

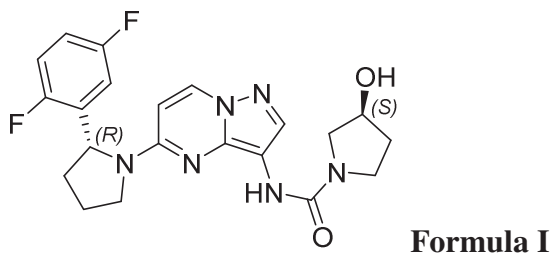
compound of Formula I. The compound may also be prepared as disclosed in US Application Ser. No. 14/943,014, filed November 16, 2015, incorporated by reference herein in its entirety.

- 5 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

Disclosed herein is a process for preparing a compound of Formula I

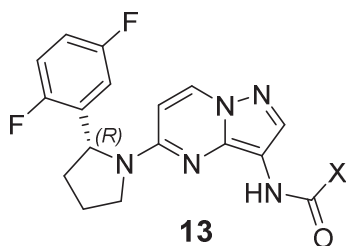
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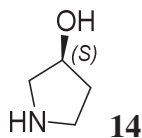
or a salt thereof,
comprising:

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

15



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



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

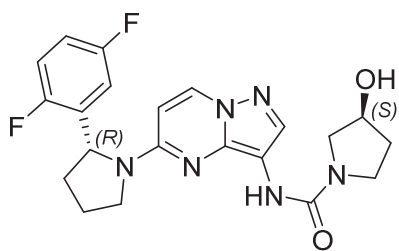
and

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

wherein X is halogen, C₁-C₆ alkoxy, C₆-C₁₀ aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula **13**, each

5 optionally substituted with one or more substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH, C₁-C₆ alkoxy, and NR¹R², where R¹ and R² are each independently selected from hydrogen and C₁-C₆ alkyl.

In one aspect, provided herein is a process for preparing a compound of Formula I

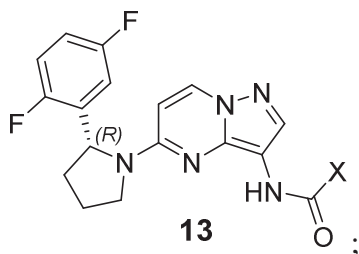


Formula I

or a salt thereof,

comprising:

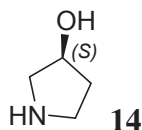
(a) providing an isolated compound of formula **13**



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(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**



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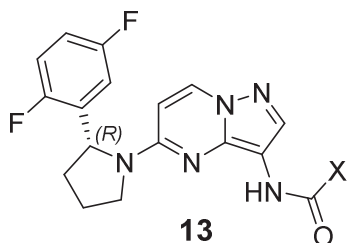
or a salt thereof to form a compound of Formula I;

and

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

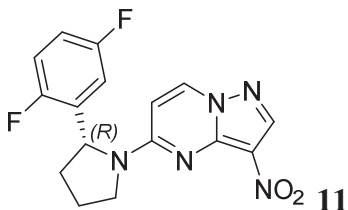
5 wherein X is halogen, C₁-C₆ alkoxy, C₆-C₁₀ aryloxy or a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of the compound of formula 13, each optionally substituted with one or more substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH, C₁-C₆ alkoxy, and NR¹R², where R¹ and R² are each independently selected from hydrogen and C₁-C₆ alkyl.

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



or a salt thereof by a process comprising

(a) treating a compound of formula 11



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

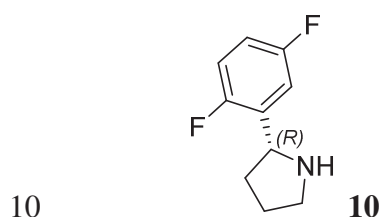
(b) treating the first mixture with XC(O)Z to form a compound of formula 13 or a salt thereof,

20 wherein Z is a leaving group selected from halogen, C₁-C₆ alkoxy, C₆-C₁₀ 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

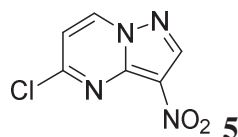
consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH, C₁-C₆ alkoxy, and NR⁵R⁶, where R⁵ and R⁶ are each independently selected from hydrogen and C₁-C₆ alkyl; provided that if Z is optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

5

In some examples, 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**



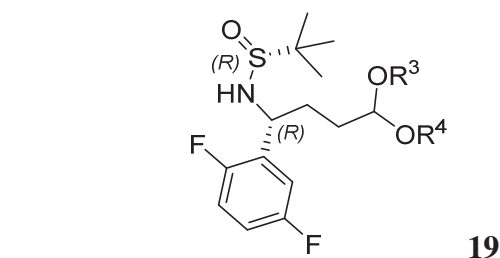
or a salt thereof, with a compound of formula **5**



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

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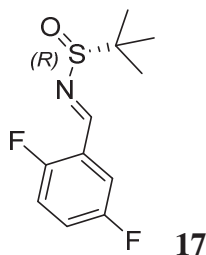
In some examples, the process for preparing the compound of Formula I further comprises preparing the compound of formula **10** or a salt thereof by a process comprising treating a compound of formula **19**



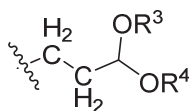
or a salt thereof, with an acid in the presence of a first reducing agent, to form a compound of formula **10** or a salt thereof, wherein each of R³ and R⁴ is independently C₁-C₄ alkyl;

or R³ and R⁴ taken together with the atoms connecting them form a five- to seven-membered ring.

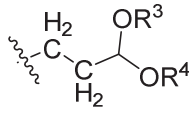
- 5 In some examples, the process for preparing the compound of Formula I further comprises preparing the compound of formula **19** or a salt thereof by a process comprising treating a compound of formula **17**



- 10 with a reagent system comprising the group



- to form a compound of formula **19**,
wherein each of R³ and R⁴ is independently C₁-C₄ alkyl;
15 or R³ and R⁴ taken together with the atoms connecting them form a five- to seven-membered ring.

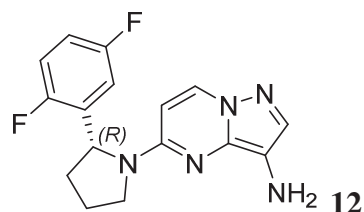
- In some examples, the reagent system comprising  comprises a metal or compound of a metal. In some examples, the metal or the compound of a metal is capable
20 of acting as an electron transfer agent.

In some examples, 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**

wherein X is halogen, C₁-C₆ alkoxy, C₆-C₁₀ 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 C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH, C₁-C₆ alkoxy, and NR¹R²,
5 where R¹ and R² are each independently selected from hydrogen and C₁-C₆ alkyl; and wherein Z is a leaving group selected from halogen, C₁-C₆ alkoxy, C₆-C₁₀ 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 C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH, C₁-C₆ alkoxy,
10 and NR⁵R⁶, where R⁵ and R⁶ are each independently selected from hydrogen and C₁-C₆ alkyl;
provided that if Z is optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

In some examples, provided herein is a process for preparing a compound of formula
15 **13** or a salt thereof comprising

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

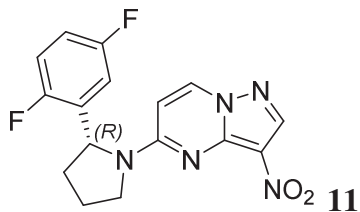


or a salt thereof;

b) treating a compound of formula **12** with XC(O)Z to form a compound of formula
20 **13** or a salt thereof; and
c) optionally isolating the compound of formula **13**.

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

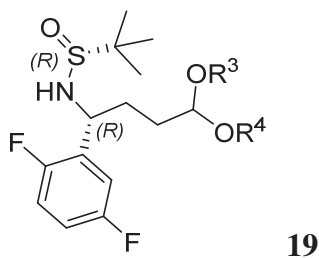
a) isolating a compound of formula **12**



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

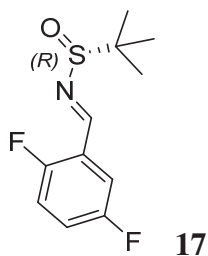
b) isolating the compound of formula **12** or a salt thereof.

- 5 Disclosed herein is a process for preparing a compound of formula **10** or a salt thereof, comprising treating a compound of formula **19**

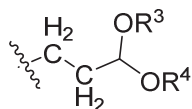


- 10 or a salt thereof, with an acid in the presence of a first reducing agent, to form a compound of formula **10** or a salt thereof.

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

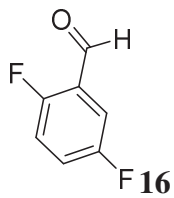


- 15 with a reagent system comprising the group



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

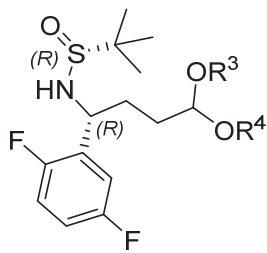
17 or a salt thereof, comprising treating a compound of formula **16**



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

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

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

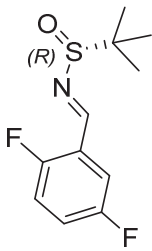


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19

or a salt thereof.

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

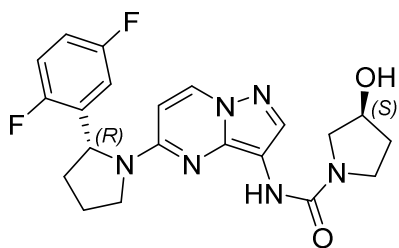


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or a salt thereof.

WE CLAIM:

1. A process for preparing a compound of Formula I

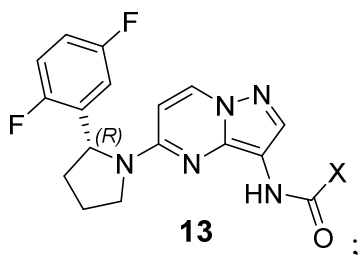


Formula I

or a salt thereof,

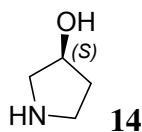
comprising:

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



- 10 (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**



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

- 15 and

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

wherein X is halogen, C₁-C₆ alkoxy, C₆-C₁₀ 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

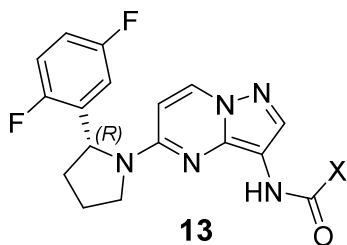
- 20 selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH,

C₁-C₆ alkoxy, and NR¹R², where R¹ and R² are each independently selected from hydrogen and C₁-C₆ alkyl.

2. The process of claim 1, wherein X is C₆-C₁₀ aryloxy.

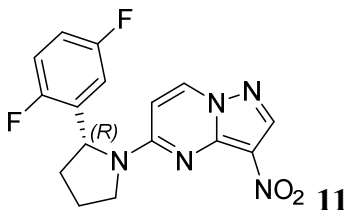
3. The process of claim 2, wherein X is phenoxy.

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



or a salt thereof by a process comprising

(a) treating a compound of formula **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, C₁-C₆ alkoxy, C₆-C₁₀ 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

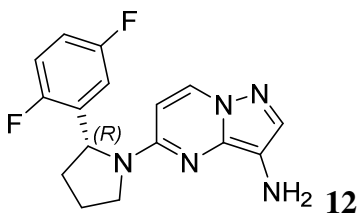
consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, CN, OH, C₁-C₆ alkoxy, and NR⁵R⁶, where R⁵ and R⁶ are each independently selected from hydrogen and C₁-C₆ alkyl; provided that if Z is optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

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5. The process of claim 4, wherein the process comprises:
forming the compound of formula **13** in a second mixture; and
isolating the compound of formula **13** from the second mixture.

10

6. The process of claim 4 or 5, wherein the first mixture comprises a compound of formula **12**



15

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.

7. The process of claim 6, wherein the salt of the compound of formula **12** is the fumarate salt.

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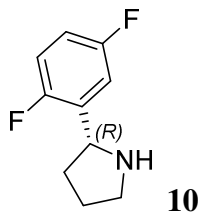
8. The process of claim 6 or 7, wherein Z is halogen or is a 5-membered heteroaryl containing at least one nitrogen directly bonded to the C=O of XC(O)Z.

9. The process of claim 6 or 7, wherein Z is chlorine, bromine, or imidazolyl.

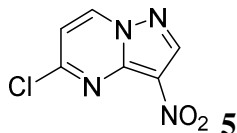
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10. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises a metal, a metal salt, or an oxide of a metal.

11. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises palladium, platinum, rhodium, ruthenium, nickel, copper, iron, tin, or zinc.
- 5 12. The process of any one of claims 4 to 11, wherein the nitro reduction system comprises an acid.
13. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises a metal hydride or a mixed metal hydride.
- 10 14. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises LiAlH_4 , NaBH_4 , or diisobutylaluminium hydride (*DIBAL*).
- 15 15. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises H_2 .
16. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises an organic compound capable of providing hydrogen.
- 20 17. The process of claim 16, wherein the nitro reduction system comprises cyclohexene.
18. The process of any one of claims 4 to 9, wherein the nitro reduction system comprises Pd, Pd/C, Raney nickel, Pt/C, PtO_2 , Fe/acid, or Zn/acid.
- 25 19. The process of claim 32, wherein the nitro reduction system comprises Pt/C.
20. 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**



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.

21. The process of claim 20, wherein the salt of the compound of formula **10** is a malate salt.

10 22. The process of claim 20 or 21, wherein the salt of the compound of formula **10** is the D-malate salt.

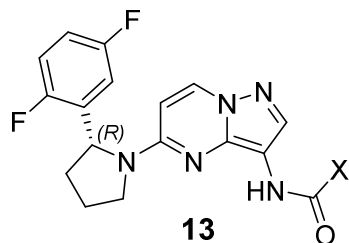
23. The process of any of claims 1-22, wherein X is phenoxy, Z is chlorine, and XC(O)Z is phenyl chloroformate.

15 24. 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.

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

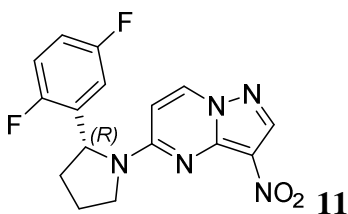
26. A process for preparing a compound of formula **13**

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or a salt thereof by a process comprising

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



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

and

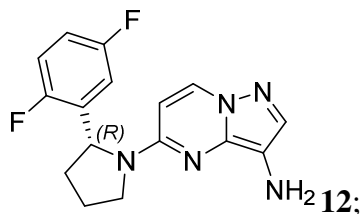
- b) treating the first mixture with XC(O)Z to form a compound of formula **13** or a salt thereof,

wherein X is halogen, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_6\text{-C}_{10}$ 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 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, halogen, CN, OH, $\text{C}_1\text{-C}_6$ alkoxy, and NR^1R^2 ,
 wherein Z is a leaving group selected from halogen, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_6\text{-C}_{10}$ 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 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, halogen, CN, OH, $\text{C}_1\text{-C}_6$ alkoxy, and NR^5R^6 ,
 where R^5 and R^6 are each independently selected from hydrogen and $\text{C}_1\text{-C}_6$ alkyl;
 provided that if Z is optionally substituted $\text{C}_1\text{-C}_6$ alkoxy, optionally substituted $\text{C}_6\text{-C}_{10}$ aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

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

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



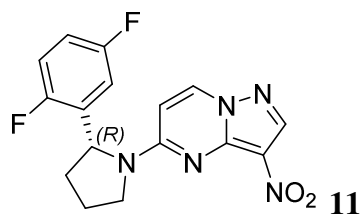
- 5 b) treating a compound of formula **12** with XC(O)Z to form a compound of formula **13** or a salt thereof; and
- c) optionally isolating the compound of formula **13**,

wherein X is halogen, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_6\text{-C}_{10}$ aryloxy or a 5-membered heteroaryl containing
10 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 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, halogen, CN, OH, $\text{C}_1\text{-C}_6$ alkoxy, and NR^1R^2 , where R^1 and R^2 are each independently selected from hydrogen and $\text{C}_1\text{-C}_6$ alkyl, and wherein Z is a leaving group selected from halogen, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_6\text{-C}_{10}$ aryloxy and a 5-
15 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 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, halogen, CN, OH, $\text{C}_1\text{-C}_6$ alkoxy, and NR^5R^6 , where R^5 and R^6 are each independently selected from hydrogen and $\text{C}_1\text{-C}_6$ alkyl;
20 provided that if Z is optionally substituted $\text{C}_1\text{-C}_6$ alkoxy, optionally substituted $\text{C}_6\text{-C}_{10}$ aryloxy, or optionally substituted 5-membered heteroaryl, then Z and X are the same.

28. A process for preparing a compound of formula **12** or a salt thereof comprising

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

25



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.