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Preparation of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo(1,5-A)pyrimidin-3-y l)-3-hydroxypyrrolidine-1-carboxamide

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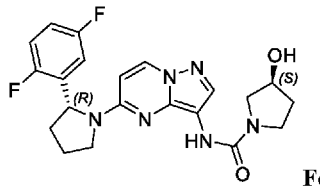
(54) Title: PREPARATION OF (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-Y L)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE



Formula I

(57) Abstract: Process for preparing (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l- yl)pyrazolo[l,5-a] pyrimidin-3-yl)-3-hydroxypyrrolidine-l-carboxamide (formula I) or a salt thereof by reacting phenyl(5-((R)-2-(2,5- difluorophenyl)pyrrolidin-l-yl)-3,3a-dihydropyrazolo[l,5-a]pyrimidin-3- yl)carbamate or a similar derivative (formula 13) with (S)-pyrrolidin-3- ol (formula 14). Process for preparing phenyl(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-l- yl)-3,3a-dihydropyrazolo[l,5-a]pyrimidin-3-yl)carbamate (formula 13) or a similar derivative by reduction of (R)-5-(2-(2,5-difluorophenyl) pyrrolidin-l-yl)-3-nitropyrazolo[l,5-a]pyrimidine (formula 11) to (R) -5-(2-(2,5-difluorophenyl)pyrrolidin-l-yl)pyrazolo[l,5-a]pyrimidin-3- amine (formula 12). Process for preparing (R)-2-(2,5-difluorophenyl)pyrrolidine(R) -2-hydroxysuccinate (formula 10) by treating (R)-N-((R)-l-(2,5- difluorophenyl)-3-(l,3-dioxan-2-yl)propyl)-2-methylpropane-2- sulfinamide (formula 19) with an acid and a reducing agent. (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-l-yl)-pyrazolo[l,5- a]pyrimidin-3-yl)-3-hydroxypyrrolidine-l-carboxamide, is a tyrosin kinase (TRK) inhibitor for trearing e.g. cancer.

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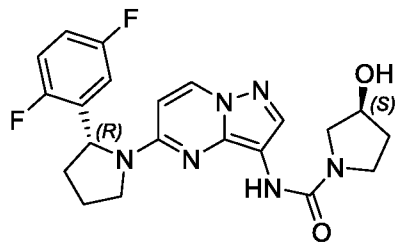
PROCESS FOR THE PREPARATION OF (*S*)-N-(5-((*R*)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)-PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE AND SALTS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/338,359, filed May 18, 2016, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

Provided herein are processes and intermediates useful for the preparation of a compound of Formula I

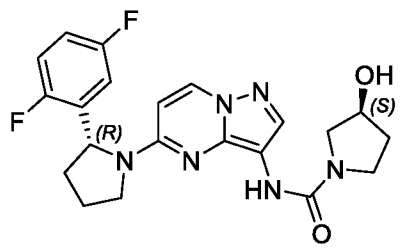


Formula I

or a salt thereof.

BACKGROUND OF THE INVENTION

The compound of Formula I



Formula I,

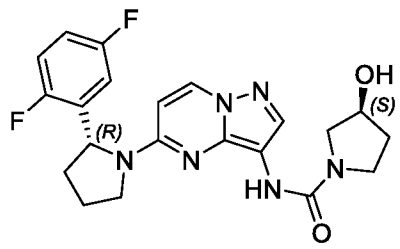
(S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, is a TRK kinase inhibitor. The compound of Formula I may be prepared as disclosed in WO 2010/048314, incorporated by reference herein in its entirety. WO 2010/048314 discloses in Example 14A a hydrogen sulfate salt of the

compound of Formula I. The compound may also be prepared as disclosed in US Application Ser. No. 14/943,014, filed November 16, 2015, incorporated by reference herein in its entirety.

There exists a need for alternative synthetic procedures for the preparation of the compound of Formula I. Such alternative synthetic procedures are disclosed herein.

SUMMARY OF THE INVENTION

In some embodiments, provided herein is a process for preparing a compound of Formula I

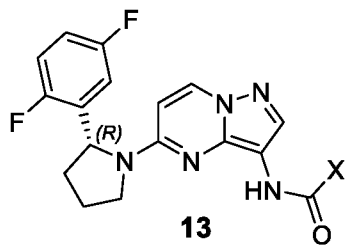


Formula I

or a salt thereof,

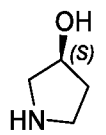
comprising:

(a) treating a compound of formula **13**



13

or a salt thereof with a compound of formula **14**



14

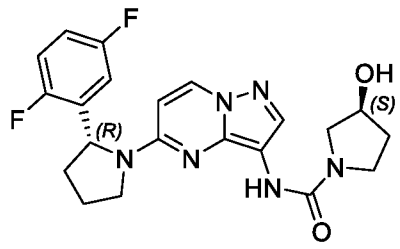
or a salt thereof to form a compound of Formula I;

and

(b) optionally forming a salt of the compound of Formula I;

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl.

In some embodiments, provided herein is a process for preparing a compound of Formula I

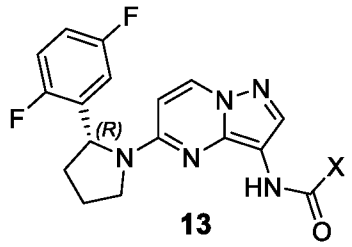


Formula I

or a salt thereof,

comprising:

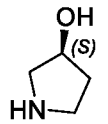
(a) isolating a compound of formula **13**



13 ;

(b) optionally forming a salt of formula **13**;

(c) treating the compound of formula **13** or a salt thereof with a compound of formula **14**



14

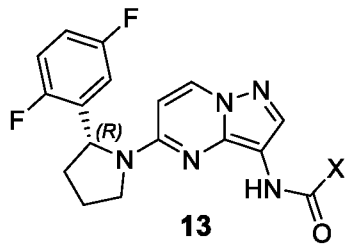
or a salt thereof to form a compound of Formula I;

and

(d) optionally forming a salt of the compound of Formula I;

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl.

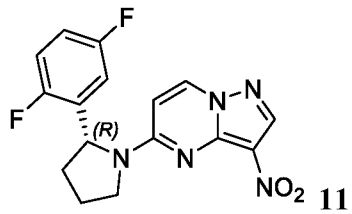
In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **13**



13

or a salt thereof by a process comprising

(a) treating a compound of formula **11**



11

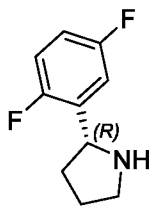
or a salt thereof with a nitro reduction system to form a first mixture; and

(b) treating the first mixture with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group

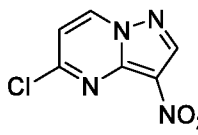
consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl; provided that if Z is optionally substituted C_1-C_6 alkoxy, optionally substituted C_6-C_{10} aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **11** or a salt thereof by a process comprising treating a compound of formula **10**



10

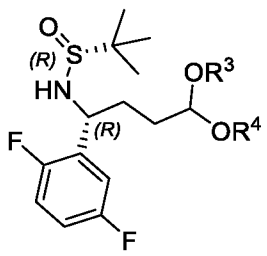
or a salt thereof, with a compound of formula **5**



5

or a salt thereof, to form the compound of formula **11** or salt thereof.

In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **10** or a salt thereof by a process comprising treating a compound of formula **19**



19

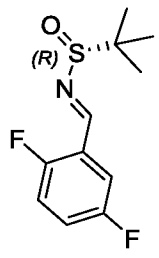
or a salt thereof, with an acid in the presence of a first reducing agent, to form a compound of formula **10** or a salt thereof,

wherein each of R^3 and R^4 is independently C_1-C_4 alkyl;

or R^3 and R^4 taken together with the atoms connecting them form a five- to seven-membered ring.

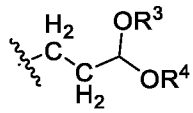
In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **19** or a salt thereof by a process comprising treating

a compound of formula **17**



17

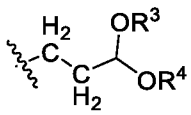
with a reagent system comprising the group



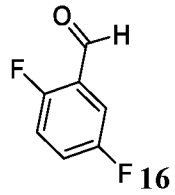
to form a compound of formula **19,**

wherein each of R^3 and R^4 is independently C_1-C_4 alkyl;

or R^3 and R^4 taken together with the atoms connecting them form a five- to seven-membered ring.

In some embodiments, the reagent system comprising  comprises a metal or compound of a metal. In some embodiments, the metal or the compound of a metal is capable of acting as an electron transfer agent.

In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **17** or a salt thereof by a process comprising treating a compound of formula **16**



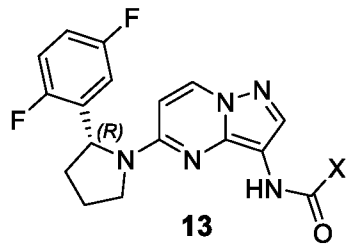
16

with (R)-2-methylpropane-2-sulfinamide,

to form a compound of formula **17**.

In some embodiments, provided herein is a process for preparing a pharmaceutical composition, comprising mixing (i) a compound of **Formula I** or salt thereof prepared according to any of the processes described herein, and (ii) a pharmaceutically acceptable carrier, to form the composition.

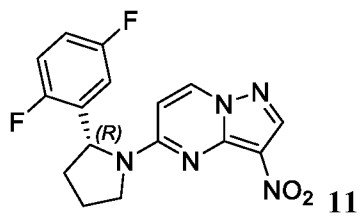
In some embodiments, provided herein is a process for preparing a compound of formula **13**



13

or a salt thereof by a process comprising

a) treating a compound of formula **11**



11

or a salt thereof with a nitro reduction system to form a first mixture; and

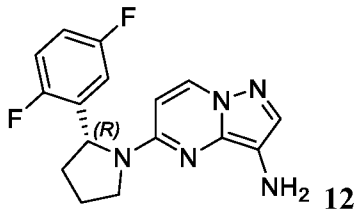
b) treating the first mixture with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl; and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z**,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl;

provided that if Z is optionally substituted C_1-C_6 alkoxy, optionally substituted C_6-C_{10} aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

In some embodiments, provided herein is a process for preparing a compound of formula **13** or a salt thereof comprising

a) isolating a compound of formula **12**



12

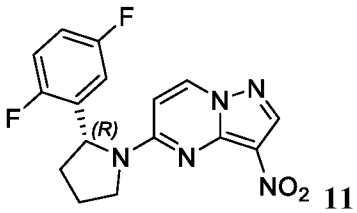
or a salt thereof;

b) treating a compound of formula **12** with XC(O)Z to form a compound of formula **13** or a salt thereof; and

c) optionally isolating the compound of formula **13**.

In some embodiments, provided herein is a process for preparing a compound of formula **12** or a salt thereof comprising

a) treating a compound of formula **11**

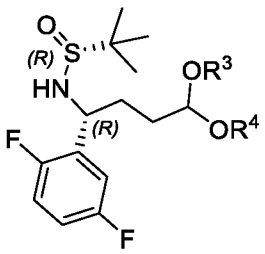


11

with a nitro reduction system to form the compound of formula **12** or a salt thereof; and

b) isolating the compound of formula **12** or a salt thereof.

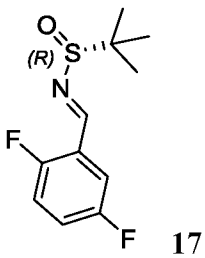
In some embodiments, provided herein is a process for preparing a compound of formula **10** or a salt thereof, comprising treating a compound of formula **19**



19

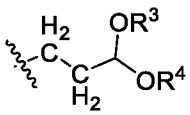
or a salt thereof, with an acid in the presence of a first reducing agent, to form a compound of formula **10** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **19** or a salt thereof, comprising treating a compound of formula **17**



17

with a reagent system comprising the group



to form a compound of formula **19**.

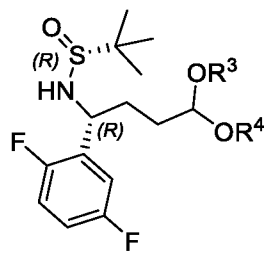
In some embodiments, provided herein is a process for preparing a compound of formula **17** or a salt thereof**,** comprising treating a compound of formula **16**

16

with (R)-2-methylpropane-2-sulfinamide

to form a compound of formula **17**.

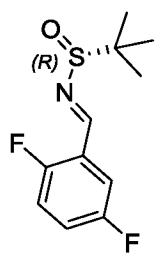
In some embodiments, provided herein is a compound of formula **19:**



19

or a salt thereof.

In some embodiments, provided herein is a compound of formula **17:**



or a salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

A "nitro reduction system" is any substance or plurality of substances capable of converting a NO_2 group to an NH_2 group. Nitro reduction systems may include, for example, heterogeneous systems, homogeneous systems, catalytic systems, and non-catalytic systems. Examples of nitro reduction systems include systems comprising a metal or a compound of a metal, such as a salt of the metal or an oxide of the metal. Examples of such metals include palladium, platinum, rhodium, ruthenium, nickel, copper, iron, tin, and zinc. Examples of nitro reduction systems include systems comprising an acid. Such systems comprising an acid can also comprise a metal or a compound of a metal such as are disclosed herein. Examples of nitro reduction systems include systems comprising H_2. Examples of nitro reduction systems include metal hydrides, which can be, for example, mixed metal hydrides. Examples of such metal hydrides include $LiAlH_4$, $NaBH_4$, diisobutylaluminium hydride (DIBAL), and the like. Examples of nitro reduction systems include systems comprising an organic compound capable of providing hydrogen. An example of such an organic compound capable of providing hydrogen is cyclohexene.

More particular examples of nitro reduction systems are systems comprising Pd, Pd/C, Raney nickel, PtO_2, Fe/acid, Zn/acid.

The terms "hydrogen" and "H" are used interchangeably herein.

The term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_{1-6} indicates that the group may have from 1 to 6 (inclusive) carbon atoms in it. Examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

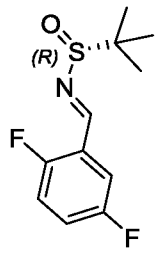
The term "alkoxy" refers to an -O-alkyl radical (e.g., $-OCH_3$).

The term "aryl" as used herein includes an aromatic monocyclic or bicyclic hydrocarbon radical having 6 to 10 carbons. Examples of aryl include phenyl and naphthyl.

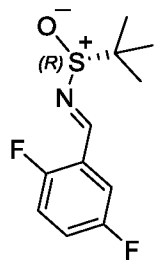
The term "heteroaryl" refers to an aromatic radical having 1-4 heteroatoms. Examples of heteroatoms are N, O, and S. Examples of heteroaryl include pyridyl, pyrimidinyl, furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, and the like.

A salt can form from a compound in any manner familiar to the skilled artisan. Accordingly, the recitation "to form a compound or salt thereof" includes embodiments where a compound is formed and the salt is subsequently formed from the compound in a manner familiar to the killed artisan.

The compounds disclosed herein include compounds having a sulfoxide group, as shown, by way of example, in the structure of compound **17**, below:



. The sulfur-oxygen bond may also be rendered pictorially as being in ionic form. Thus, for example, compound **17** may also be rendered as shown the structure below:



. It is intended throughout this disclosure that the recitation of a given structure for a compound having a sulfoxide group encompasses all representations of the compound, whether the sulfur-oxygen bond is rendered as being an ionic bond, a covalent bond, a dative bond, or in any form that may be envisioned by the skilled artisan.

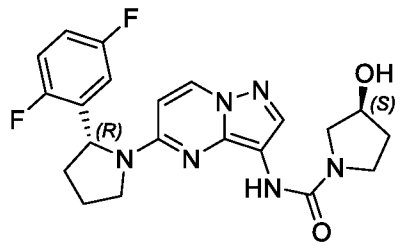
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

All combinations of the embodiments pertaining to the aspects described herein are specifically embraced by the present invention just as if each and every combination was

individually explicitly recited, to the extent that such combinations embrace possible aspects. In addition, all subcombinations of the embodiments contained within the aspects described herein, as well as all subcombinations of the embodiments contained within all other aspects described herein, are also specifically embraced by the present invention just as if each and every subcombination of all embodiments are explicitly recited herein.

Examples of embodiments

In some embodiments, provided herein is a process for preparing a compound of Formula I

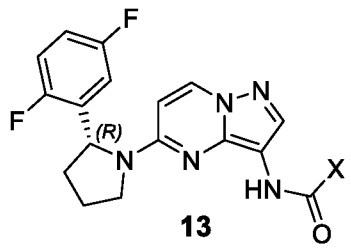


Formula I

or a salt thereof,

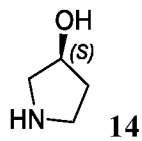
comprising:

(a) treating a compound of formula **13**



13

or a salt thereof with a compound of formula **14**



14

or a salt thereof to form a compound of Formula I;

and

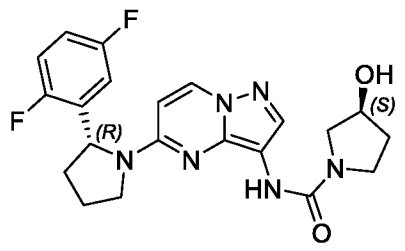
(b) optionally forming a salt of the compound of Formula I;

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl.

In some embodiments, X is halogen. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is C_1-C_6 alkoxy. In some embodiments, X is C_6-C_{10} aryloxy. In some embodiments, X is phenoxy. In some embodiments, X is a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13. In some embodiments, X is imidazolyl.

In some embodiments, the compound of formula **13** or salt thereof is in isolated form prior to the treatment with the compound of formula **14** or salt thereof.

In some embodiments, provided herein is a process for preparing a compound of Formula I

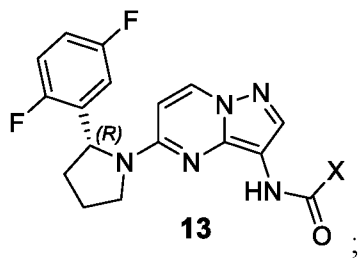


Formula I

or a salt thereof,

comprising:

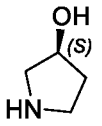
(a) isolating a compound of formula **13**



13 ;

(b) optionally forming a salt of formula **13**;

(c) treating the compound of formula **13** or a salt thereof with a compound of formula **14**



14

or a salt thereof to form a compound of Formula I;

and

(d) optionally forming a salt of the compound of Formula I;

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl.

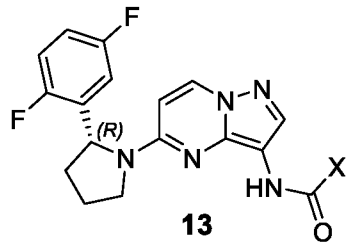
In some embodiments, X is halogen. In some embodiments, X is Cl. In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is C_1-C_6 alkoxy. In some embodiments, X is C_6-C_{10} aryloxy. In some embodiments, X is phenoxy. In some embodiments, X is a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13. In some embodiments, X is imidazolyl.

In some embodiments, the salt of the compound of formula I is the hydrogen sulfate salt.

In some embodiments, forming a salt of the compound of formula I comprises treating the compound of formula I with an acid to form the salt.

In some embodiments, forming a salt of the compound of formula I comprises treating a salt of the compound of formula I with an acid to form a different salt via anion exchange.

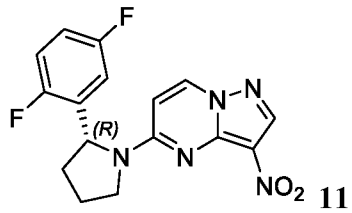
In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **13**



13

or a salt thereof by a process comprising

(a) treating a compound of formula **11**



11

or a salt thereof with a nitro reduction system to form a first mixture; and

(b) treating the first mixture with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group

consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6,

where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl;

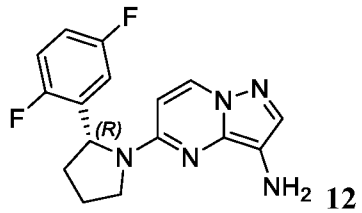
provided that if Z is optionally substituted C_1-C_6 alkoxy, optionally substituted C_6-C_{10} aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

In some embodiments, preparing the compound of formula **13** comprises:

forming the compound of formula **13** in a second mixture; and

isolating the compound of formula **13** from the second mixture.

In some embodiments, the first mixture comprises a compound of formula **12**



12

or a salt thereof, and the processes comprises isolating the compound of formula **12** or a salt thereof from the first mixture prior to treating with XC(O)Z.

In some embodiments, the salt of the compound of formula **12** is the fumarate salt.

In some embodiments, Z is halogen.

In some embodiments, Z is chlorine.

In some embodiments, Z is bromine.

In some embodiments, Z is imidazolyl.

In some embodiments, the nitro reduction system with which compound **11** is treated is a heterogeneous system.

In some embodiments, the nitro reduction system is a homogeneous system.

In some embodiments, the nitro reduction system is a catalytic system.

In some embodiments, the nitro reduction system is a non-catalytic systems.

In some embodiments, the nitro reduction system comprises a metal or a compound of a metal, such as a salt of the metal or an oxide of the metal.

In some embodiments, the nitro reduction system comprises palladium, platinum, rhodium, ruthenium, nickel, copper, iron, tin, or zinc.

In some embodiments, the nitro reduction system comprises an acid. In some embodiments, the nitro reduction system comprising an acid comprises a metal or a compound of a metal.

In some embodiments, the nitro reduction system comprises H_2.

In some embodiments, the nitro reduction system comprises a metal hydride. In some embodiments, the nitro reduction system comprises a mixed metal hydride. In some embodiments, the mixed metal hydride is $LiAlH_4$, $NaBH_4$, or diisobutylaluminium hydride (DIBAL).

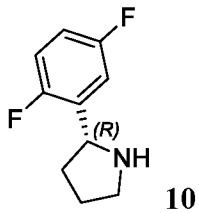
In some embodiments, the nitro reduction system comprises an organic compound capable of providing hydrogen. In some embodiments, the organic compound capable of providing hydrogen is cyclohexene.

In some embodiments, the nitro reduction system comprises Pd, Pd/C, Raney nickel, PtO_2, Fe/acid, or Zn/acid.

In some embodiments, the nitro reduction system comprises Pd.

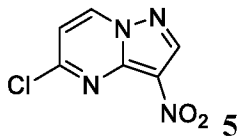
In some embodiments, the nitro reduction system comprises Pd/C.

In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **11** or a salt thereof by a process comprising treating a compound of formula **10**



10

or a salt thereof, with a compound of formula **5**

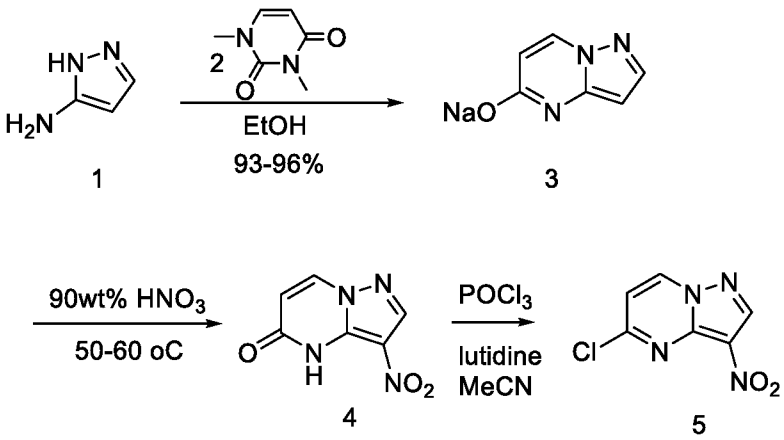


5

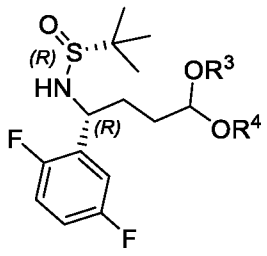
or a salt thereof, to form the compound of formula **11** or salt thereof.

In some embodiments, the salt of the compound of formula **10** is a malate salt. In some embodiments, the salt of the compound of formula **10** is the D-malate salt.

The compound of formula **5** is disclosed in US Application Ser. No. 14/943,014, filed November 16, 2015, incorporated by reference herein in its entirety. The compound of formula **5** may be prepared as follows:



In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **10** or a salt thereof by a process comprising treating a compound of formula **19**

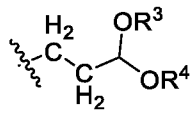


19

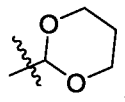
or a salt thereof, with an acid in the presence of a first reducing agent, to form a compound of formula **10** or a salt thereof.

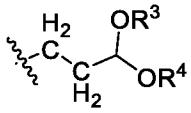
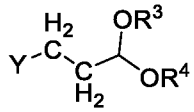
In some embodiments, the first reducing agent is a silane. In some embodiments, the first reducing agent is triethylsilane.

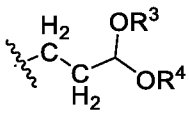
In some embodiments, each of R^3 and R^4 in the reagent system comprising the group

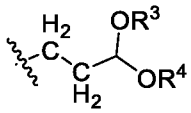


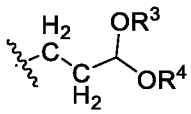
is the same. In some embodiments, each of R^3 and R^4 in **19** is the same. In some embodiments, each of R^3 and R^4 is methyl. In some embodiments, each of R^3 and R^4 is ethyl. In some embodiments, each of R^3 and R^4 is n-propyl. In some embodiments, each of R^3 and R^4 is i-propyl. In some embodiments, R^3 and R^4 taken together with the atoms connecting them form a five-membered ring. In some embodiments, R^3 and R^4 taken together with the atoms connecting them form a six-membered ring. In some embodiments,

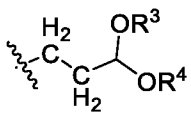
R^3 and R^4 taken together with the atoms connecting them form a seven-membered ring. In some embodiments, R^3 and R^4 taken together with the atoms connecting them form the ring  .

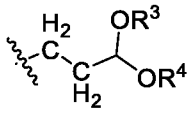
In some embodiments, the reagent system comprising  comprises (i)  , wherein Y is halogen, and (ii) a second reducing agent. In some embodiments, the second reducing agent is samarium iodide. In some embodiments, Y is Cl. In some embodiments, Y is Br. In some embodiments, Y is I.

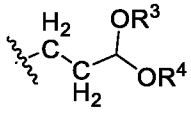
In some embodiments, the reagent system comprising  comprises a metal or compound of a metal. In some embodiments, the metal or the compound of a metal is capable of acting as an electron transfer agent.

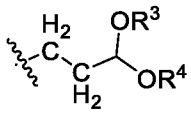
In some embodiments, the reagent system comprising  comprises Zn.

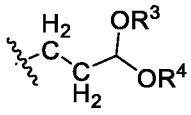
In some embodiments, the reagent system comprising  comprises Sn.

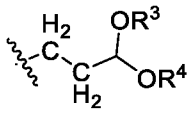
In some embodiments, the reagent system comprising  comprises Fe.

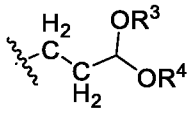
In some embodiments, the reagent system comprising  comprises Ge.

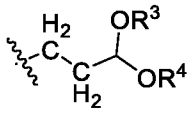
In some embodiments, the reagent system comprising  comprises Cu.

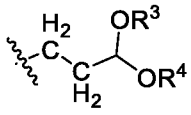
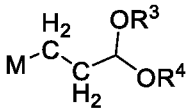
In some embodiments, the reagent system comprising  comprises a salt of Zn.

In some embodiments, the reagent system comprising  comprises a salt of Sn.

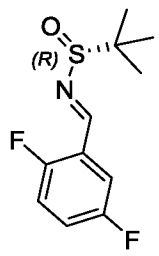
In some embodiments, the reagent system comprising  comprises a salt of Fe.

In some embodiments, the reagent system comprising  comprises a salt of Ge.

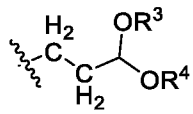
In some embodiments, the reagent system comprising  comprises a salt of Cu.

In some embodiments, the reagent system comprising  comprises  , wherein M is either (i) M^1, wherein M^1 is a monovalent metal, or (ii) M^2Y, wherein Y is halogen and M^2 is a divalent metal. In some embodiments, M^1 is lithium. In some embodiments, M^2 is magnesium. In some embodiments, M^2 is Zn. In some embodiments, M^2 is Fe. In some embodiments, M^2 is Cu. In some embodiments, M^2 is Sn. In some embodiments, M^2 is Sm. In some embodiments, M^2 is Ge. In some embodiments, Y is halogen. In some embodiments, Y is Cl. In some embodiments, Y is Br. In some embodiments, Y is I.

In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **19** or a salt thereof by a process comprising treating a compound of formula **17**

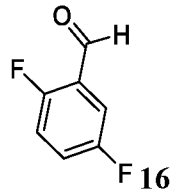
 **17**

with a reagent system comprising the group



to form a compound of formula **19**.

In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **17** or a salt thereof by a process comprising treating a compound of formula **16**



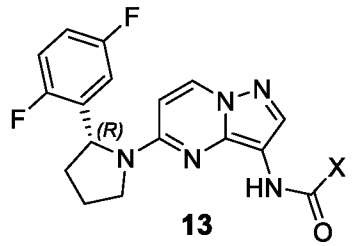
16

with (R)-2-methylpropane-2-sulfinamide,

to form a compound of formula **17**.

In some embodiments, treating a compound of formula **16** with (R)-2-methylpropane-2-sulfinamide is performed in the presence of a base.

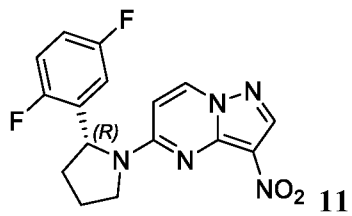
In some embodiments, provided herein is a process for preparing a compound of formula **13**



13

or a salt thereof by a process comprising

a) treating a compound of formula **11**



11

or a salt thereof with a nitro reduction system to form a first mixture; and

b) treating the first mixture with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13,** each optionally substituted with one or more substituents independently selected from the group

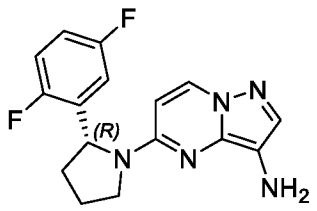
consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl; and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group

consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl;

provided that if Z is optionally substituted C_1-C_6 alkoxy, optionally substituted C_6-C_{10} aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

In some embodiments, provided herein is a process for preparing a compound of formula **13** or a salt thereof comprising

(a) isolating a compound of formula **12**



12;

(b) treating a compound of formula **12** with XC(O)Z to form a compound of formula **13** or a salt thereof; and

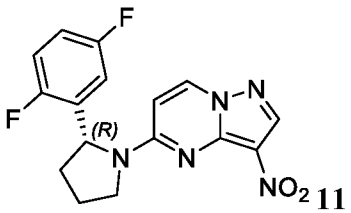
(c) optionally isolating the compound of formula **13**,

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl; and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group

consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl; provided that if Z is optionally substituted C_1-C_6 alkoxy, optionally substituted C_6-C_{10} aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

In some embodiments, provided herein is a process for preparing a compound of formula **12** or a salt thereof comprising

a) treating a compound of formula **11**



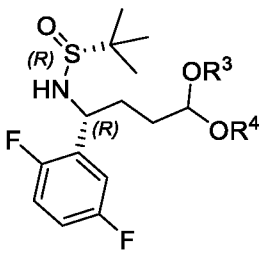
11

with a nitro reduction system to form the compound of formula **12** or a salt thereof; and

b) isolating the compound of formula **12** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **10** or a salt thereof by a process comprising

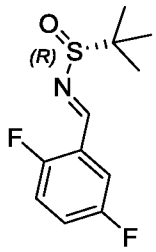
treating a compound of formula **19**



19

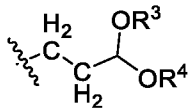
or a salt thereof, with an acid in the presence of a first reducing agent, to form a compound of formula **10** or a salt thereof

In some embodiments, provided herein is a process for preparing a compound of formula **19** or a salt thereof by a process comprising treating a compound of formula **17**



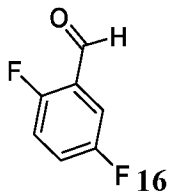
17

with a reagent system comprising the group



to form a compound of formula **19**.

In some embodiments, provided herein is a process for preparing a compound of formula **17** or a salt thereof by a process comprising treating a compound of formula **16**

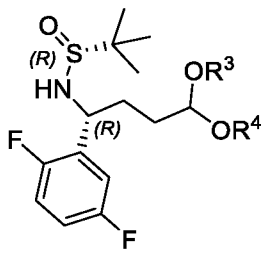


16

with (R)-2-methylpropane-2-sulfinamide,

to form a compound of formula **17**.

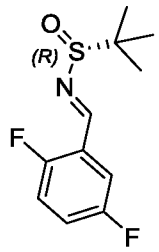
In some embodiments, provided herein is a compound of formula **19:**



19

or a salt thereof.

In some embodiments, provided herein is a compound of formula **17:**



17

or a salt thereof.

In some embodiments, provided herein is a process for preparing a pharmaceutical composition comprising mixing (i) a compound of Formula I or salt thereof prepared according to any of the processes described herein, and (ii) a pharmaceutically acceptable carrier. Pharmaceutical compositions containing the compound of Formula I or a salt thereof as the active ingredient can be prepared by intimately mixing the compound of Formula I or a salt thereof with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations may also be coated with substances such as sugars or be enteric-coated so as to modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

The compound of Formula I or a salt thereof may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature, or transdermally or dermally. The compound of Formula I or a salt thereof may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a

solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

Also provided herein are pharmaceutical compositions comprising a compound of Formula I or salt thereof. To prepare the pharmaceutical compositions provided herein, the compound of Formula I or a salt thereof as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, glycerols, oils, cyclodextrins, alcohols, e.g., ethanol, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, suspension, solution, sachet for reconstitution, powder, injection, I.V., suppository, sublingual/buccal film, teaspoonful and the like, of from about 0.1-1000 mg or any range therein, and may be given at a dosage of from about 0.01-300 mg/kg/day, or any range therein, preferably from about 0.5-50 mg/kg/day, or any range therein. In some embodiments, the pharmaceutical compositions provided herein contain, per unit dosage unit, about 25 mg to about 500 mg of a compound provided herein (for example, about 25 mg to about 400 mg, about 25 mg to about 300 mg, about 25 mg to about 250 mg, about 25 mg to about 200 mg, about 25 mg to about 150 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 50 mg to about 500 mg, about 100 mg to about 500 mg, about 150 mg to about 500 mg, about 200 mg to about 500 mg, about 250 mg to about 500 mg, about 300 mg to about 500 mg, about 400 mg to about 500 mg, about 50 to about 200 mg, about 100 to about 250 mg, about 50 to about 150 mg). In some embodiments, the pharmaceutical compositions provided herein contain, per unit dosage unit, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg of a compound provided herein. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. In some embodiments, the dosages are administered once daily (QD) or twice daily (BID).

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the compound of Formula I or a salt thereof is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid composition containing a compound of Formula I or salt thereof. When referring to

these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 1000 mg, or any amount or range thereof, of the active ingredient provided herein. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions provided herein may be incorporated for administration orally or by injection include, aqueous solutions, cyclodextrins, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compound of Formula I or a salt thereof can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

To prepare a pharmaceutical compositions provided herein, the compound of Formula I or a salt thereof as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques,

which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in *The Handbook of Pharmaceutical Excipients*, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating pharmaceutical compositions have been described in numerous publications such as *Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded,* Volumes 1-3, edited by Lieberman et al; *Pharmaceutical Dosage Forms: Parenteral Medications*, Volumes 1-2, edited by Avis et al; and *Pharmaceutical Dosage Forms: Disperse Systems*, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

Compounds provided herein may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of cancer, pain, inflammation, neurodegenerative disease or Trypanosoma cruzi infection is required.

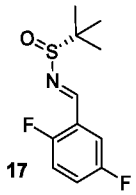
The daily dosage of the compound of Formula I or a salt thereof may be varied over a wide range from 1.0 to 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein. Preferably, the range is from about 0.5 to about 500 mg/kg of body weight per day, or any range therein. More preferably, from about 1.0 to about 250 mg/kg of body weight per day, or any range therein. More preferably, from about 0.1 to about 100 mg/kg of body weight per day, or any range therein. In an example, the range may be from about 0.1 to about 50.0 mg/kg of body weight per day, or any amount or range therein. In another example, the range may be from about 0.1 to about 15.0 mg/kg of body weight per day, or any range therein. In yet another example, the range may be from about 0.5 to about 7.5 mg/kg of body weight per day, or any amount to range therein. The compound of Formula I or a salt thereof may be administered on a regimen of 1 to 4 times per day or in a single daily dose.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

Examples

Preparation of **10:**

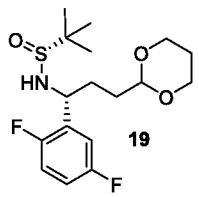
1)



17

(R,E)-N-(2,5-difluorobenzylidene)-2-methylpropane-2-sulfinamide (17): Compound **16** and (R)-2-methylpropane-2-sulfinamide (1.05 eq.) were charged to a reactor outfitted with a mechanical stirrer, reflux condensor, J-Kem temperature probe under N_2. DCM (3 mL/g of **14**) was added (endothermic from 22 °C to about 5 °C) followed by addition of cesium carbonate (0.70 eq.) (exothermic to ~50 °C). Once the addition was complete, the reaction mixture was stirred at room temperature for 3 h (slowly cools from about 40 °C). When the reaction was called complete (HPLC) the mixture was filtered through Celite. The Celite pad (0.3 wt eq) was equilibrated with DCM (1 mL/g of **16**), and the reaction mixture was poured through the pad. The Celite cake was washed with DCM (2 x 1 mL/g), and the filtrate concentrated partially to leave about 0.5 to 1 mL/g DCM remaining. The orange solution was stored at room temperature (generally overnight) and used directly in the next reaction. (100% yield was assumed).

2)

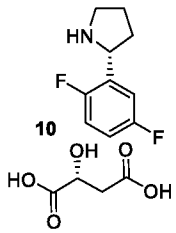


19

(R)-N-((R)-1-(2,5-difluorophenyl)-3-(1,3-dioxan-2-yl)propyl)-2-methylpropane-2-sulfinamide (19): To a reactor equipped with overhead stirring, reflux condensor, under

nitrogen, was added magnesium turnings (2.0 eq), and THF (8 mL/g of **17**). The mixture was heated to 40 °C. Dibal-H (25% wt in toluene, 0.004 eq) was added to the solution, and the suspension heated at 40 °C for 25 minutes. A solution of 2-(2-bromoethyl)-1,3-dioxane (**18**) (2 eq) in THF (4.6 mL/g of **17**) was added dropwise to the Mg solution via addition funnel. The solution temperature was maintained ≤ 55 °C. The reaction progress was monitored by GC. When the Grignard formation was judged complete, the solution was cooled to -30 °C, and **17** (1.0 eq, in DCM) was added dropwise via addition funnel. The temperature was kept between -30 °C and -20 °C and the reaction was monitored for completion (HPLC). Once the reaction was called complete, the suspension (IT = -27.7 °C) was vacuum transferred to a prepared and cooled (10 °C) 10% aqueous citric acid solution (11 mL/g of **17**). The mixture temperature rose to 20 °C during transfer. The milky solution was allowed to stir at ambient temperature overnight. MTBE (5.8 mL/g) was added to the mixture, and it was transferred to a separatory funnel. The layers were allowed to separate, and the lower aqueous layer was removed. The organic layer was washed with sat. NaHCO3 (11 mL/g) and then sat. NaCl (5.4 mL/g). The organic layer was removed and concentrated to minimum volume via vacuum distillation. MTBE (2 mL/g) was added, and the mixture again concentrated to minimum volume. Finally MTBE was added to give 2 mL/g total MTBE (GC ratio of MTBE:THF was about 9:1), and the MTBE mixture was heated to 50 °C until full dissolution occurred. The MTBE solution was allowed to cool to about 35 °C, and heptane was added portion-wise. The first portion (2 mL/g) is added, and the mixture allowed to stir and form a solid for 1-2 h, and then the remainder of the heptane is added (8 mL/g). The suspension was allowed to stir for >1h. The solids were collected via filtration through polypropylene filter cloth (PPFC) and washed with 10% MTBE in heptane (4 mL/g. The wet solid was placed in trays and dried in a vacuum oven at 55 °C until constant weight (3101 g, 80.5%, dense white solid, 100a% and 100wt%).

3)

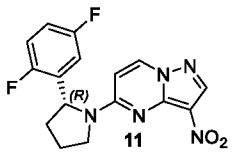


(R)-2-(2,5-difluorophenyl)pyrrolidine (R)-2-hydroxysuccinate (10): To a flask containing 4:1 TFA:water (2.5 mL/g, pre-mixed and cooled to <35 °C before adding **19**) was added (R)-N-((R)-1-(2,5-difluorophenyl)-3-(1,3-dioxan-2-yl)propyl)-2-methylpropane-2-sulfinamide **(19)** (1 eq). The mixture temperature rose from 34 °C to 48 °C and was stirred at ambient temperature for 1 h. Additional TFA (7.5 mL/g) was added, followed by triethylsilane (3 eq) over 5 minutes. The biphasic mixture was stirred vigorously under nitrogen for 21 h until judged complete (by GC, <5% of imine). The mixture was then concentrated under vacuum until ~10 kg target mass (observed 10.8 kg after concentration). The resulting concentrate was transferred to a separatory funnel and diluted with MTBE (7.5 mL/g), followed by water (7.5 mL/g). The layers were separated. The MTBE layer was back-extracted with 1M HCl (3 mL/g). The layers were separated, and the aqueous layers were combined in a round-bottomed flask with DCM (8 mL/g). The mixture was cooled in an ice bath and 40% NaOH was charged to adjust the pH to ≥12 (about 0.5 mL/g; the temperature went from 24 °C to 27 °C, actual pH was 13), and the layers separated in the separatory funnel. The aqueous layer was back-extracted twice with DCM (2 x 4 mL/g). The organic layers were concentrated to an oil (<0.5 mL/g) under vacuum (rotovap) and EtOH (1 mL/g based on product) was added. The yellow solution was again concentrated to an oil (81% corrected yield, with 3% EtOH, 0.2% imine and Chiral HPLC showed 99.7%ee).

Salt formation: To a solution of (R)-2-(2,5-difluorophenyl)pyrrolidine **10** (1 eq) in EtOH (15 mL/g) was added *D*-(+)-Malic Acid (1 eq). The suspension was heated to 70 °C for 30 minutes (full dissolution had occurred before 70 °C was reached), and then allowed to cool to room temperature slowly (mixture was seeded when the temperature was < 40 °C). The slurry was stirred at room temperature overnight, then cooled to <5 °C the next morning. The suspension was stirred at <5 °C for 2h, filtered (PPFC), washed with cold EtOH (2 x 2 mL/g), and dried (50-55 °C) under vacuum to give the product as a white solid (96% based on 91% potency, product is an EtOH solvate or hemi-solvate).

Preparation of the compound of Formula I:

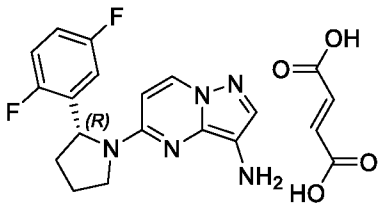
1)



11

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-nitropyrazolo[1,5-a]pyrimidine (11): Compound **5** and **10** (1.05 eq) were charged to a reactor outfitted with a mechanical stirrer, J-Kem temperature probe, under N_2. EtOH and THF (4:1, 10 mL/g of **5**) were added and the mixture was cooled to 15-25 °C. Triethylamine (3.5 eq) was added and the internal temp generally rose from 17.3 - 37.8 °C. The reaction was heated to 50 - 60 °C and held at that temperature for 7 h. Once the reaction is judged complete (HPLC), water (12 mL/g of 5) is added maintaining the temperature at 50 - 60 °C. The heat is removed and the suspension was slowly cooled to 21 °C over two h. After stirring at ~21 °C for 2 h, the suspension was centrifuged and the cake was washed with water (3 x 3 mL/g of **5**). The solid was transferred to drying trays and placed in a vacuum oven at 50 - 55 °C to give **11**.

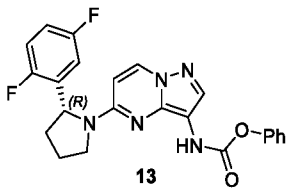
2)



(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine fumarate Pt/C hydrogenation (12 fumarate): To a Parr reactor was charged **11** (1.0 eq), 5% Pt/C ~ 50 wt% water (2 mol% Pt / Johnson Matthey B103018-5 or Sigma Aldrich 33015-9), and MeOH (8 mL/g). The suspension was stirred under hydrogen at 25-30 psi and the temperature was maintained below 65 °C for ~8 h. When the reaction was called complete (HPLC), the reaction was cooled to 15 – 25 °C and the hydrogen atmosphere was replaced with a nitrogen atmosphere. The reaction mixture was filtered through a 2 micron bag filter and a 0.2 micron line filter in series. The filtrate from the Pt/C hydrogenation was transferred to a reactor under nitrogen with mechanical stirring and then MTBE (8 mL/g) and fumaric acid (1.01 eq) were charged. The mixture was stirred under nitrogen for 1 h and solids formed after ~15 min. The mixture was cooled to -10 to -20 °C and stirred for 3 h. The suspension

was filtered (PPFC), washed with MTBE (~2.5 mL/g), and the solids was dried under vacuum at 20-25 °C with a nitrogen bleed to yield an off-white solid (83% yield).

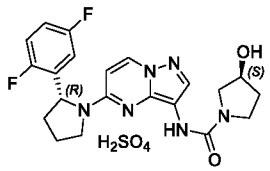
3)



13

Phenyl (5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3,3a-dihydropyrazolo[1,5-a]pyrimidin-3-yl)carbamate (13): To a 5 to 15°C solution of **12-fumarate** (1.0 eq) in 2-MeTHF (15 mL/g) was added a solution of potassium carbonate (2.0 eq.) in water (5 mL/g) followed by phenyl chloroformate (1.22 eq.) (over 22 min, an exotherm from 7 °C to 11 °C occurred). The mixture was stirred for 2 h and then the reaction was called complete (HPLC). The stirring ceased and the aqueous layer was removed. The organic layer was washed with brine (5 mL/g) and concentrated to ca. 5 mL/g of 2-MeTHF under vacuum and with heating to 40 °C. To the 2-MeTHF solution was added heptanes (2.5 mL/g) followed by seeds (20 mg, 0.1 wt%). This mixture was allowed to stir at room temperature for 2 h (until a solid formed), and then the remainder of the heptanes (12.5 mL/g) was added. The mixture was stirred at ambient temperature for 2 h and then the solids were collected via filtration (PPFC), washed with 4:1 heptanes:MeTHF (2 x 2 mL/g), and dried to give **13** (96%).

4)



(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate: To a flask containing **13** (1.0 eq) was added a solution of (S)-pyrrolidin-3-ol (1.1 eq.) in EtOH (10 mL/g). The mixture was heated at 50 - 60 °C for 5 h, called complete (HPLC), and then cooled to 20-35 °C. Once <35°C, the reaction was polish-filtered (0.2 micron) into a clean reaction vessel and the mixture was cooled to -5 to 5 °C. Sulfuric acid (1.0 eq.) was added over 40 minutes, the temperature rose to 2 °C and the mixture was seeded. A solid formed, and the mixture was allowed to stir at -5 to 5 °C for 6.5 h. Heptanes (10 mL/g) was added, and the mixture stirred for 6.5 h. The

suspension was filtered (PPFC), washed with 1:1 EtOH:heptanes (2 x 2 mL/g), and dried (under vacuum at ambient temperature) to give **Formula I** (92.3%).

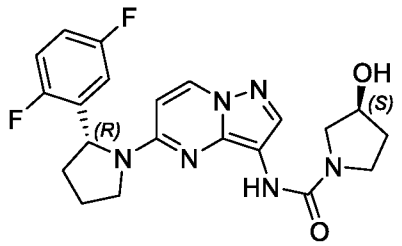
Preparation of the hydrogen sulfate salt of the compound of Formula I:

Concentrated sulfuric acid (392 mL) was added to a solution of 3031 g of (*S*)-N-(5-((*R*)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide in 18322 mL EtOH to form the hydrogen sulfate salt. The solution was seeded with 2 g of (*S*)-N-(5-((*R*)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate and the solution was stirred at room temperature for at least 2 hours to form a slurry of the hydrogen sulfate salt. Heptane (20888 g) was added and the slurry was stirred at room temperature for at least 60 min. The slurry was filtered and the filter cake was washed with 1:1 heptane/EtOH. The solids were then dried under vacuum at ambient temperature (oven temperature set at 15° Celsius).

The dried hydrogen sulfate salt (6389 g from 4 combined lots) was added to a 5:95 w/w solution of water/2-butanone (total weight 41652 g). The mixture was heated at about 68° Celsius with stirring until the weight percent of ethanol was about 0.5%, during which time a slurry formed. The slurry was filtered, and the filter cake was washed with a 5:95 w/w solution of water/2-butanone. The solids were then dried under vacuum at ambient temperature (oven temperature set at 15° Celsius) to provide the crystalline form of (*S*)-N-(5-((*R*)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate.

Definitions of specific embodiments of the invention as claimed herein follow.

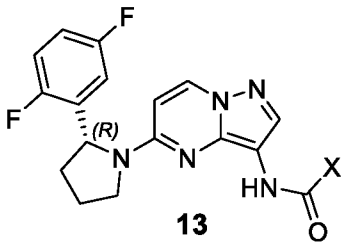
According to a first embodiment of the invention, there is provided a process for preparing a compound of Formula I



Formula I

or a salt thereof, comprising:

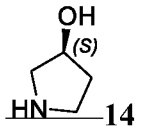
(a) providing an isolated compound of formula **13**



13

or salt thereof; wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl;

(b) treating the compound of formula **13** or a salt thereof with a compound of formula **14**



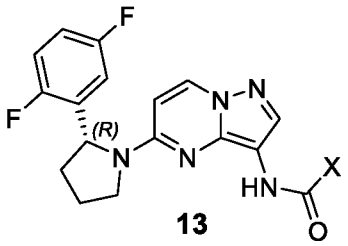
14

or a salt thereof to form a compound of Formula I; and

(c) optionally forming a salt of the compound of Formula I.

According to a second embodiment of the invention, there is provided a process for preparing a pharmaceutical composition, comprising mixing (i) a compound of **Formula I** or salt thereof prepared according to the process of the first embodiment and (ii) a pharmaceutically acceptable carrier, to form the pharmaceutical composition.

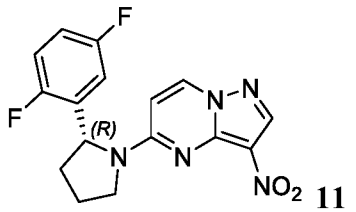
According to a third embodiment of the invention, there is provided a process for preparing a compound of formula **13**



13

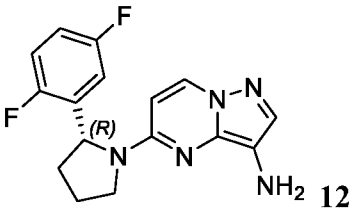
or a salt thereof by a process comprising

a) treating a compound of formula **11**



11

or a salt thereof with a nitro reduction system to form a compound of Formula **12:**



12

or a salt thereof,

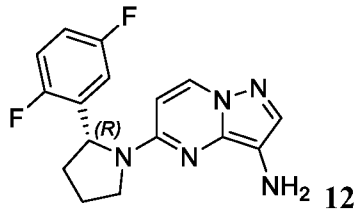
b) treating the compound of Formula 12 with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13**,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl, and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z**,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl; and

c) isolating the compound of Formula **13**.

According to a fourth embodiment of the invention, there is provided a process for preparing a compound of formula **13** or a salt thereof comprising

a) providing a compound of formula **12**



12

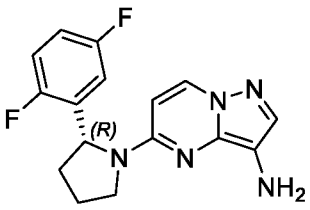
or salt thereof;

b) treating a compound of formula **12** or salt thereof with XC(O)Z to form a compound of formula **13** or a salt thereof; and

c) isolating the compound of formula **13**,

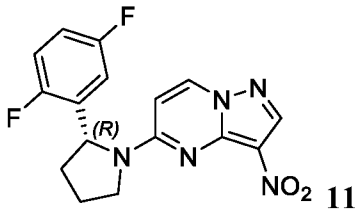
wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl, and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl.

According to a fifth embodiment of the invention, there is provided a process for preparing a compound of formula **12**



or a salt thereof comprising

a) treating a compound of formula **11**

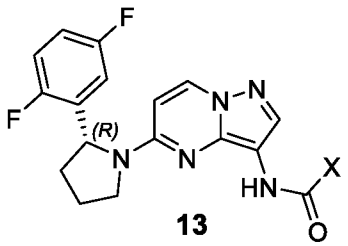


11

with a nitro reduction system to form the compound of formula **12** or a salt thereof; and

b) isolating the compound of formula **12** or a salt thereof.

According to a sixth embodiment of the invention, there is provided a compound of Formula **13**



13

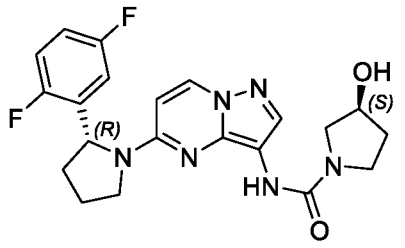
wherein X is halogen, C_1-C_6-alkoxy or C_6-C_{10} aryloxy.

In the present specification and claims, the word 'comprising' and its derivatives including 'comprises' and 'comprise' include each of the stated integers but does not exclude the inclusion of one or more further integers.

The reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

CLAIMS

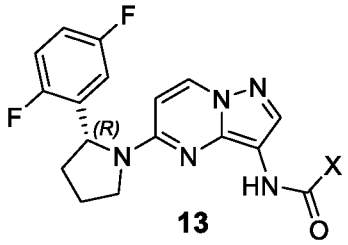
1. A process for preparing a compound of Formula I



Formula I

or a salt thereof, comprising:

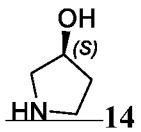
(a) providing an isolated compound of formula **13**



13

or salt thereof; wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13,** each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl;

(b) treating the compound of formula **13** or a salt thereof with a compound of formula **14**



14

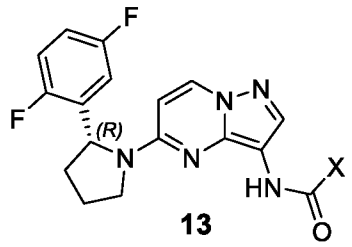
or a salt thereof to form a compound of Formula I; and

(c) optionally forming a salt of the compound of Formula I.

2. The process of claim 1, wherein X is C_6-C_{10} aryloxy.

3. The process of claim 2, wherein X is phenoxy.

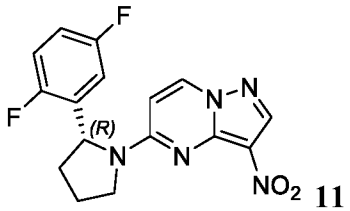
4. The process of any one of the preceding claims, further comprising preparing the compound of formula **13**



13

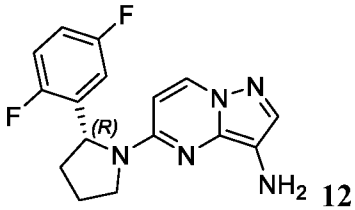
or a salt thereof by a process comprising

(a) treating a compound of formula **11**



11

or a salt thereof with a nitro reduction system to form a compound of Formula **12:**



12

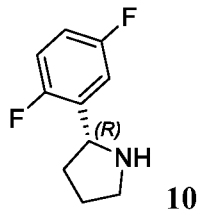
or a salt thereof, and

(b) treating the compound of Formula **12** or salt thereof with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl.

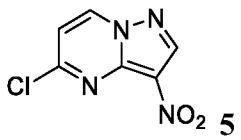
5. The process of claim 4, wherein X is phenoxy and Z is Cl.
6. The process of claim 4 or 5, wherein the compound of formula **12** is the fumarate salt.
7. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises a metal, a metal salt, or an oxide of a metal.

8. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises palladium, platinum, rhodium, ruthenium, nickel, copper, iron, tin, or zinc.
9. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises an acid.
10. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises a metal hydride or a mixed metal hydride.
11. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises $LiAlH_4$, $NaBH_4$, or diisobutylaluminium hydride (*DIBAL*).
12. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises H_2.
13. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises an organic compound capable of providing hydrogen.
14. The process of claim 13, wherein the organic compound capable of providing hydrogen comprises cyclohexene.
15. The process of any one of claims 4 to 6, wherein the nitro reduction system comprises Pd, Pd/C, Raney nickel, Pt/C, PtO_2, Fe/acid, or Zn/acid.
16. The process of claim 15, wherein the nitro reduction system comprises Pt/C.
17. The process of any one of the preceding claims, further comprising preparing the compound of formula **11** or a salt thereof by a process comprising treating a compound of formula **10**



10

or a salt thereof, with a compound of formula **5**



5

or a salt thereof, to form the compound of formula **11** or salt thereof.

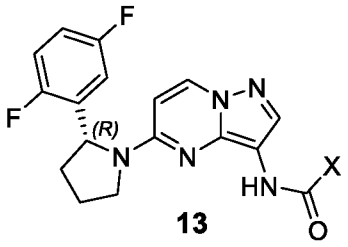
18. The process of claim 17, wherein the compound of formula **10** is a malate salt.

19. The process of claim 17 or 18, wherein the salt of the compound of formula **10** is a D-malate salt.

20. A process for preparing a pharmaceutical composition, comprising mixing (i) a compound of **Formula I** or salt thereof prepared according to the process of any one of the preceding claims and (ii) a pharmaceutically acceptable carrier, to form the pharmaceutical composition.

21. The process of any one of the preceding claims, wherein the salt of the compound of **Formula I** is the hydrogen sulfate salt.

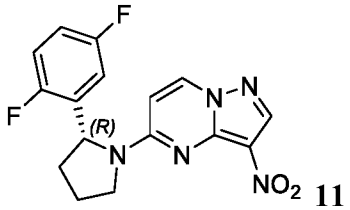
22. A process for preparing a compound of formula **13**



13

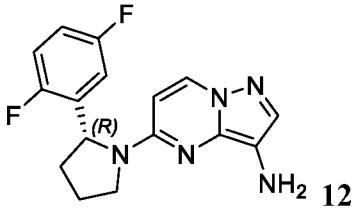
or a salt thereof by a process comprising

a) treating a compound of formula **11**



11

or a salt thereof with a nitro reduction system to form a compound of Formula **12:**



12

or a salt thereof,

b) treating the compound of Formula 12 with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group

consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl, and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl; and

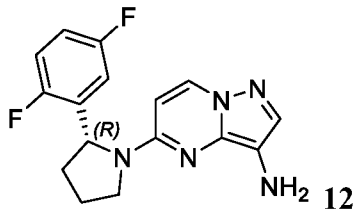
c) isolating the compound of Formula **13**.

23. The process of claim 22, wherein X is phenoxy.

24. The process of claim 22 or 23, wherein Z is Cl.

25. A process for preparing a compound of formula **13** or a salt thereof comprising

a) providing a compound of formula **12**



12

or salt thereof;

b) treating a compound of formula **12** or salt thereof with XC(O)Z to form a compound of formula **13** or a salt thereof; and

c) isolating the compound of formula **13**,

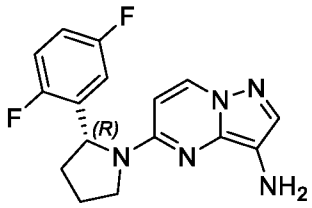
wherein X is halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy, and NR^1R^2, where R^1 and R^2 are each independently selected from hydrogen and C_1-C_6 alkyl, and wherein Z is a leaving group selected from halogen, C_1-C_6 alkoxy, C_6-C_{10} aryloxy and a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z, each optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, CN, OH, C_1-C_6 alkoxy,

and NR^5R^6, where R^5 and R^6 are each independently selected from hydrogen and C_1-C_6 alkyl.

26. The process of claim 25, wherein X is phenoxy.

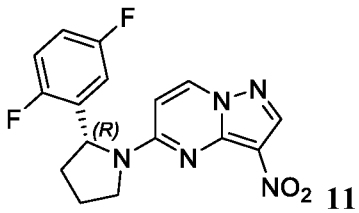
27. The process of claim 25 or 26, wherein Z is Cl.

28. A process for preparing a compound of formula **12**



or a salt thereof comprising

a) treating a compound of formula **11**



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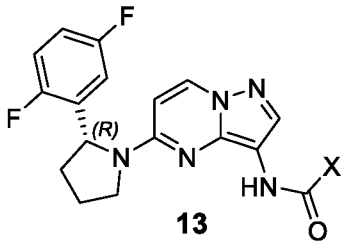
with a nitro reduction system to form the compound of formula **12** or a salt thereof; and

b) isolating the compound of formula **12** or a salt thereof.

29. A compound of Formula **13**



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wherein X is halogen, C_1-C_6-alkoxy or C_6-C_{10} aryloxy.

30. The compound of claim 29, wherein X is phenoxy.