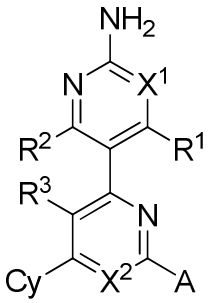
reactants and reagents may be used in some of the reaction steps; low reactant concentrations may be used in some of the process steps with associated throughput penalties; multiple chromatographic purification steps may be used or required requiring specialized process equipment with associated cost and throughput penalties; solvent extraction steps may be required; solvent stripping steps for isolating intermediates and finished product as solids may be required; and yield may be low.

[0005] A need therefore exists for improved processes for preparing compounds of formula I.

SUMMARY

[0005a] In one aspect, the present disclosure provides a process for preparing a compound of Formula I



I

wherein

R^1, R^2 and R^3 are each independently selected from the group consisting of H, F, Cl, Br, I, C_{1-6} alkyl and C_{1-6} haloalkyl;

X^1 is C-R^4, wherein R^4 is selected from the group consisting of -F, -Cl, -Br, -I, -$(L^1)_{0-1}$-C_{1-6} alkyl, -$(L^1)_{0-1}$-C_{1-6} haloalkyl, -$(L^1)_{0-1}$-C_{1-6} heteroalkyl, -$(L^2)_{0-1}$-C_{3-8} cycloalkyl, -$(L^2)_{0-1}$-3-7-membered heterocycloalkyl, -$(L^2)_{0-1}$-6-10-membered aryl, and -$(L^2)_{0-1}$-5-10-membered heteroaryl, wherein

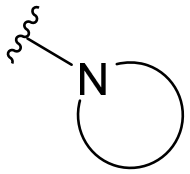
L^1 is selected from the group consisting of -O-, -N(H)-, -S-, -N(C_{1-6} alkyl)- and =O, and

L^2 is selected from the group consisting of -O-, -N(H)-, -N(C_{1-6} alkyl)-, -S-, =O, C_{1-4} alkylene, C_{1-4} alkenylene, C_{1-4} alkynylene, C_{1-4} alkoxylene, C_{1-4} aminoalkylene, C_{1-4} thioalkylene and C_{1-4} heteroalkylene, and

wherein R^4 is optionally substituted on carbon atoms and heteroatoms with R^{R4} substituents selected from the group consisting of F, Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-5-membered cycloalkyl, 3-5-membered heterocycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, =O, -NH_2, -CN, -NO_2 and -SF_5;

wherein R^5 and R^6 are independently selected from straight or branched C_{1-6} alkyl, or R^5 and R^6 together with the oxygen atoms to which they are attached and the boron atom form 5- to 7-membered heterocyclic ring, wherein the each ring carbon atom may be substituted with 1 or 2 C_{1-4} straight chain alkyl groups;

X^2 is N;



A is a 3- to 12-membered N-containing heterocycloalkyl,

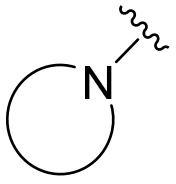
wherein A is optionally substituted with 1-5 R^A substituents selected from the group consisting of F, Cl, Br, I, -OH, -CN, $-NO_2$, $-SF_5$, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} heteroalkyl, $-(L^A)_{0-1}$-3-8-membered cycloalkyl, $-(L^A)_{0-1}$-3-8-membered heterocycloalkyl, $-(L^A)_{0-1}$-5-6-membered heteroaryl, $-(L^A)_{0-1}$-C_6 aryl, $-(L^A)_{0-1}$-$NR^{R1a}R^{R1b}$, $-(L^A)_{0-1}$-OR^{R1a}, $-(L^A)_{0-1}$-SR^{R1a}, $-(L^A)_{0-1}$-$N(R^{R1a})C(=Y^1)OR^{R1c}$, $-(L^A)_{0-1}$-$OC(=O)N(R^{R1a})(R^{R1b})$, $-(L^A)_{0-1}$-$N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(L^A)_{0-1}$-$C(=O)N(R^{R1a})(R^{R1b})$, $-(L^A)_{0-1}$-$N(R^{R1a})C(=O)R^{R1b}$, $-(L^A)_{0-1}$-$C(=O)OR^{R1a}$, $-(L^A)_{0-1}$-$OC(=O)R^{R1a}$, $-(L^A)_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(L^A)_{0-1}$-$S(O)_{1-2}R^{R1c}$, $-(L^A)_{0-1}$-$S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(L^A)_{0-1}$-$N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(L^A)_{0-1}$-$N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein

Y^1 is O or S;

L^A is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{1-4} alkoxylene, C_{1-4} aminoalkylene, C_{1-4} thioalkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene;

R^{R1a} and R^{R1b} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, 3-8-membered cycloalkyl, phenyl, benzyl, 5-6-membered heteroaryl and 3-8-membered heterocycloalkyl;

R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, 3-8- membered cycloalkyl, phenyl, benzyl, 5-6-membered heteroaryl and 3-7-membered heterocycloalkyl, and wherein R^A is optionally substituted on carbon atoms and heteroatoms with R^{RA} substituents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, $-SF_5$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-$N(H)S(O)_{0-2}$-, C_{1-4} (halo)alkyl-$S(O)_{0-2}N(H)$-, (halo)alkyl-N(H)-$S(O)_{0-2}N(H)$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)$_2$N-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)$_2$N-C(=O)O-, C_{1-4} alkylthio, C_{1-4} alkylamino and C_{1-4} dialkylamino; and



Cy is a 3- to 12-membered N-containing heterocycloalkyl,

wherein Cy optionally comprises one or two additional heteroatoms selected from the group consisting of O, S, and N,

wherein Cy is optionally substituted on carbon or heteroatoms with R^{Cy} substituents selected from the group consisting of F, Cl, Br, I, -OH, -CN, $-NO_2$, $-SF_5$, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} heteroalkyl, $-(L^{Cy})_{0-1}$-3-8-membered cycloalkyl, $-(L^{Cy})_{0-1}$-3-8-membered heterocycloalkyl, $-(L^{Cy})_{0-1}$-5-6-membered heteroaryl, $-(L^{Cy})_{0-1}$-phenyl, $-(L^{Cy})_{0-1}$-$NR^{RCa}R^{RCb}$, -

$(L^{Cy})_{0-1}$-OR^{RCa}, -$(L^{Cy})_{0-1}$-SR^{RCa}, -$(L^{Cy})_{0-1}$-$N(R^{RCa})C(=Y^1)OR^{RCc}$, -$(L^{Cy})_{0-1}$-$OC(=O)N(R^{RCa})(R^{RCb})$, -$(L^{Cy})_{0-1}$-$N(R^{RCa})C(=O)N(R^{RCa})(R^{RCb})$, -$(L^{Cy})_{0-1}$-$C(=O)N(R^{RCa})(R^{RCb})$, -$(L^{Cy})_{0-1}$-$N(R^{RCa})C(=O)R^{RCb}$, -$(L^{Cy})_{0-1}$-$C(=O)OR^{RCa}$, -$(L^{Cy})_{0-1}$-$OC(=O)R^{RCa}$, -$(L^{Cy})_{0-1}$-$P(=O)(OR^{RCa})(OR^{RCb})$, -$(L^{Cy})_{0-1}$-$S(O)_{1-2}R^{RCc}$, -$(L^{Cy})_{0-1}$-$S(O)_{1-2}N(R^{RCa})(R^{RCb})$, -$(L^{Cy})_{0-1}$-$N(R^{RCa})S(O)_{1-2}N(R^{RCa})(R^{RCb})$ and -$(L^{Cy})_{0-1}$-$N(R^{RCa})S(O)_{1-2}(R^{RCc})$, wherein

L^{Cy} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{1-4} alkoxylene, C_{1-4} aminoalkylene, C_{1-4} thioalkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene;

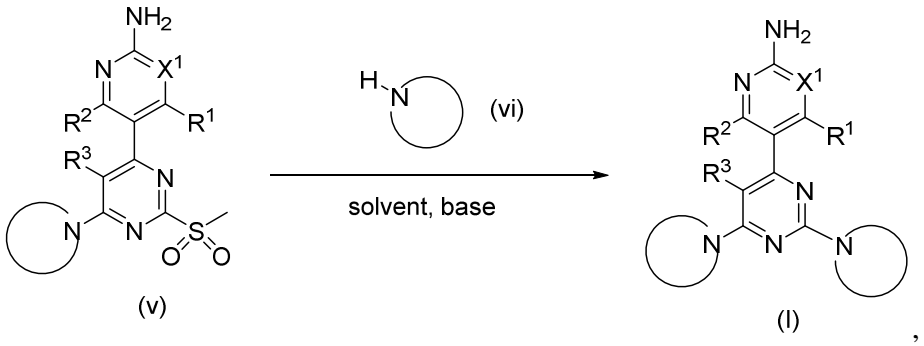
R^{RCa} and R^{RCb} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, 3-8-membered cycloalkyl, phenyl, benzyl, 5-6-membered heteroaryl and 3-8-membered heterocycloalkyl;

R^{RCc} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, 3-8-membered cycloalkyl, phenyl, benzyl, 5-6-membered heteroaryl and 3-7-membered heterocycloalkyl, and

wherein R^{Cy} is optionally substituted on carbon atoms and heteroatoms with from 1 to 5 R^{RCy} substituents selected from the group consisting of F, Cl, Br, I, -NH_2, -OH, -CN, -NO_2, =O, -SF_5, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-$N(H)S(O)_{0-2}$-, C_{1-4} (halo)alkyl-$S(O)_{0-2}N(H)$-, (halo)alkyl-$N(H)S(O)_{0-2}N(H)$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)$_2$N-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)$_2$N-C(=O)O-, C_{1-4} alkylthio, C_{1-4} alkylamino and C_{1-4} dialkylamino;

said process comprising:

displacing the methoxysulfonyl group of compound (v) under basic conditions in a solvent with a 3 to -12-membered amine-containing heterocycloalkyl compound (vi) to provide the compound of Formula (I)



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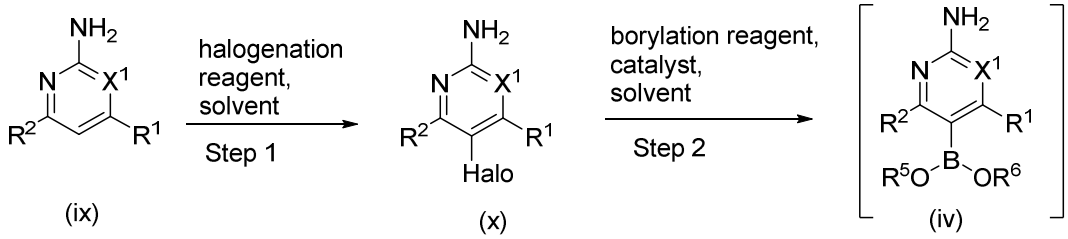
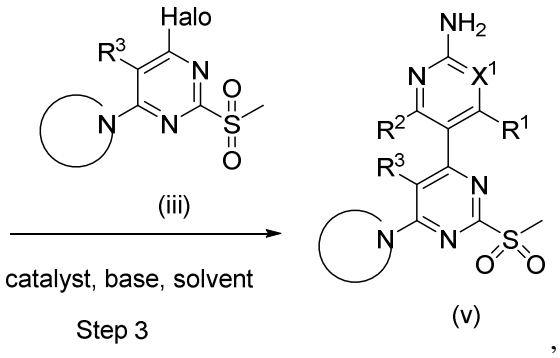
wherein said process further comprises preparing compound (v) according to one of schemes (A) to (C):

scheme (A) wherein sulfone compound (v) is prepared according to the following reaction scheme





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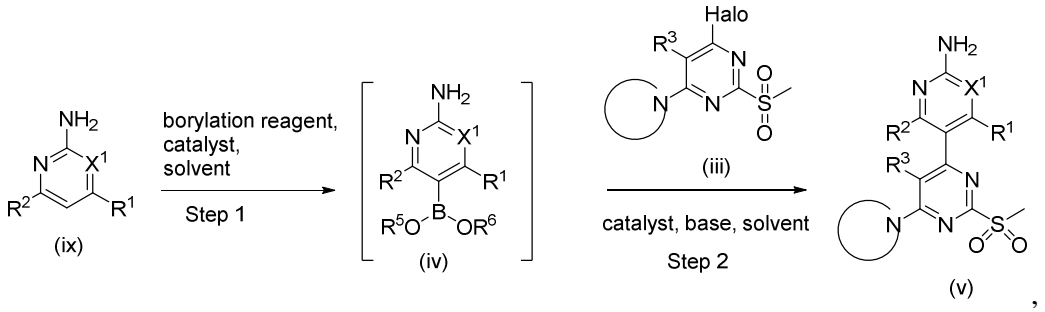
scheme (A) comprising

step 1 wherein compound (ix) is combined with a halogenation reagent in a solvent and reacted to form compound (x),

step 2 wherein compound (x) is borylated with a borylation reagent to form a solution of compound (iv), and

step 3 wherein a solution of compound (iv), compound (iii), a catalyst, a base and a solvent is formed and reacted to form compound (v);

scheme (B) wherein sulfone compound (v) is prepared according to the following reaction scheme



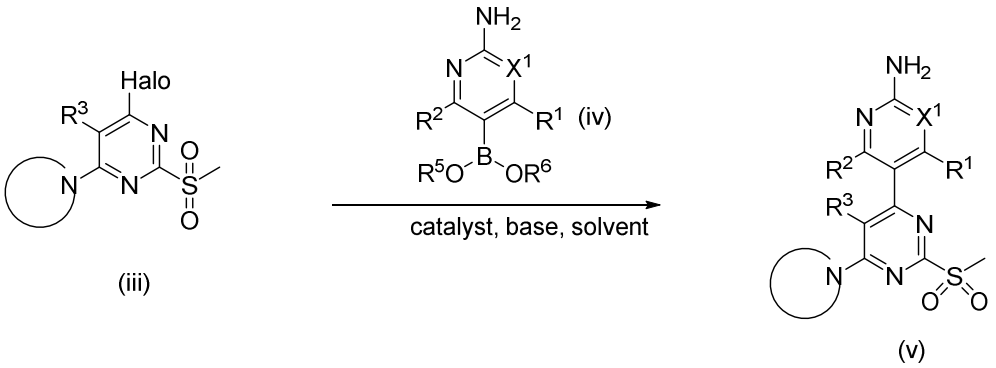
,

scheme (B) comprising

step 1 wherein compound (ix) is directly borylated with a borylation reagent to form a reaction product mixture comprising compound (iv) predominantly in solution, and

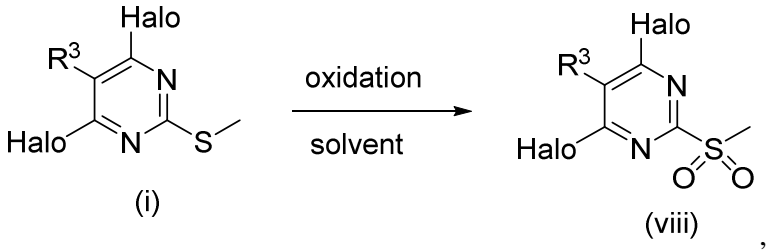
step 2 wherein the reaction product mixture from step 1 is combined with compound (iii), a catalyst, a base and a solvent, and reacted to form compound (v); and

scheme (C) wherein sulfone compound (v) is prepared according to the following reaction scheme by performing a coupling reaction between a sulfone compound (iii) and a boronate reagent (iv) with a catalyst in the presence of a base and a solvent to provide compound (v)



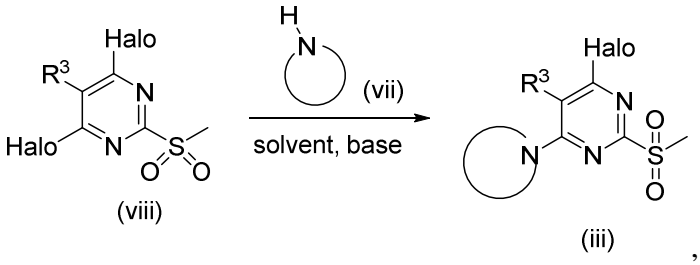
wherein scheme (C) further comprises scheme (1), scheme (2), or a combination of scheme (1) and scheme (2),

wherein scheme (1) comprises preparing sulfone compound (iii) according to the following reaction scheme comprising treating an alkylthio compound (i) with at least one oxidizing agent in a solvent to provide a mixture of oxidized sulfone compound (viii)



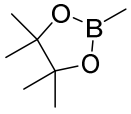
, and

displacing a halogen atom from sulfone compound (viii) with an optionally substituted 3- to 12-membered amine-containing heterocycloalkyl compound (vii) under basic conditions in a solvent to form a reaction product mixture comprising sulfone compound (iii)

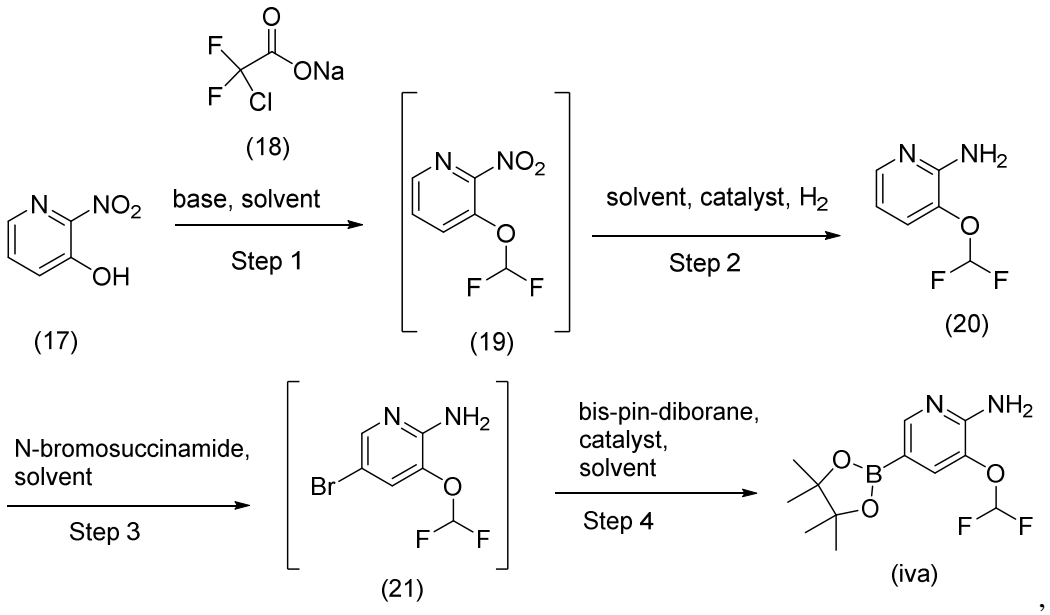


, and

scheme (2) wherein the sulfone compound (iv) is the species compouind (iva) wherein



X^1 is C-O-CHF_2, R^1 and R^2 are each H, and the moiety -B(OR^5)(OR^6) is , and wherein compound (iva) is prepared according to the following reaction scheme,



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scheme (2) comprising

step 1 wherein a reaction mixture comprising compound (17), compound (18), a solvent and base is formed and reacted to form a reaction product mixture comprising compound (19) predominantly in solution,

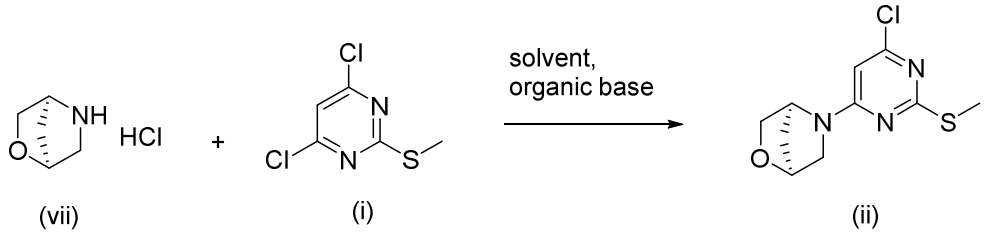
step 2 wherein a reaction mixture comprising the solution of compound (19) is hydrogenated in the presence of catalyst to form a reaction product mixture comprising compound (20),

step 3 wherein a reaction mixture comprising compound (20), N-bromosuccinamide and a polar aprotic solvent is reacted to form a reaction product mixture comprising compound (21) predominantly in solution, and

step 4 wherein a reaction mixture comprising compound (21) in solution, bis-pin-diborane, and a precious metal catalyst is formed and reacted to form a reaction product mixture comprising compound (iva).

[0005b] In one aspect, the present disclosure provides a process for preparing compound 1, the process comprising the following steps:

(1) reacting compound (vii) with compound (i) in the presence of a solvent and an organic base to form a reaction mixture comprising compound (ii) according to the following scheme

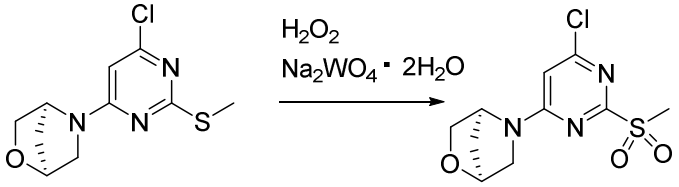


wherein

the solvent is selected from the group consisting of dimethylsulfoxide, acetonitrile, and ethanol, and

the equivalents of the organic base to compound (vii) is from about 2.2:1 to about 2.6:1;

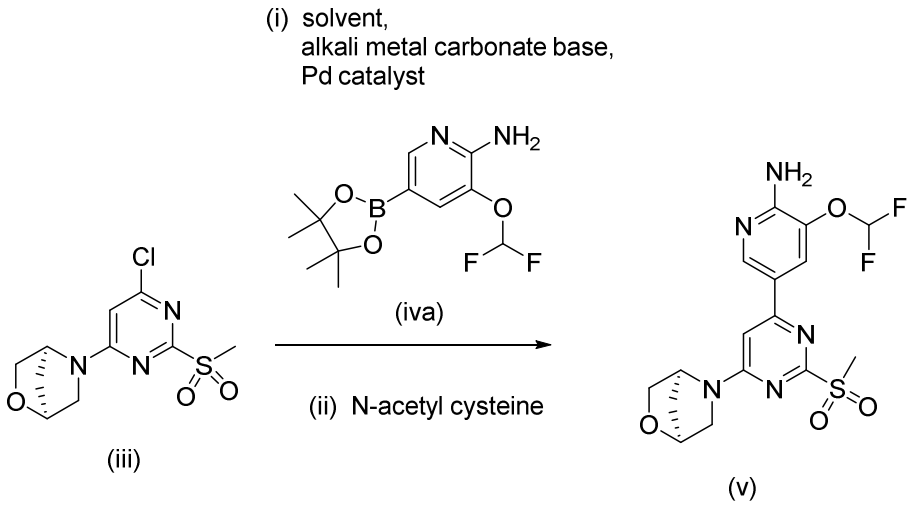
(2) oxidizing compound (ii) with hydrogen peroxide in the presence of sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) to form a reaction product mixture comprising compound (iii) according to the following reaction scheme



(ii) (iii)

wherein the hydrogen peroxide is added to the reaction product mixture from step (1) and the equivalent ratio of hydrogen peroxide to compound (ii) is from about 2:1 to about 3.5:1;

(3) (i) performing a Suzuki coupling of compound (iii) with compound (iva) in the presence of an alkali metal carbonate base, a palladium catalyst, and a solvent to form a reaction product mixture compound (v), and (ii) adding a catalyst scavenger to the reaction product mixture to scavenge palladium, according to the following scheme

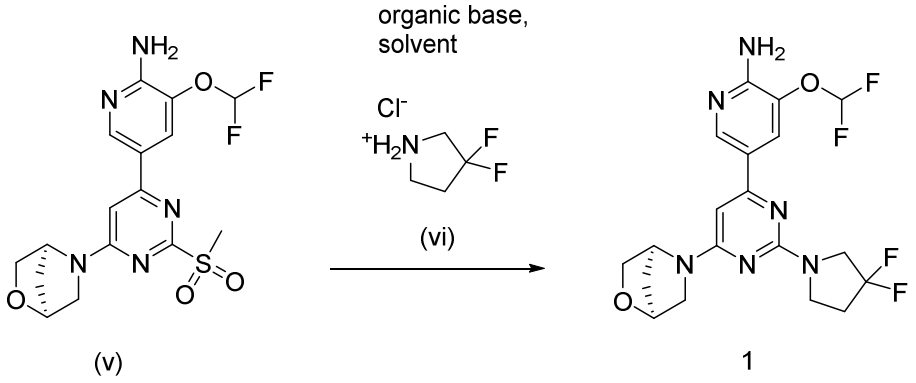


(iii) (v)

wherein the solvent is tetrahydrofuran and water, and the palladium catalyst is $PdCl_2$(dppf); and

(4) reacting compound (v) with compound (vi) in the presence of at least one organic base, and a solvent to form a reaction product mixture comprising

compound 1 according to the following reaction scheme



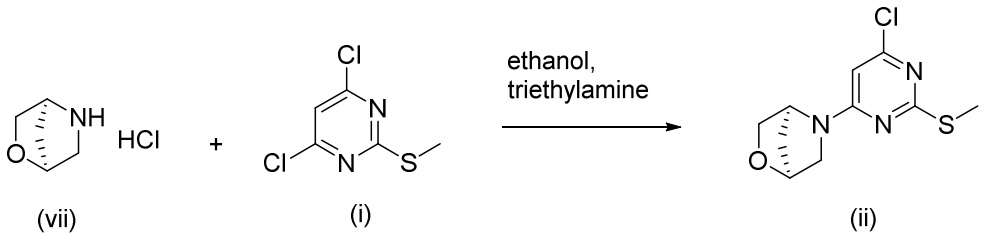
(v) 1

wherein

the at least one organic base is selected from the group consisting of 1,1,3,3-tetramethylguanidine and 1,8-diazabicyclo[5.4.0]undec-7-ene, and the solvent is selected from the group consisting of toluene, anisole, mesitylene, diethylamine, di-*n*-propylamine, di-isopropylamine, di-*n*-butylamine, and combinations thereof.

[0005c] In one aspect, the present disclosure provides a process for preparing compound 1 Form A, the process comprising:

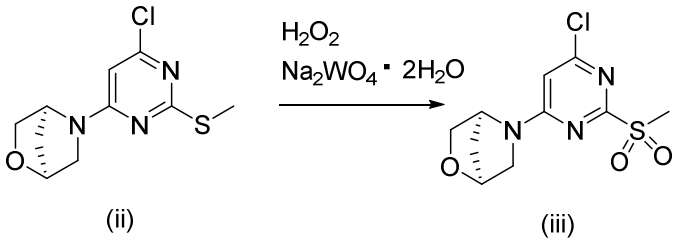
(1) reacting compound (vii) with compound (i) in the presence of ethanol and triethylamine to form compound (ii) according to the following reaction scheme



(vii) (i) (ii)

wherein the equivalents of trimethylamine to compound (vii) is about 2.4:1;

(2) oxidizing compound (ii) with hydrogen peroxide in the presence of sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) to form a reaction product mixture comprising compound (iii) according to the following reaction scheme

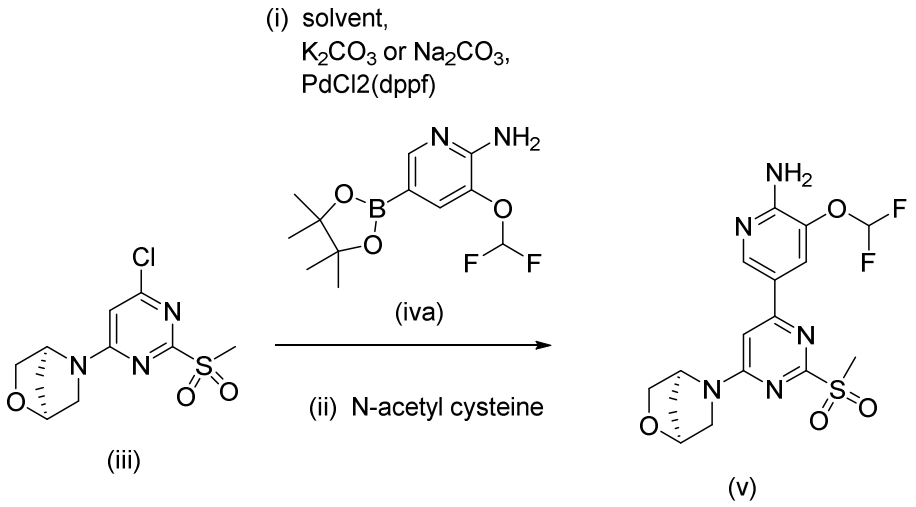


(ii) (iii)

wherein the hydrogen peroxide is added to the reaction product mixture from step (1) and the equivalent ratio of hydrogen peroxide to compound (ii) is about 3:1;

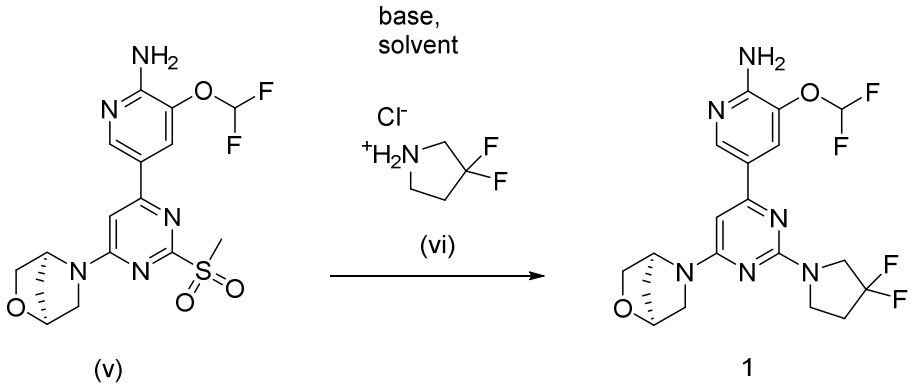
(3) (i) performing a Suzuki coupling of compound (iii) with compound (iva) in the presence of K_2CO_3 or Na_2CO_3, PdCl2(dppf) catalyst, and a tetrahydrofuran

and water solvent to form a reaction product mixture compound (v), and (ii) adding a N-acetyl cysteine to the reaction product mixture to scavenge palladium, according to the following scheme



wherein the equivalent ratio of K_2CO_3 or Na_2CO_3 to compound (iii) is about 3:1, and the PdCl2(dppf) content is about 0.5 mol% based on compound (iii);

(4) reacting compound (v) with compound (vi) in the presence of at least one base, and a solvent to form a reaction product mixture comprising compound 1 according to the following reaction scheme



wherein

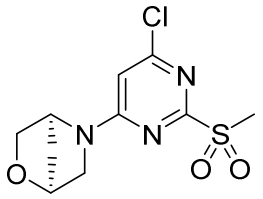
the at least one base is selected from the group consisting of 1,1,3,3-tetramethylguanidine and 1,8-diazabicyclo[5.4.0]undec-7-ene, and

the solvent is selected from the group consisting of toluene, anisole, mesitylene, diethylamine, di-*n*-propylamine, di-isopropylamine, di-*n*-butylamine, and combinations thereof; and

(5) isolating compound 1 from the step (4) reaction product mixture by the following order of steps: adding an anti-solvent selected from isopropanol and *n*-propanol to the reaction product mixture; cooling the reaction product mixture to form a slurry comprising solid compound 1; and isolating solid compound 1 from the reaction product mixture; and

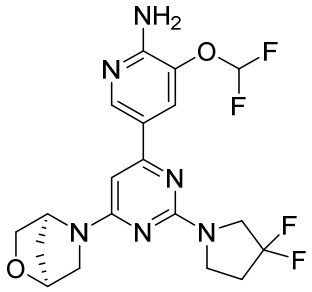
(6) forming a supersaturated solution of compound 1 and methyl isobutyl ketone; seeding the supersaturated solution with crystalline compound 1 Form A; cooling the solution to form a slurry comprising crystalline compound 1 Form A; and isolating crystalline compound 1 Form A from the slurry.

[0005d] In one aspect, the present disclosure provides a compound of formula (iii)



(iii) .

[0005e] In one aspect, the present disclosure provides a crystalline form of compound I



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wherein the crystalline form has an X-ray powder diffraction pattern having at least two peaks at positions selected from the group consisting of 7.7 ± 0.3 (º2θ), 12.1 ± 0.3 (º2θ), 16.2 ± 0.3 (º2θ), 16.4 ± 0.3 (º2θ), 16.6 ± 0.3 (º2θ), 17.1 ± 0.3 (º2θ), 18.8 ± 0.3 (º2θ), 19.4 ± 0.3 (º2θ), 19.8 ± 0.3 (º2θ), 20.3 ± 0.3 (º2θ), 20.5 ± 0.3 (º2θ), 23.3 ± 0.3 (º2θ), 24.7 ± 0.3 (º2θ), 25.3 ± 0.3 (º2θ), and 26.5 ± 0.3 (º2θ).

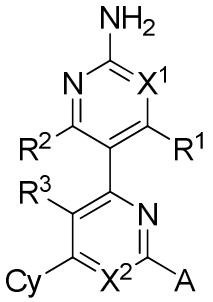
[0005f] In one aspect, the present disclosure provides a pharmaceutical composition comprising the crystalline form as disclosed herein and at least one excipient.

[0005g] In one aspect, the present disclosure provides a process of preparing the crystalline form of compound I as disclosed herein, the method comprising dissolving compound I in a solvent to form a solution, forming a slurry of crystals of compound I therefrom, and isolating crystallilzed compound I.

[0005h] In one aspect, the present disclosure provides use of the crystalline form as disclosed herein in the manufacture of a medicament for treating a neurodegenerative condition.

BRIEF DESCRIPTION

[0006] A first aspect of the present disclosure is directed to a process for preparing a compound of Formula I



I .

[0007] R^1, R^2 and R^3 are each independently selected from the group consisting of H, F, Cl, Br, I, C_{1-6} alkyl and C_{1-6} haloalkyl.

[0008] X^1 is C-R^4, wherein R^4 is selected from the group consisting of -F, -Cl, -Br, -I, -$(L^1)_{0-1}$-C_{1-6} alkyl, -$(L^1)_{0-1}$-C_{1-6} haloalkyl, -$(L^1)_{0-1}$-C_{1-6} heteroalkyl, -$(L^2)_{0-1}$-C_{3-8} cycloalkyl, -$(L^2)_{0-1}$-3-7-membered heterocycloalkyl, -$(L^2)_{0-1}$-6-10-membered aryl, and -$(L^2)_{0-1}$-5-10-membered heteroaryl. L^1 is selected from the group consisting of -O-, -N(H)-, -S-, -N(C_{1-6} alkyl)- and =O. L^2 is selected from the group consisting of -O-, -N(H)-, -N(C_{1-6} alkyl)-, -S-, =O, C_{1-4} alkylene, C_{1-4} alkenylene, C_{1-4} alkynylene, C_{1-4} alkoxylene, C_{1-4} aminoalkylene, C_{1-4} thioalkylene and C_{1-4} heteroalkylene.

[0009] R^4 is optionally substituted on carbon atoms and heteroatoms with R^{R4} substituents selected from the group consisting of F, Cl, Br, I, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-5-