 2020
		WO 2013175205 A1	28 November 2013
		ZA 201408253 B	23 December 2015
WO 2017075056 A1	04 May 2017	WO 2017075056 A1	04 May 2017
		AR 106472 A1	17 January 2018
		AU 2016344392 A1	10 May 2018
		BR 112018008227 A2	23 October 2018
		CA 3003275 A1	04 May 2017
		CN 108368125 A	03 August 2018
		EA 201890749 A1	30 November 2018
		EP 3368540 A1	05 September 2018
		IL 258636 D0	28 June 2018
		JP 2018538246 A	27 December 2018
		KR 20180067603 A	20 June 2018
		MX 2018005292 A	01 August 2018
		SG 11201802989Q A	30 May 2018
		US 2017145028 A1	25 May 2017
		US 10179793 B2	15 January 2019
		US 2019330224 A1	31 October 2019