PROCESSES AND INTERMEDIATES FOR THE PREPARATION OF A PYRIMIDINE AMINOPYRAZOLE COMPOUND

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. §119(e) to U.S. Provisional Application Number 63/427,303, filed November 22, 2022, which is incorporated by reference in its entirety.

FIELD

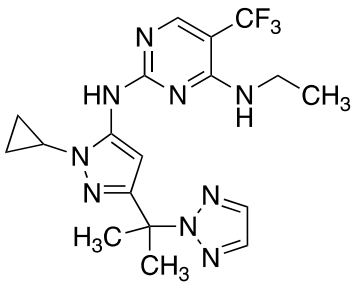
The present disclosure relates to methods of making a pyrimidine aminopyrazole compound and intermediates thereof. The compound is an inhibitor of LRRK2 kinase and find use for treatment of LRRK2-mediated diseases such as Parkinson's disease.

DESCRIPTION

Leucine-rich repeat kinase 2 (LRRK2) is a complex signaling protein that is a key therapeutic target, particularly in Parkinson's disease (PD). Combined genetic and biochemical evidence implicates certain kinase function in the pathogenesis of neurodegenerative disorders (Christensen, K.V. (2017) Progress in medicinal chemistry 56:37-80; Fuji, R.N. et al (2015) Science Translational Medicine 7(273):273ra15; Taymans, J.M. et al (2016) Current Neuropharmacology 14(3):214-225). Kinase inhibitors are under investigation for treatment of Alzheimer's disease, Parkinson's disease, ALS and other diseases (Estrada, A.A. et al (2015) J. Med. Chem. 58(17): 6733-6746; Estrada, A.A. et al (2013) J. Med. Chem. 57:921-936; Chen, H. et al (2012) J. Med. Chem. 55:5536-5545; Estrada, A.A. et al (2015) J. Med. Chem. 58:6733-6746; Chan, B.K. et al (2013) ACS Med. Chem. Lett. 4:85-90; WO2017218843; US 8354420; US 8569281; US8791130; US 8796296; US 8802674; US 8809331; US 8815882; US 9145402; US 9212173; US 9212186; US 9932325, US 10590114, US 11111235, and WO 2012/062783.

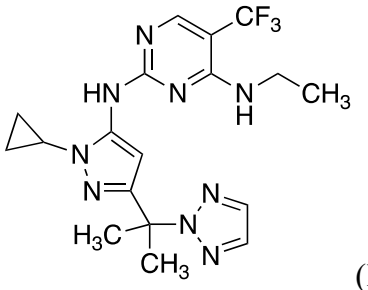
SUMMARY

The present disclosure relates to methods of making a LRRK2 inhibitor N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine and intermediates thereof, the inhibitor also referred to herein as the Formula I compound and having the structure:



(I).

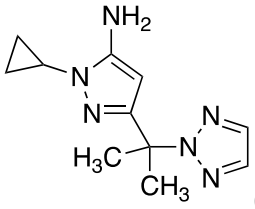
In one example, provided is a method for preparing compound I or a salt thereof



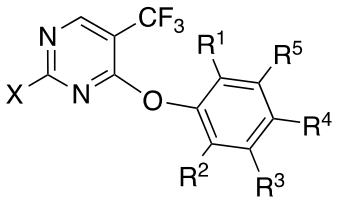
(I)

comprising:

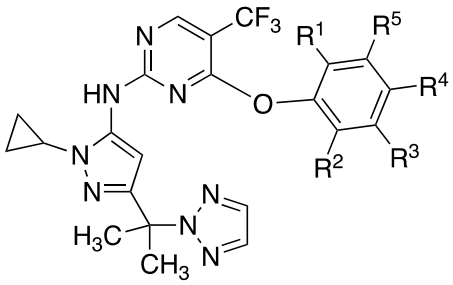
a) contacting compound II with a compound Formula B and a base to produce a compound of Formula C



(II)



(B)



(C)

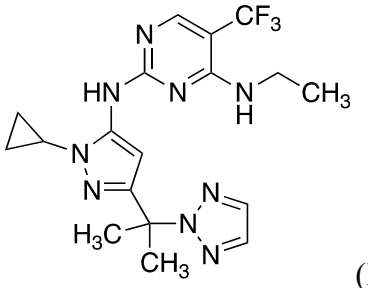
wherein R^1, R^2, R^3, R^4, and R^5 are independently H, cyano, halo, methyl, or NO_2;

and

b) contacting a compound of Formula C with ethylamine;

under conditions sufficient to produce compound I.

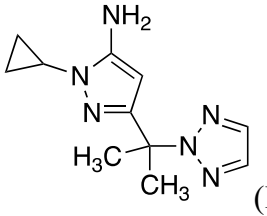
In one aspect, provided is a method for preparing compound I or a salt thereof



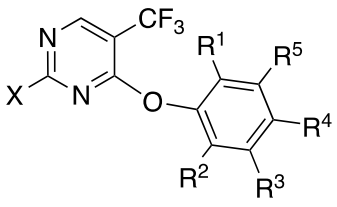
(I)

comprising:

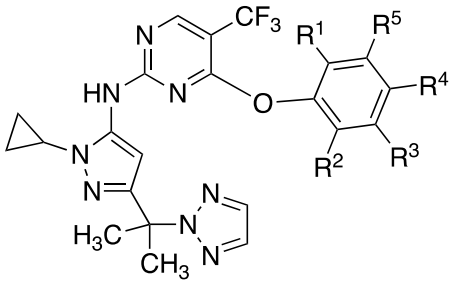
a) contacting compound II with a compound Formula B and a base to produce a compound of Formula C



(II)



(B)



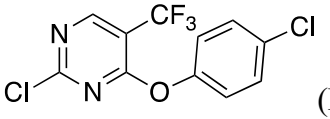
(C)

wherein R^1, R^2, R^3, R^4, and R^5 are independently H, cyano, halo, methyl, or NO_2; and

b) contacting a compound of Formula C with ethylamine;

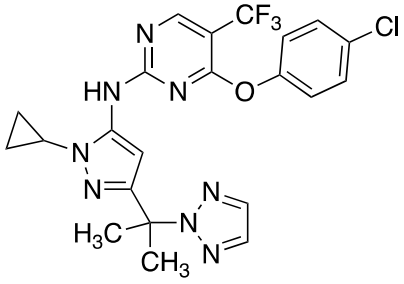
to produce compound I.

In some examples, the compound of Formula B is compound B-1



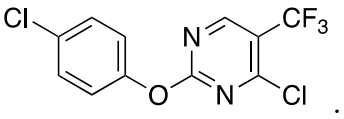
(B-1),

and the compound of Formula C is compound C-1



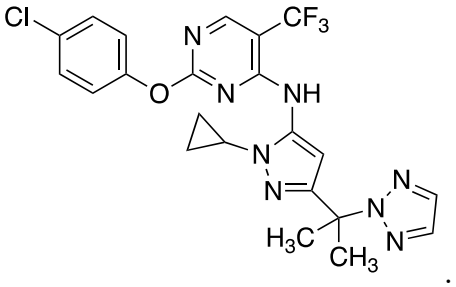
(C-1).

In some examples, provided is B-1 in 90% or greater regioisomeric purity. In other examples, provided is B-1 in 95% or greater regioisomeric purity. In some examples, provided is B-1 in 96% or greater regioisomeric purity. In other examples, provided is B-1 in 97% or greater regioisomeric purity. In still other examples, provided is B-1 in 98% or greater regioisomeric purity. In some examples, provided is compound B-1 in 99% or greater regioisomeric purity. The regioisomer of B-1 is meant to be a compound having the structure:



.

In some examples, provided is C-1 in 96% or greater regioisomeric purity. In other examples, provided is C-1 in 97% or greater regioisomeric purity. In still other examples, provided is C-1 in 98% or greater regioisomeric purity. In some examples, the compound C-1 is produced in 99% or greater regioisomeric purity. The regioisomer of C-1 is meant to be a compound having the structure:



.

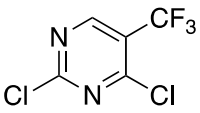
In some examples, the base is 2,6-lutidine or 2,4,6-collidine. In some examples, the reaction is done in NMP or DMSO. In other examples, the reaction is done in DMF or DMAc.

In some examples, compound II is contacted with compound B-1 at a temperature from about 60 ºC to about 70 ºC.

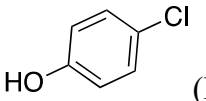
In some examples, Formula C is contacted with ethylamine in a polar aprotic solvent. In other examples, the solvent is THF. In still other examples the solvent is DMF, DMAc, NMP, and DMSO. In another example, the solvent is NMP.

In one example, the compound B-1 is prepared by

a) contacting compound D-1 with compound D-2 and a base under conditions sufficient to the produce the compound B-1; and



(D-1)



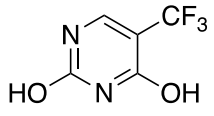
(D-2)

b) optionally crystallizing the compound B-1 from heptane, isopropanol, or an isopropanol/water mixture.

In some examples, the compound B-1 is crystallized from heptane. In some such examples, the compound B-1 is crystallized from heptane in 99% or greater regioisomeric purity. In other examples, the compound B-1 is crystallized from isopropanol. In some examples, compound B-1 is crystallized from isopropanol in 99% or greater regioisomeric purity. In some such examples, the compound B-1 is crystallized from an isopropanol/water mixture in 99% or greater regioisomeric purity. In certain examples, the isopropanol/water mixture contains at least 50%, 60%, 70%, 80%, or 90% by volume isopropanol.

In some such examples, the base is an inorganic base. In some such examples, the inorganic base is K_2CO_3 or NaOH. In other examples, the base is an organic amine base. In some such examples, the organic amine base is TEA or DIPEA. In some examples, the reaction is conducted at a temperature of about 30 °C or less. In other examples, the reaction is conducted at 20 °C or less.

In one example, the compound D-1 is prepared *in situ* by contacting compound E-1 with $POCl_3$



(E-1)

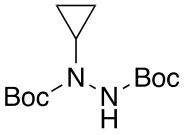
under conditions sufficient to produce the compound D-1.

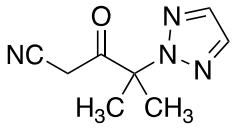
In some examples, the compound E-1 is contacted with $POCl_3$ and diisopropylethylamine.

In some examples, the compound I is obtained in greater than 98% purity. In

some examples, the compound I is obtained in greater than 99% purity. In other examples, the compound I is obtained in greater than 99.5% purity.

In one example, compound II is prepared by contacting compound III with compound IV and an acid


(III)

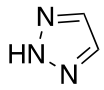

(IV).

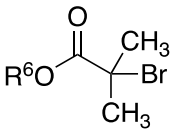
In some examples, the acid is a strong acid. In other examples, the acid is MSA, BSA, PTSA, HBr, or TFA. In still other examples, the acid is H_2SO_4 or HCl in an alcoholic solvent. In some such examples, the alcoholic solvent is *i*-PrOH, or MeOH. In other examples, the alcoholic solvent is EtOH.

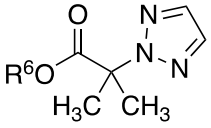
In some examples, compound III is contacted with compound IV at a temperature from about 50 ºC to about 60 ºC.

In another example, compound IV is prepared by

a) contacting compound V with a compound of Formula VI and a first base to produce a compound of Formula VII


(V)


(VI)

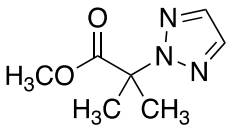

(VII),

wherein R^6 is alkyl;

b) washing the compound of Formula VII with an aqueous solution to remove N^1-triazole regioisomer and obtain the compound of Formula VII in 95% or greater regioisomeric purity; and

c) contacting the compound of Formula VII with a second base and CH_3CN; under conditions sufficient to produce the compound IV.

In some examples, R^6 is methyl and the compound of Formula VII is VII-1


(VII-1)

having 95% or greater regioisomeric purity.

In some examples, the compound of Formula VII is obtained in 98% or greater

regioisomeric purity.

In some examples, the compound of Formula VII is washed with an aqueous solution at least twice. In some examples, the aqueous solution is water. In other examples, the aqueous solution is an acidic aqueous solution. In still other examples, the acidic aqueous solution is aqueous HCl.

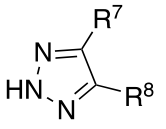
In some examples, the first base is an inorganic base. In some examples, the base is an alkoxide base. In some such examples, the first base is NaOt-Bu. In some examples, the solvent is THF, CH_3CN, NMP, DMF, or DMAc.

In some examples, the second base is *n*-BuLi, KOt-Bu, LiHMDS, LDA, NaOt-Bu, or KOt-Amyl. In other examples, the second base is *n*-BuLi. In still other examples, the second base is LiHMDS.

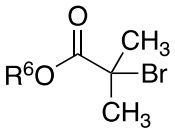
In some examples, the compound IV is obtained in at least 99% or greater purity.

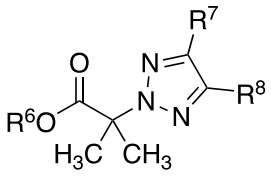
In another example, the compound IV is prepared by

a) contacting a compound of formula VIII


(VIII)

with a compound of Formula VI and a first base to produce a compound of Formula IX


(VI)

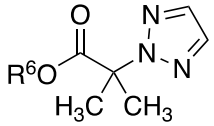

(IX),

wherein R^6 is alkyl and R^7 and R^8 are independently Br or trimethylsilyl (TMS);

b) contacting the compound of Formula IX when at least one of R^7 and R^8 is Br with H_2 or HCO_2H and a hydrogenation catalyst;

and/or contacting the compound of Formula IX when at least one of R^7 and R^8 is TMS with base;

to produce a compound of Formula VII


(VII); and

c) contacting a compound of Formula VII with a second base and CH_3CN;

under conditions sufficient to produce the compound IV.

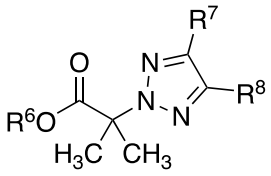
In some examples, R^6 is CH_3 and R^7 is Br.

In some examples, the hydrogenation catalyst is a Pd catalyst.

In some examples, the first base is an inorganic base. In some such examples, the first base is K_2CO_3.

In some examples, the second base is *n*-BuLi, KO*t*-Bu, LiHMDS, LDA, NaO*t*-Bu or KOtAmyl. In some examples, the second base is *n*-BuLi, KO*t*-Bu, LiHMDS, or KOtAmyl. In some such examples, the second base is *n*-BuLi. In still other examples, the second base is LiHMDS.

In another aspect, provided is a compound of Formula IX

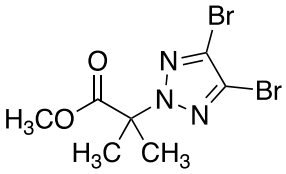


(IX)

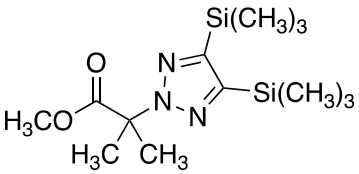
or a salt thereof, wherein:

R^6 is alkyl and R^7 and R^8 are independently Br or trimethylsilyl (TMS).

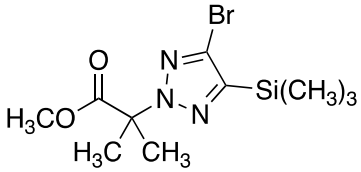
In one example, provided is a compound that is



(IX-1) ,

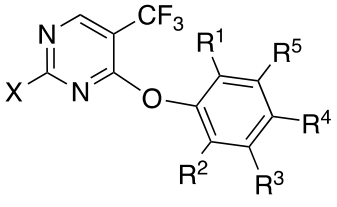


(IX-2), or



(IX-3).

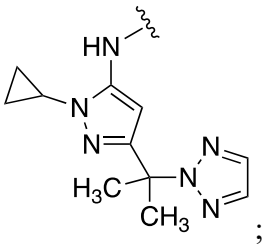
In another aspect, provided is a compound of Formula B:



(B),

or a salt thereof, wherein:

X is chloro or



; and

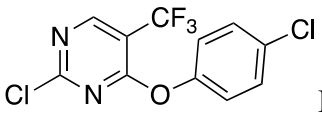
R^1, R^2, R^3, R^4, and R^5 are independently H, cyano, halo, methyl, or NO_2, provided that

a) when X is Cl and R^1, R^2, R^3, and R^5 are H, then R^4 is not NO_2 or H;

b) when X is Cl and R^1 and R^2 are CH_3, then R^4 is not cyano; and

c) when X is Cl, then R^3 is not NO_2.

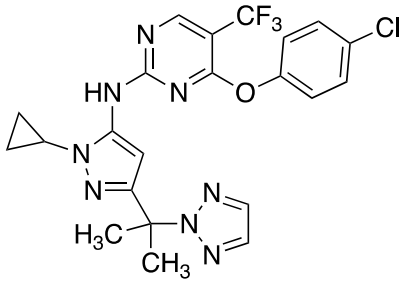
In one example, provided is a compound that is



B-1.

or a salt thereof. In another example, provided is a compound that is B-1.

In one example, provided is a compound that is



C-1.

DEFINITIONS

As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.