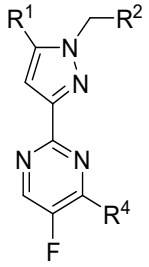
reduced responsiveness to endogenously produced NO contributes to the development of diseases.

[0005] sGC stimulators are NO-independent, heme-dependent modulators of the sGC enzyme, and display strong synergistic enzyme activation with NO. These are clearly differentiated from NO-independent, heme-independent sGC activators.

[0006] There is a need to develop novel sGC stimulators because compounds that stimulate sGC in an NO-independent manner offer considerable advantages over other current alternative therapies that target the aberrant NO pathway. As a result, there is also a need to develop efficient processes that are amenable to large scale manufacturing for the synthesis of these new sGC stimulators. There is a need for processes that are efficient and amenable to large scale manufacturing, which provide stable sGC stimulators in high purity and yields.

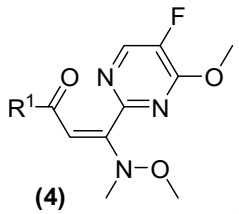
SUMMARY

[0007] Novel processes for preparing compounds of Formula I are described herein.



Formula I

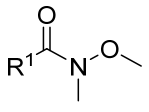
[0007a] In one aspect of the present disclosure, there is provided a process for preparing a compound of formula (**4**):



(4) ,

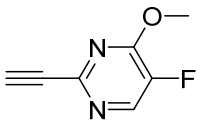
comprising the steps of:

i) coupling an amide of formula **(1)**:



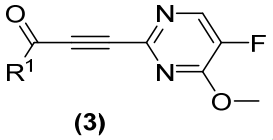
(1)

with a pyrimidine compound of formula **(2):**



(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**

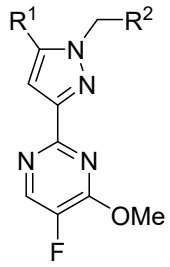


(3) , and

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4)**, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O.

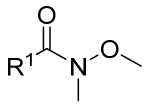
[0007b] In another aspect of the present disclosure, there is provided a process for preparing a compound of Formula II:



Formula II ,

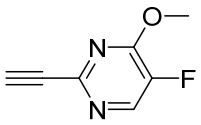
comprising the steps of:

i) coupling an amide of formula **(1)**:



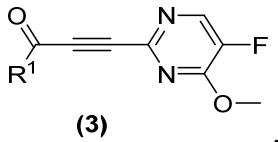
(1)

with a pyrimidine compound of formula **(2)**:



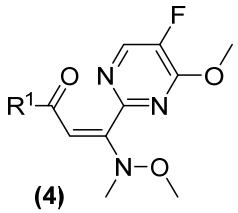
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3)**:



(3) ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4)**:



(4) , and

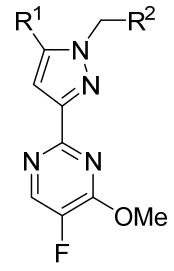
iii) condensing the compound of formula **(4)** with a hydrazine of formula R^2-CH_2-NH-NH_2 or a salt thereof, optionally in the presence of a base, to form the compound of Formula II, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; and

each R^5 is independently methyl, methoxy or halogen.

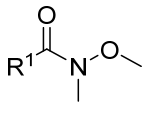
[0007c] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula II:



Formula II ,

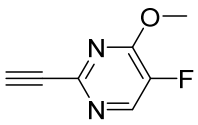
comprising the steps of:

i) coupling an amide of formula **(1)**:



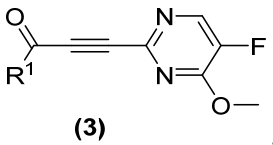
(1)

with a pyrimidine compound of formula **(2):**



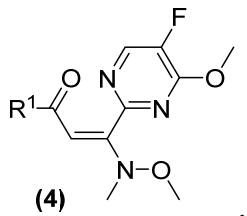
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:



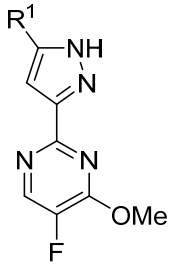
(3) ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4)**:



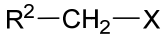
(4) ,

iiia) condensing the compound of formula **(4)** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24**):



(24) ; and

iiib) alkylating intermediate of formula (**24**) with an alkylating agent of formula (**22**) to provide the compound of Formula II



(22) ;

wherein:

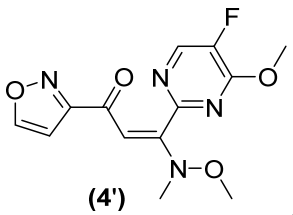
R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

each R^5 is independently methyl, methoxy or halogen;

X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

[0007d] In another aspect of the present disclosure, there is provided a process of preparing a compound of formula **(4')**:

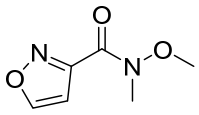


(4')

,

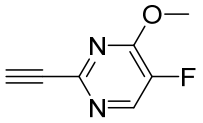
comprising the steps of:

i) coupling an amide of formula **(1')**:



(1')

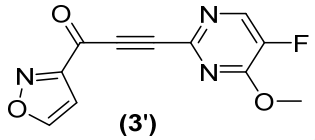
with a pyrimidine compound of formula **(2)**:



(2)

,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:

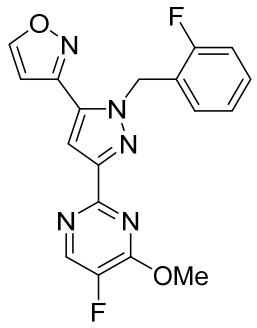


(3')

, and

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**.

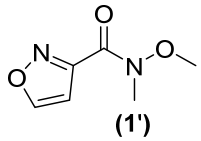
[0007e] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula V:



Formula V ,

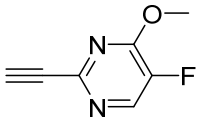
comprising the steps of:

i) coupling an amide of formula **(1')**:



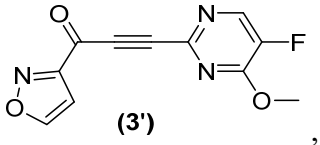
(1')

with a pyrimidine compound of formula **(2)**:



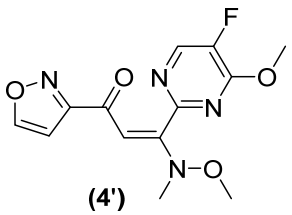
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3') ,

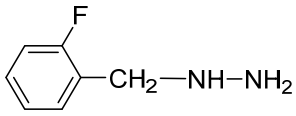
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4')

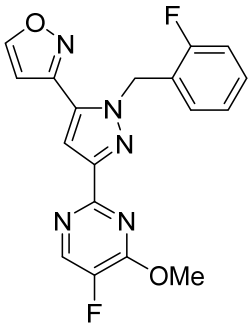
, and

iii) condensing the compound of formula **(4')** with a hydrazine of formula



or a salt thereof, optionally in the presence of a base, to form the compound of Formula V.

[0007f] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula V:

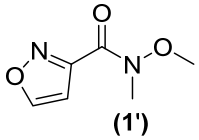


Formula V

,

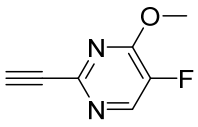
comprising the steps of:

i) coupling an amide of formula **(1')**:



(1')

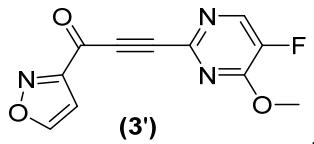
with a pyrimidine compound of formula **(2)**:



(2)

,

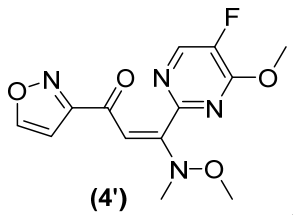
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3')

,

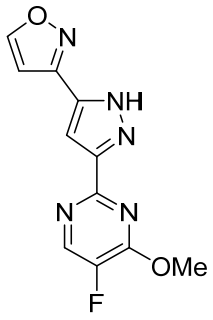
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4')

,

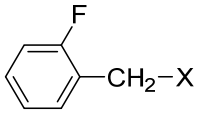
iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



(24')

; and

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:

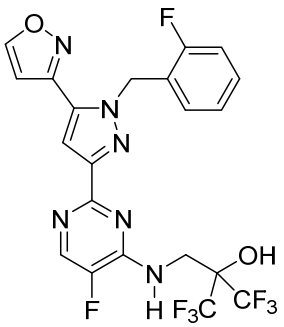


(23A)

,

wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

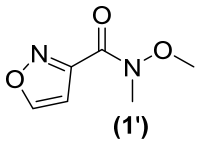
[0007g] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula IA:



Formula IA ,

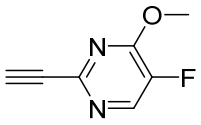
comprising the step of:

i) coupling an amide of formula **(1')**:



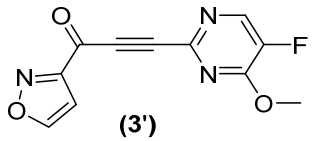
(1')

with a pyrimidine compound of formula **(2)**:



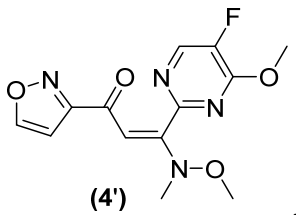
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3') ,

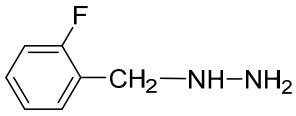
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



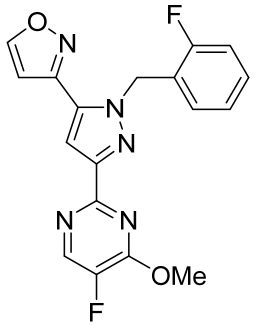
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



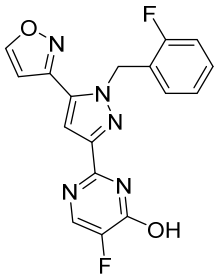
or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



Formula V

,

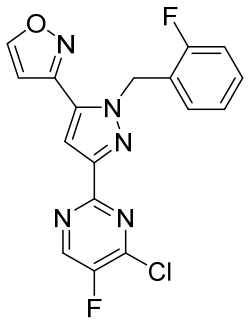
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9')

,

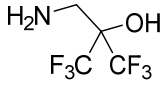
v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI

,

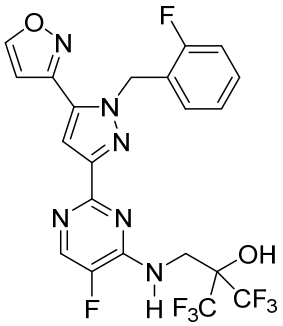
vi) reacting an amine of formula **(17)**:



(**17**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IA.

[0007h] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula IA:

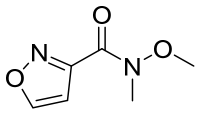


Formula IA

,

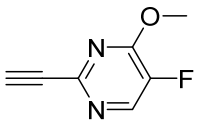
comprising the step of:

i) coupling an amide of formula **(1')**:



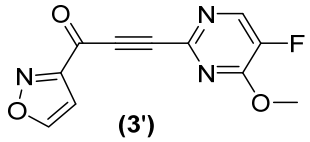
(1')

with a pyrimidine compound of formula **(2)**:



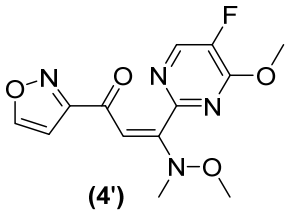
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



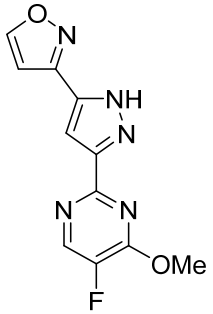
(3') , and

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



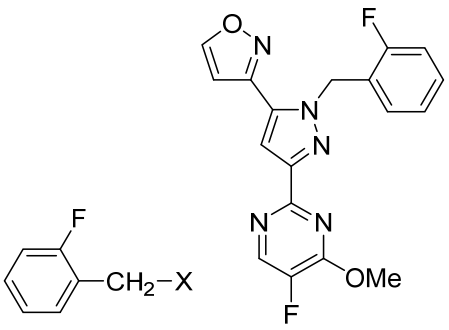
(4') ;

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



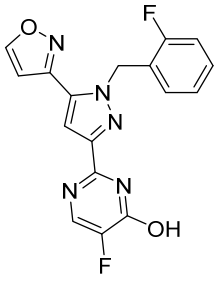
(24') ;

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



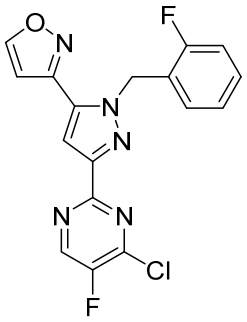
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



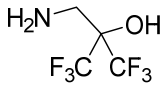
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride o form a compound of Formula VI:



Formula VI , and

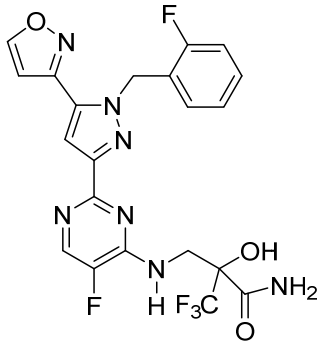
vi) reacting an amine of formula **(17)**:



(**17**)

with the compound of Formula VIA, optionally in the presence of a base, to yield the compound of Formula IA, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

[0007i] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula IB:

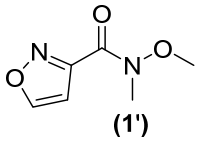


Formula IB

,

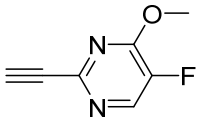
comprising the step of:

i) coupling an amide for formula **(1')**:



(1')

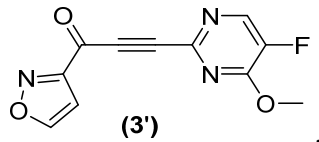
with a pyrimidine compound of formula **(2)**:



(2)

,

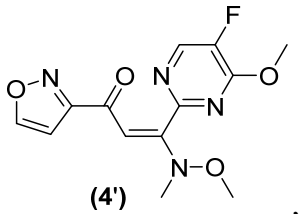
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3')

,

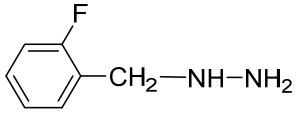
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



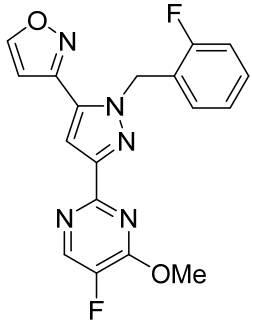
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



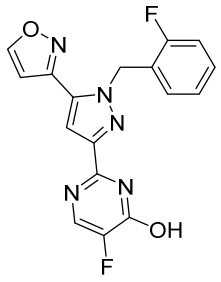
or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



Formula V

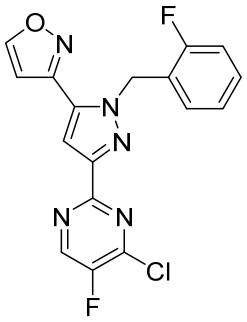
,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



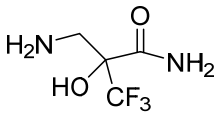
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI , and

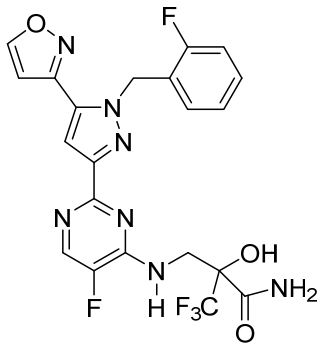
vi) reacting an amine of formula **(13)**:



(**13**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IB.

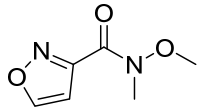
[0007j] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula IB:



Formula IB ,

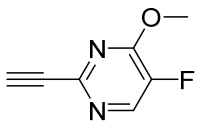
comprising the step of:

i) coupling an amide of formula **(1')**:



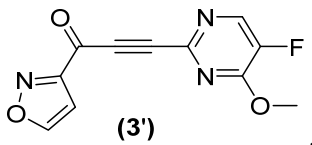
(1')

with a pyrimidine compound of formula **(2)**:



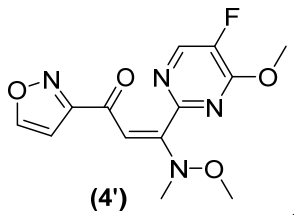
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



(3') ,

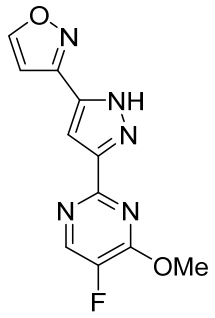
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4')

,

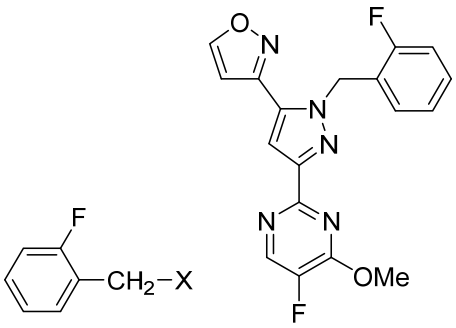
iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



(24')

;

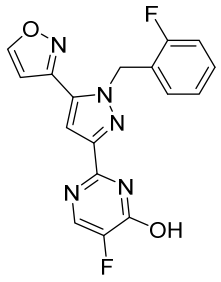
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) Formula V

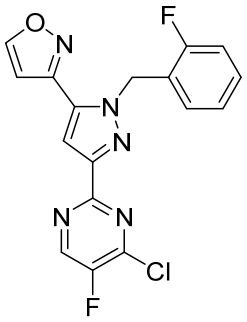
,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



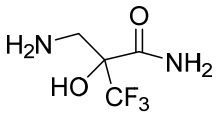
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI , and

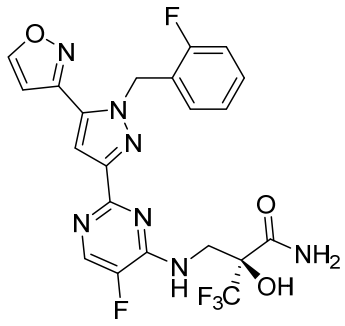
vi) reacting an amine of formula **(13)**:



(13)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IB, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

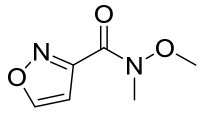
[0007k] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula IC:



Formla IC ,

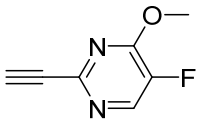
comprising the steps of:

i) coupling an amide for formula **(1')**:



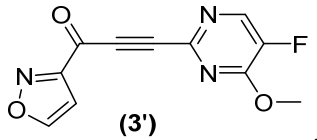
(1')

with a pyrimidine compound of formula **(2)**:



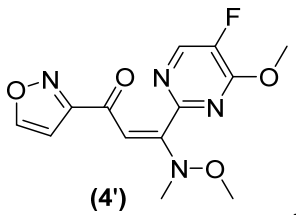
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



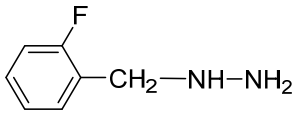
(3') ,

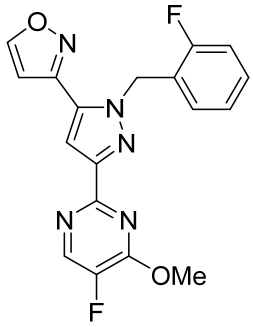
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4') ,

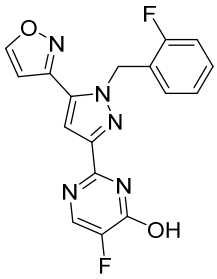
iii) condensing the compound of formula **(4')** with a hydrazine of formula

 or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



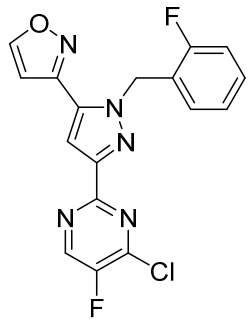
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



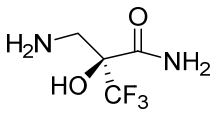
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

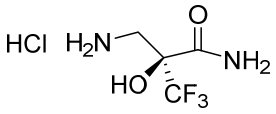


Formula VI , and

vi) reacting an amine of formula **(19A)** or its HCl salt of formula **(19)**:



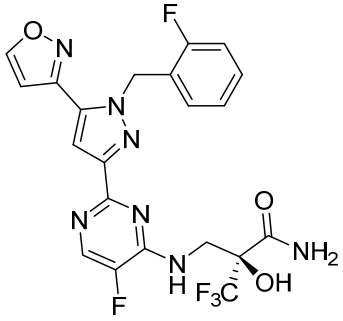
(**19A**)



(**19**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC.

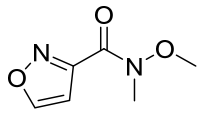
[0007l] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula IC:



Formula IC ,

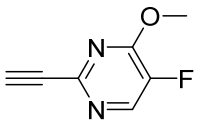
comprising the steps of:

i) coupling an amide of formula **(1')**:



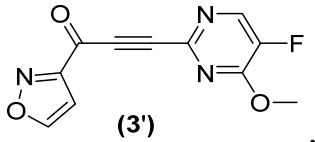
(1')

with a pyrimidine compound of formula **(2)**:



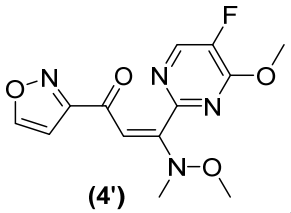
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



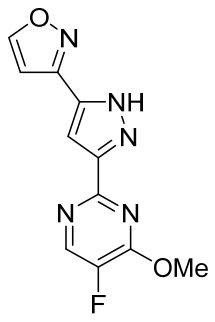
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



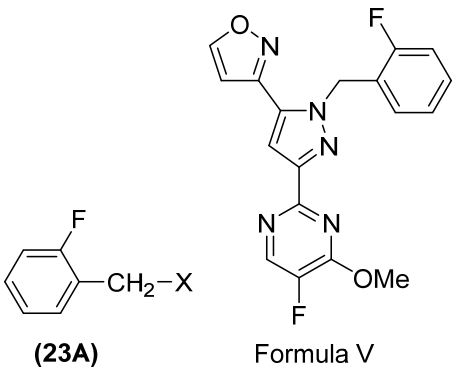
(4') ,

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



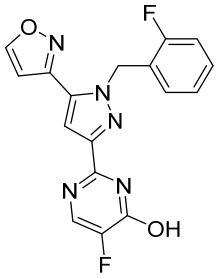
(24') ;

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



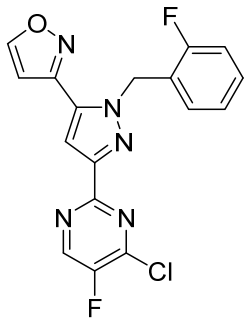
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



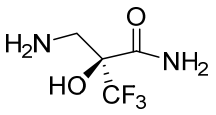
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

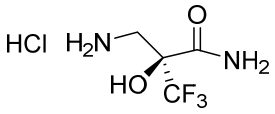


Formula VI , and

vi) reacting an amine of formula **(19A)** or its HCl salt of formula **(19)**:



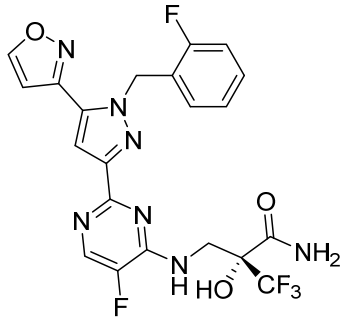
(**19A**)



(**19**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

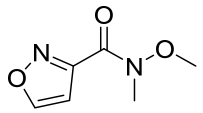
[0007m] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula ID:



Formula ID ,

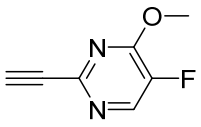
comprises the steps of:

i) coupling an amide for formula **(1')**:



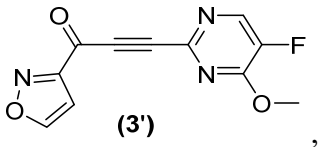
(1')

with a pyrimidine compound of formula **(2)**:



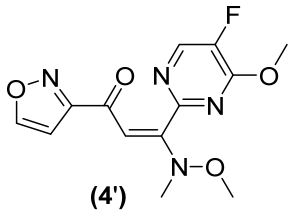
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



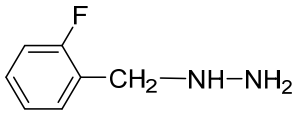
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:

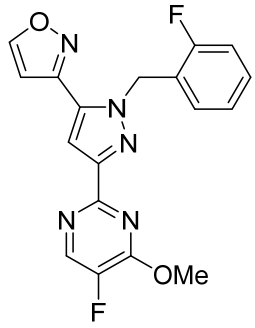


(4') ,

iii) condensing the compound of formula **(4')** with a hydrazine of formula

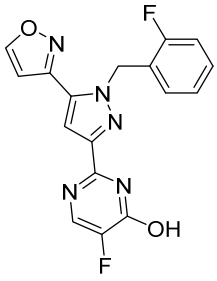


or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



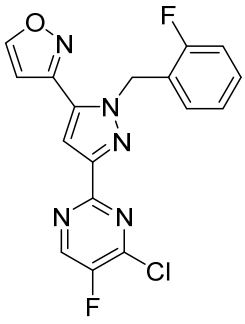
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



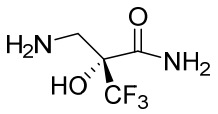
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

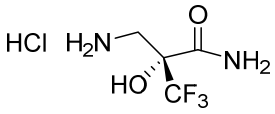


Formula VI , and

vi) reacting an amine of formula **(15A)** or its HCl salt of formula **(15)**:



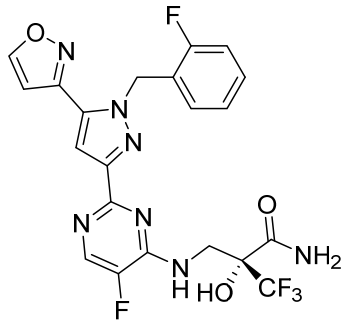
(**15A**)



(**15**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID.

[0007n] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula ID:

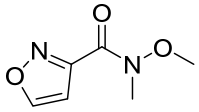


Formula ID

,

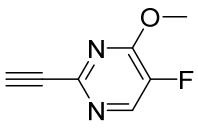
comprising the steps of:

i) coupling an amide of formula **(1')**:



(1')

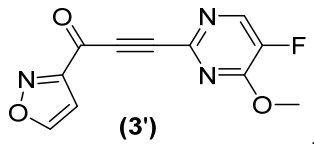
with a pyrimidine compound of formula **(2)**:



(2)

,

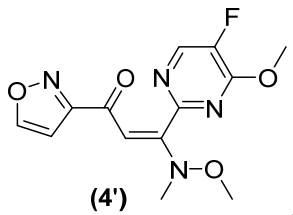
in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



(3')

,

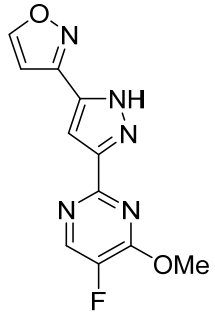
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4')

,

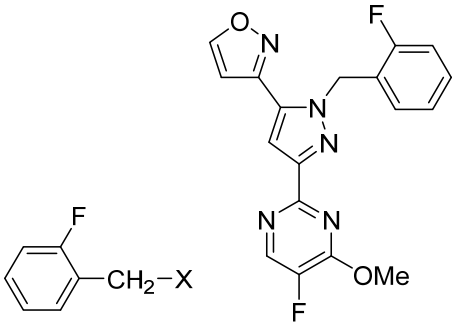
iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



(24')

,

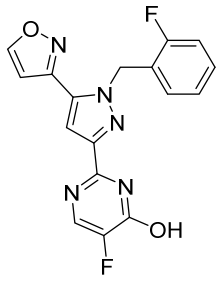
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) Formula V

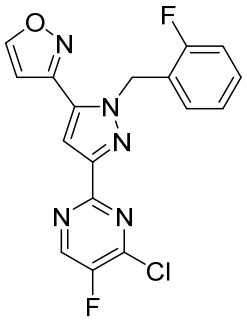
,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



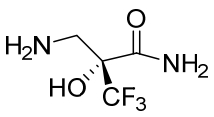
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

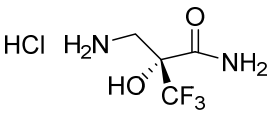


Formula VI , and

vi) reacting an amine of formula **(15A)** or its HCl salt of formula **(15)**:



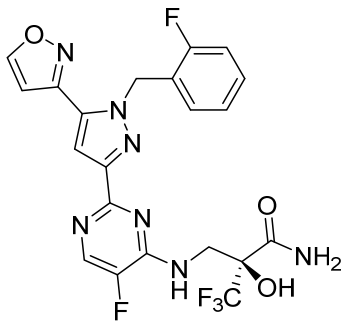
(**15A**)



(**15**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate).

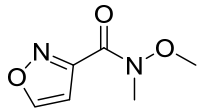
[0007o] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula IC:



Formula IC ,

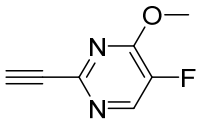
comprises the steps of:

i) coupling an amide for formula **(1')**:



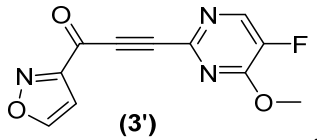
(1')

with a pyrimidine compound of formula **(2)**:



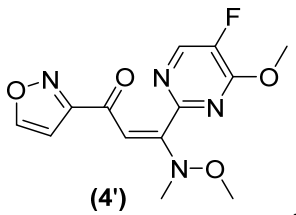
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3') ,

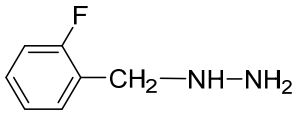
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



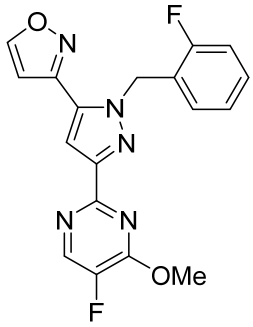
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



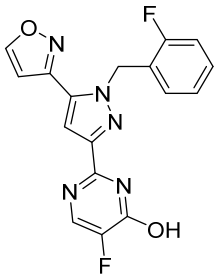
or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



Formula V

,

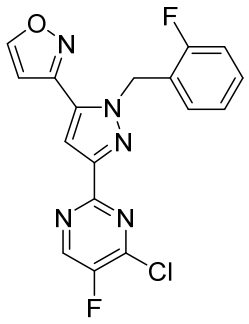
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9')

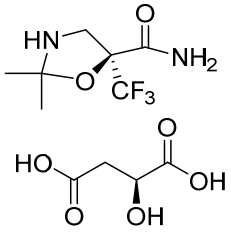
,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

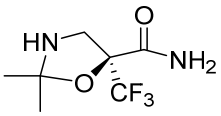


Formula VI ; and

vi) reacting an (*L*)-malic acid salt of an amine **(21)** represented by formula **(18)**:



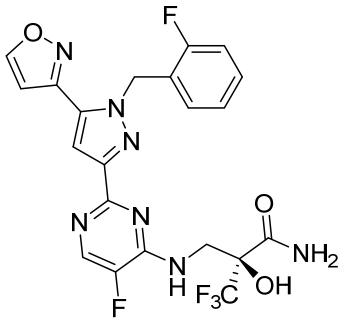
(**18**)



(**21**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC.

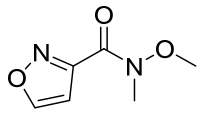
[0007p] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula IC:



Formula IC ,

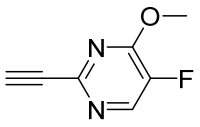
comprising the steps of:

i) coupling an amide of formula **(1')**:



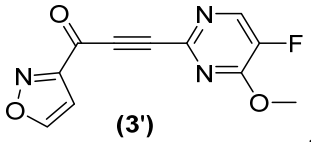
(1')

with a pyrimidine compound of formula **(2)**:



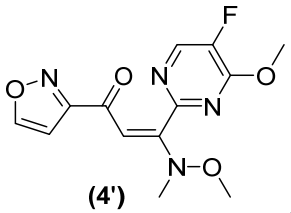
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



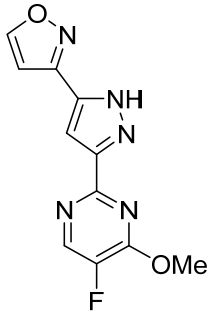
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



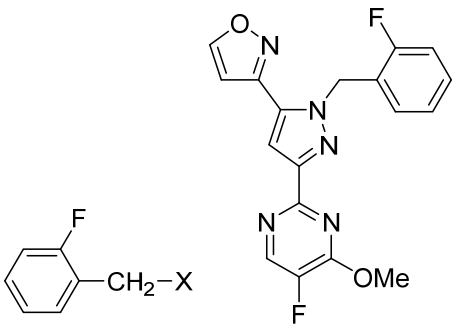
(4') ,

iiia) condensing the compound of formula **(4')** with a hydrazine (*e.g.*, hydrazine hydrate) to form a compound of formula (**24')**:



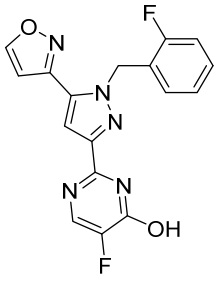
(24') ,

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



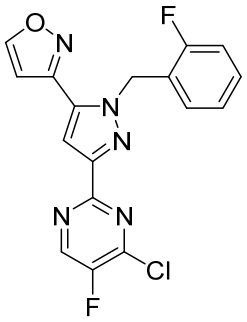
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



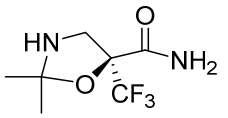
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

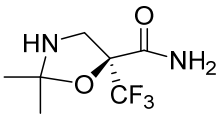


Formula VI , and

vi) reacting an (*L*)-malic acid salt of an amine **(21**) represented by formula **(18)**:



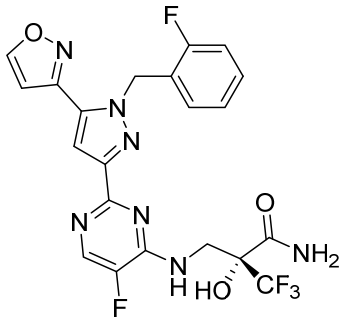
(**18**)



(**21**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

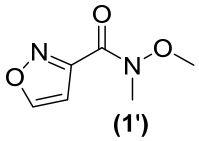
[0007q] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula ID:



Formula ID

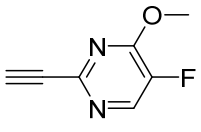
comprising the steps of:

i) coupling an amide of formula **(1')**:



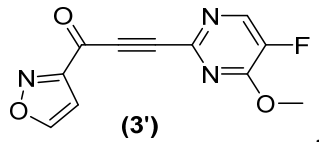
(**1'**)

with a pyrimidine compound of formula **(2)**:



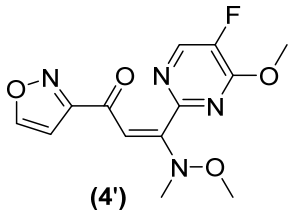
(**2**) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**



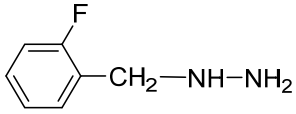
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:

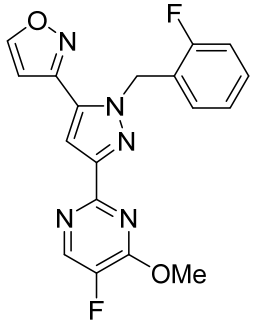


(4') ,

iii) condensing the compound of formula **(4')** with a hydrazine of formula

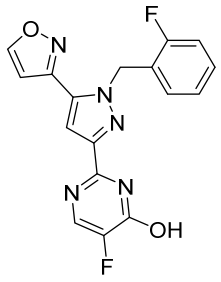


or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



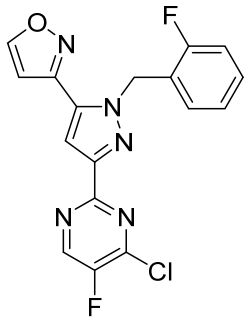
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



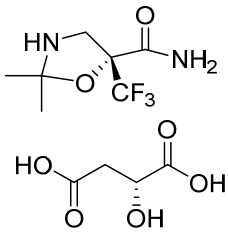
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

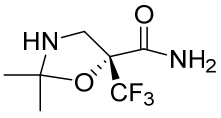


Formula VI , and

vi) reacting a (*D*)-malic acid salt of an amine (**20**) represented by formula (**14**):



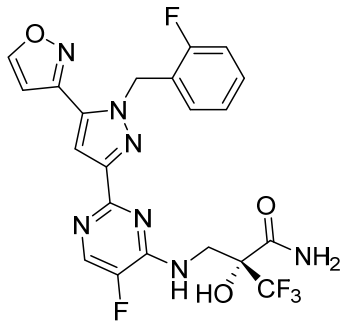
(**14**)



(**20**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID.

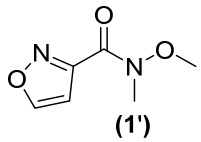
[0007r] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula ID:



Formula ID ,

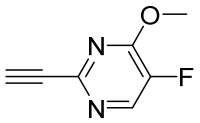
comprising the steps of:

i) coupling an amide of formula **(1')**:



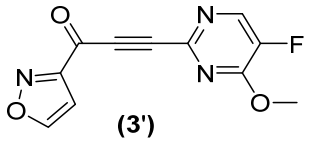
(1')

with a pyrimidine compound of formula **(2)**:



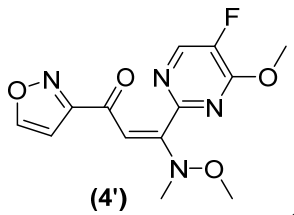
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3') ,

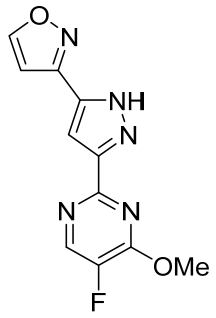
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4')

,

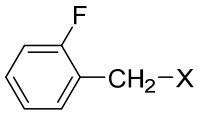
iiia) condensing the compound of formula **(4')** with a hydrazine (*e.g.*, hydrazine hydrate) to form a compound of formula (**24'**):



(24')

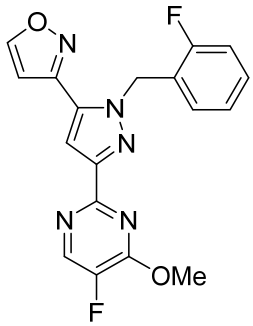
,

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**)



(23A)

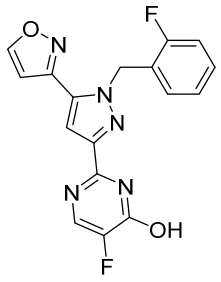
to provide the compound of Formula V:



Formula V

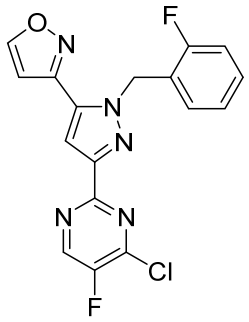
,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



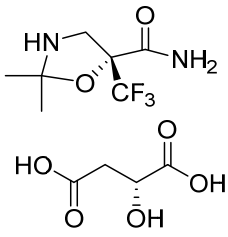
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

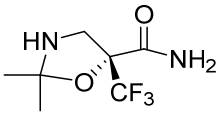


Formula VI , and

vi) reacting a (*D*)-malic acid salt of an amine (**20**) represented by formula (**14**):



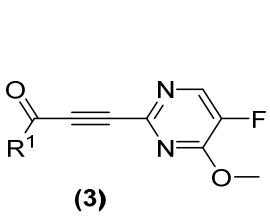
(**14**)



(**20**)

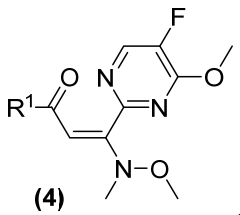
with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

[0007s] In another aspect of the present disclosure, there is provided a compound of formula **(3)** or **(4)**:



(3)

; or

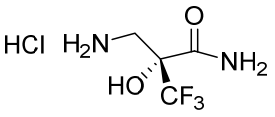


(4)

,

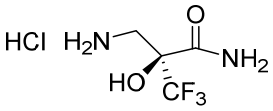
wherein R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O.

[0007t] In a further aspect of the present disclosure, there is provided ap compound represented by any one of the following formulae:



(**15**)

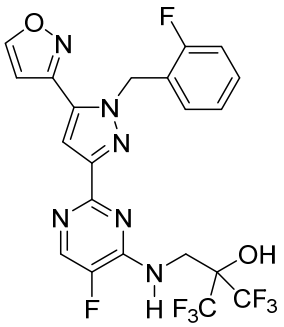
; and



(**19**)

.

[0007u] In another aspect of the present disclosure, there is provided Crystalline Form A of the compound of Formula IA:



Formula IA

,

having at least one, two, three, four, five, six, seven or eight major peaks in an x-ray powder diffraction (XRPD) pattern selected from selected from 4.2, 9.1, 9.8, 17.2, 17.7, 18.2, 27.5, and 36.0 degree 2θ angles; optionally the crystalline Form A has (i) the XRPD pattern of FIG. 1; (ii)

an endothermic onset at a temperature between 160 °C and 165 °C in a differential scanning calorimetry (DSC) profile; and/or (iii) an endothermic onset at 163.1 °C; and optionallyat least 70%, 80%, 90%, 95%, 98%, 99%, 99.5%, or 99.9% of the compound is the crystalline Form A of the compound.

[0008] In one example, compounds of Formula I and their pharmaceutically acceptable salts are sGC stimulators useful for treating diseases or disorders that benefit from sGC stimulation or from an increase in the concentration of nitric oxide (NO) and/or cyclic guanosine monophosphate (cGMP). In another example, compounds of Formula I are useful intermediates in the preparation of said sGC stimulators.

[0009] For a compound of Formula I, the following definitions apply:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O;

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5;

wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

R^4 is chloro, -OMe or $-NR^6R^7$;

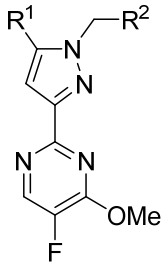
each R^5 is independently methyl, methoxy or halogen;

R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

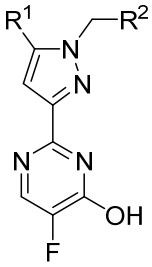
R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$.

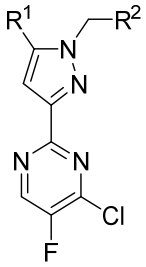
In a first example, a compound of Formula I is a compound of Formula II. In a second example, a compound of Formula I is a compound of Formula III. In a third example, a compound of Formula I is a compound of Formula IV. In a fourth example, a compound of Formula I is a compound of Formula V. In a fifth example, a compound of Formula I is a compound of Formula VI. In a sixth example, a compound of Formula I is a compound of Formula VII. In a seventh example, a compound of Formula I is Compound IA. In an eighth example, a compound of Formula I is a compound of Formula IB. In a ninth example, a compound of Formula I is a compound of Formula IC. In a tenth example, a compound of Formula I is a compound of Formula ID. In an eleventh example, a compound of Formula I is Compound (9). In a twelfth example, a compound of Formula I is Compound (9').



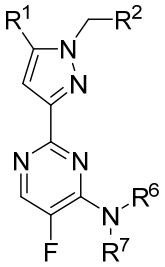
Formula II



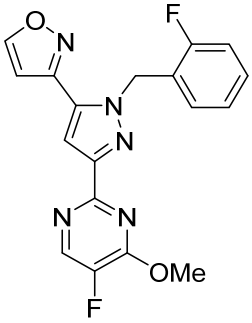
Compound 9



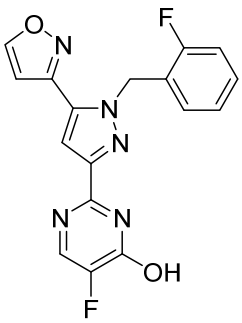
Formula III



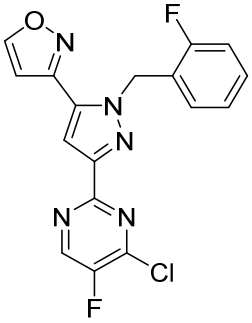
Formula IV



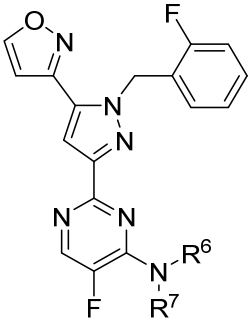
Formula V



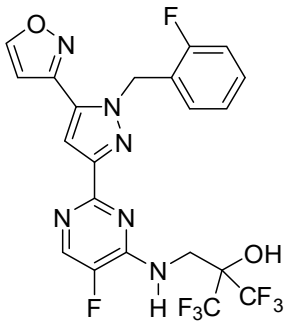
Compound 9'



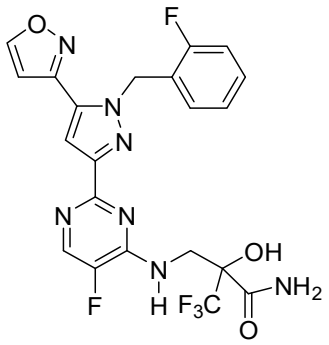
Formula VI



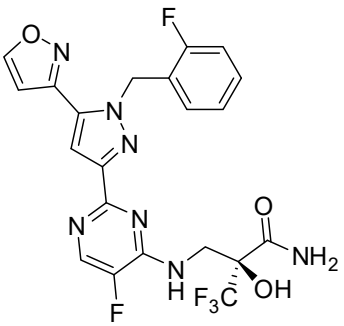
Formula VII



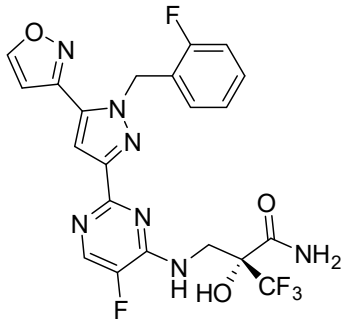
Formula IA



Formula IB

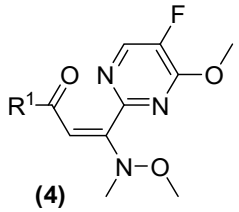


Formula IC



Formula ID

[0010] In a 1st specific example, the present invention provides a process for preparing a compound of formula **(4)**:

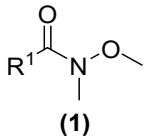


(4)

,

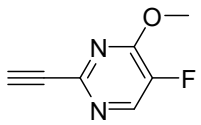
comprising the steps of:

i) coupling an amide of formula **(1)**:



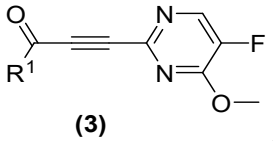
(1)

with a pyrimidine compound of formula **(2)**:



(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:

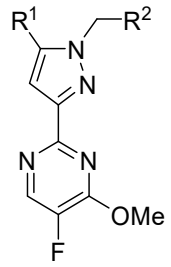


(3) , and

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.*, hydrochloride salt) thereof, allowing the mixture to react to form the compound of formula **(4)**, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O.

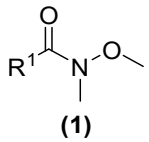
[0011] In a 2nd specific example, the present disclosure provides a process for preparing a compound of Formula II:



Formula II ,

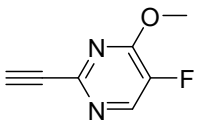
comprising the steps of:

i) coupling an amide of formula **(1)**:



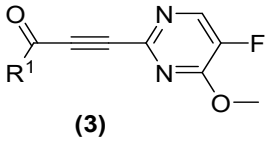
(1)

with a pyrimidine compound of formula **(2):**



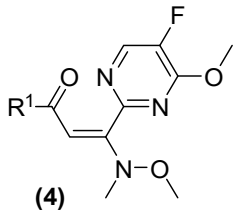
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:



(3) ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4)**:



(4) , and

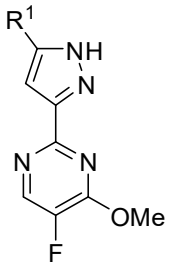
iii) condensing the compound of formula **(4)** with a hydrazine of formula R^2-CH_2-NH-NH_2 or a salt (*e.g.* HCl salt) thereof, optionally in the presence of a base, to form the compound of Formula II, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; and

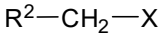
each R^5 is independently methyl, methoxy or halogen.

[0012] In a 3rd specific example, the present disclosure provides a process for preparing a compound of Formula II:



(24) ; and

iiib) alkylating intermediate of formula (**24**) with an alkylating agent of formula (**22**) to provide the compound of Formula II



(22) ;

wherein:

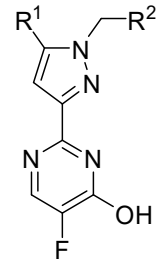
R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

each R^5 is independently methyl, methoxy or halogen; and

X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate). In a more specific example, X is –Br.

[0013] In a 4th specific example, the present disclosure provides a process for preparing Compound (**9**):



Compound (**9**),

comprising the steps of:

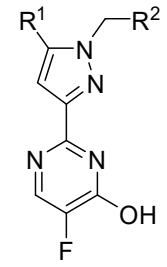
iv) de-methylating the compound of Formula II to form an alcohol Compound (**9**); wherein

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; and

each R^5 is independently methyl, methoxy or halogen.

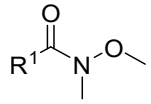
[0014] In a 5th specific example, the present disclosure provides a process for preparing Compound (**9**):



Compound (**9**),

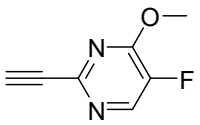
comprising the steps of:

i) coupling an amide of formula **(1)**:



(1)

with a pyrimidine compound of formula **(2):**



(2),

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:

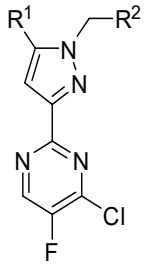
said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

each R^5 is independently methyl, methoxy or halogen; and

X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate). In a more specific example, X is –Br.

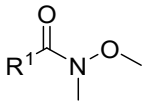
[0015] In a 6th specific example, the present disclosure provides a process for preparing a compound of formula III:



Formula III ,

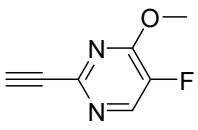
comprising the steps of:

i) coupling an amide of formula **(1)**:



(1)

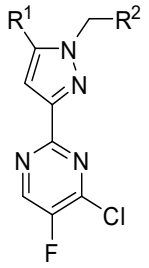
with a pyrimidine compound of formula **(2)**:



(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:

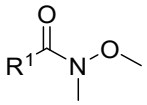
[0016] In a 7th specific example, the present disclosure provides a process for preparing a compound of formula III:



Formula III ,

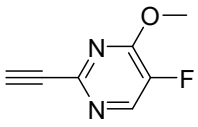
comprising the steps of:

i) coupling an amide of formula **(1)**:



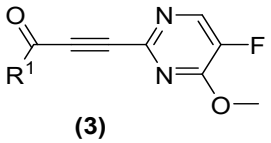
(1)

with a pyrimidine compound of formula **(2)**:



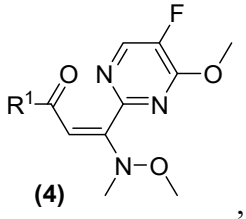
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:



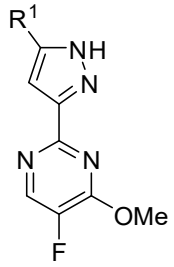
(3) ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4)**:



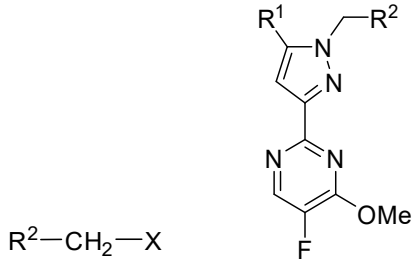
(4) ,

iiia) condensing the compound of formula **(4)** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24**):



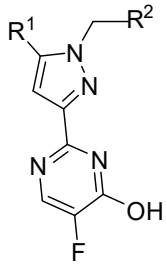
(24) ,

iiib) alkylating intermediate of formula (**24**) with an alkylating agent of formula (**22**) to provide the compound of Formula II:



(22) Formula II ,

iv) de-methylating the compound of Formula II to form an alcohol compound of formula **(9)**:



(9) ; and

v) chlorinating the alcohol compound of formula **(9)** with phosphoryl chloride to form the compound of Formula III, wherein R^1 and R^2 are as described above for Formula II; and

X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate).

[0017] In a 8th specific example, the present disclosure provides a process of preparing a compound of Formula IV:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O;

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms,

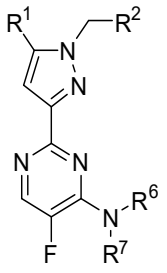
each R^5 is independently methyl, methoxy or halogen;

R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$.

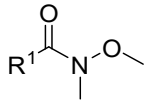
[0018] In a 9th specific example, the present disclosure provides a process of preparing a compound of Formula IV:



Formula IV ,

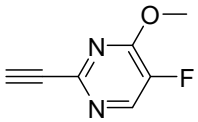
comprising the steps of:

i) coupling an amide of formula **(1)**:



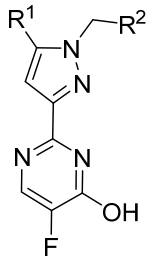
(1)

with a pyrimidine compound of formula **(2)**:



(2) ,

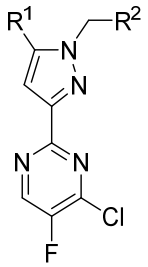
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid,



(9)

,

v) chlorinating the alcohol compound of formula **(9)** with phosphoryl chloride to form a compound of Formula III:



Formula III

, and

vi) reacting an amine compound of formula **(10)**:



(**10**)

with the compound of Formula III, optionally in the presence of a base, to yield the compound of Formula IV, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O;

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms,

each R^5 is independently methyl, methoxy or halogen;

X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

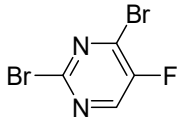
R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$.

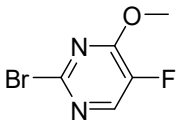
[0019] In a 10th specific example, for the process described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th and 9th specific example, the compound of formula **(2)** is prepared by a process comprising the steps of:

a) reacting dibromopyrimidine compound of formula **(5)**:



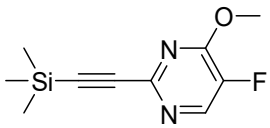
(5)

with a base in methanol or a methoxide salt in an aprotic solvent to form a bromopyrimidine compound of formula **(6)**:



(6) ,

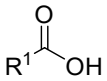
b) coupling the bromopyrimidine compound of formula **(6)** with ethynyltrimethylsilane, in an aprotic organic solvent in the presence of a base and a Pd catalyst, optionally in the presence of a Cu(I) catalyst, to form a compound of formula **(7)**:



(7) , and

c) de-silylating the compound of formula **(7)** to form the pyrimidine compound of formula **(2).**

[0020] In a 11th specific example, for the process described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th and 10th specific example, the compound of formula **(1)** is prepared by reacting a carboxylic acid of formula **(8)**:

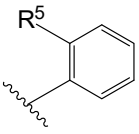


(**8**)

with oxalyl chloride or an equivalent amide coupling reagent, followed by *N,O*-dimethylhydroxylamine or a salt (*e.g.*, hydrochloride salt) thereof in the presence of a base to form the amide of formula **(1).**

[0021] In a 12th example, for steps i) and ii) of the process described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th and 11th specific example, the process comprises contacting the reaction product of the amide of formula (**1**) and the pyrimidine compound of formula (**2**) with a solution comprising *N,O*-dimethylhydroxylamine or a salt thereof and an acid to form the compound of formula (**4**). In one example, the acid is an aqueous acid. More specifically, the acid is hydrochloric acid. In another example, the acid is a non-aqueous acid. More specifically, the acid is glacial acetic acid.

[0022] In certain examples, for the process described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th specific example, R^1 is a 5-membered heteroaryl ring. In other examples, R^1 is a 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O.

[0023] In certain examples, for the process described in the 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th specific example, R^2 is phenyl optionally substituted with up to two instances of R^5. In some examples, R^2 is phenyl optionally substituted with one instance of R^5. In some examples, R^2 is represented by the formula . In some examples, R^2 is a 6-membered heteroaryl, optionally substituted with up to two instances of R^5; and wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms.

[0024] In certain examples, for the process described in the 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th specific example, each R^5 is independently methyl or halogen. In some examples, each R^5 is independently halogen. In other examples, each R^5 is fluoro.

[0025] In certain examples, for the process described in the 8th, 9th, 10th, 11th and 12th specific example, R^6 is hydrogen or $C_{1\text{-}2}$ alkyl substituted with 0 to 3 instances of R^8. In some example, R^6 is hydrogen.

[0026] In certain examples, for the process described in the 8th, 9th, 10th, 11th and 12th specific example, R^7 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8. In some examples, R^7 is C_{1-2} alkyl substituted with 3 instances of R^8.

[0027] In certain examples, for the process described in the 8th, 9th, 10th, 11th and 12th specific example, each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

[0028] In certain examples, for the process described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12thspecific example, the definitions for the variables are described below:

R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O;

R^2 is phenyl, optionally substituted with one or two instances of R^5;

each R^5 is fluoro;

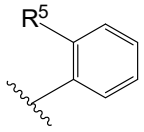
R^6 is hydrogen;

R^7 is C_{1-2} alkyl substituted with 3 instances of R^8; and

each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

[0029] In certain examples, for the process described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th specific example, the definitions for the variables are described below:

R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O;

R^2 is presented by the formula 

;

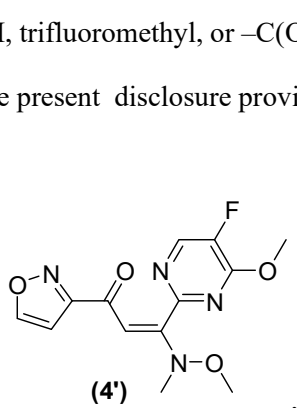
each R^5 is fluoro;

R^6 is hydrogen;

R^7 is C_{1-2} alkyl substituted with 3 instances of R^8; and

each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

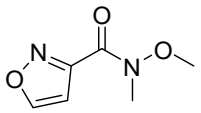
[0030] In a 13th specific example, the present disclosure provides a process of preparing a compound of formula **(4')**:



(4') ,

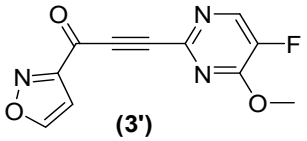
comprising the steps of:

i) coupling an amide of formula **(1')**:



(1')

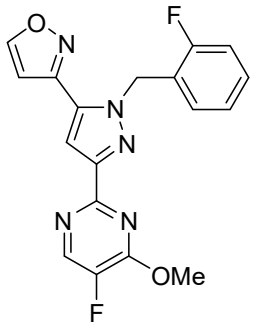
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3'), and

ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**.

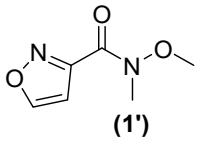
[0031] In a 14th specific example, the present disclosure provides a process of preparing a compound of Formula V:



Formula V,

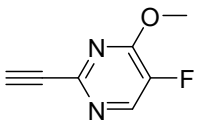
comprising the steps of:

i) coupling an amide of formula **(1')**:



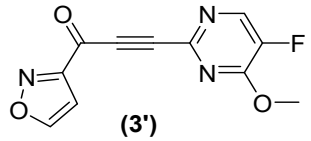
(1')

with a pyrimidine compound of formula **(2)**:



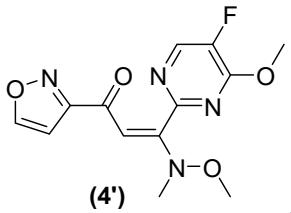
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



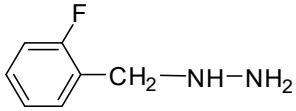
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:

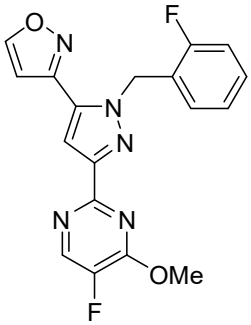


(4') ,

iii) condensing the compound of formula **(4')** with a hydrazine of formula

 or a salt (*e.g.*, HCl salt) thereof, optionally in the presence of a base, to form the compound of Formula V.

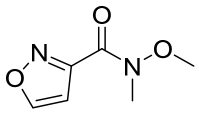
[0032] In a 15th specific example, the present disclosure provides a process of preparing a compound of Formula V:



Formula V ,

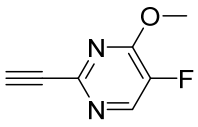
comprising the steps of:

i) coupling an amide of formula **(1')**:



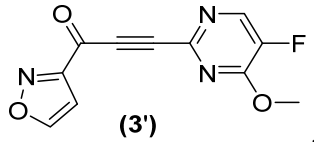
(1')

with a pyrimidine compound of formula **(2)**:



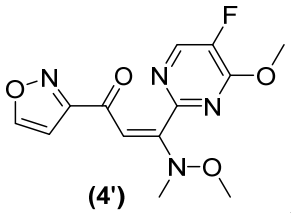
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



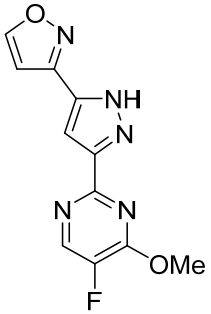
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



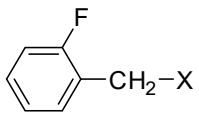
(4') ,

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



(24') ; and

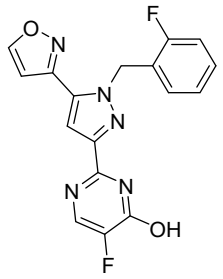
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) ,

wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate). In a more specific example, X is –Br.

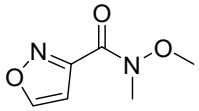
[0033] In a 16th specific example, the present disclosure provides a process for preparing Compound (**9'**):



(9') ,

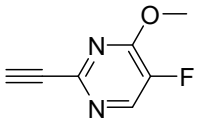
comprising the steps of:

i) coupling an amide of formula **(1')**:



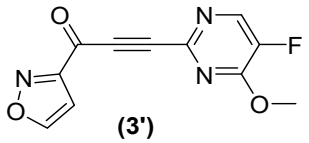
(1')

with a pyrimidine compound of formula **(2)**:



(2) ,

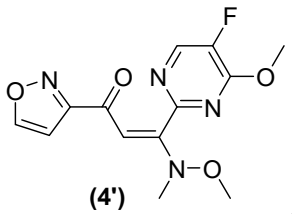
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3')

,

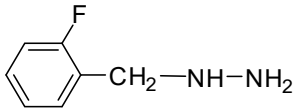
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



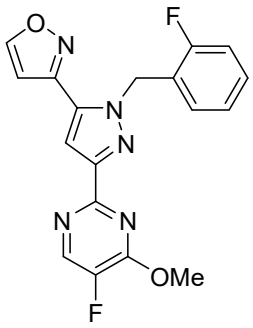
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



or a salt (*e.g.*, HCl salt) thereof, optionally in the presence of a base, to form the compound of Formula V:

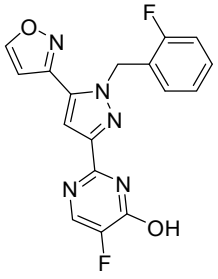


Formula V

, and

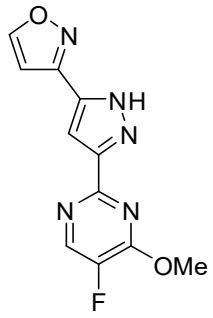
iv) de-methylating the compound of Formula V to form an alcohol Compound (**9'**).

[0034] In a 17th specific example, the present disclosure provides a process for preparing Compound (**9'**):



(9')

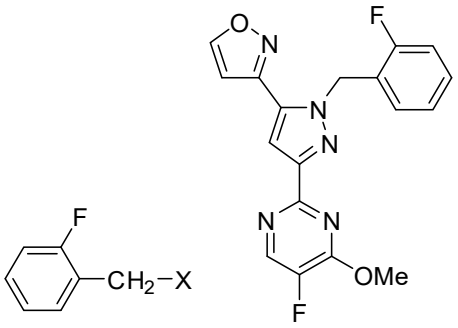
,



(24')

,

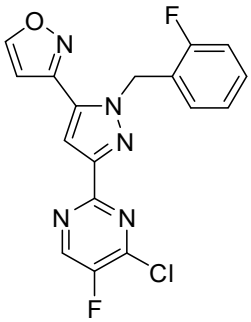
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) , Formula V , and

iv) de-methylating the compound of Formula V to form an alcohol Compound (**9'**), wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

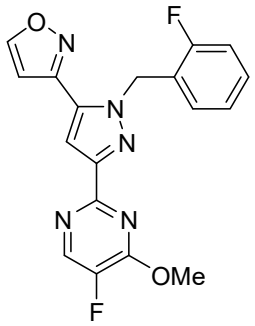
[0035] In an 18th specific example, the present disclosure provides a process of preparing a compound of Formula VI:



Formula VI

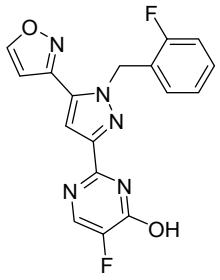
,

comprising the steps of:



Formula V ,

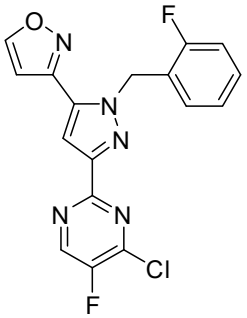
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9') , and

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form the compound of Formula VI.

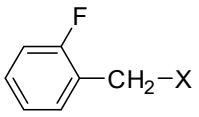
[0036] In a 19th specific example, the present disclosure provides a process of preparing a compound of Formula VI:



Formula VI ,

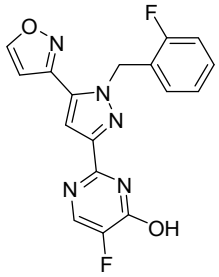
comprising the steps of:

i) coupling an amide of formula **(1')**:



(23A)

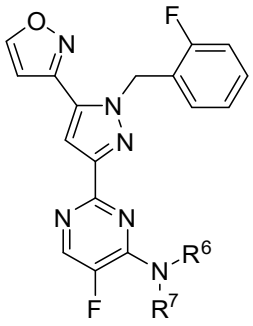
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9') , and

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form the compound of Formula VI, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

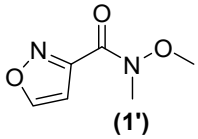
[0037] In a 20th specific example, the present disclosure provides a process of preparing a compound of formula VII:



Formula VII ,

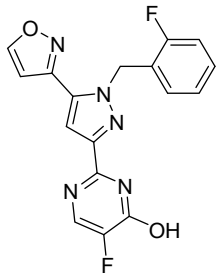
comprising the steps of:

i) coupling an amide of formula **(1')**:



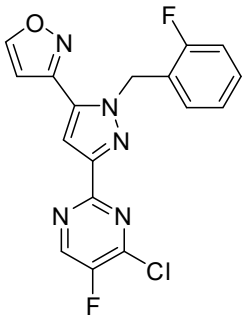
(1')

with a pyrimidine compound of formula **(2)**:



(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI , and

vi) reacting an amine compound of formula **(10):**



(**10**)

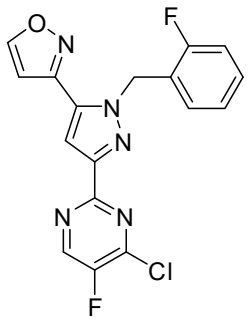
with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula VII, wherein:

R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$.

[0038] In a 21st specific example, the present disclosure provides a process of preparing a compound of formula VII:



Formula VI , and

vi) reacting an amine compound of formula **(10):**



(**10**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula VII, wherein:

X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate);

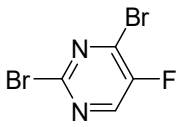
R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$. In a more specific example, X is –Br.

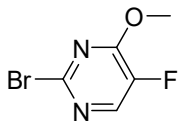
[0039] In a 22nd specific example, for the process of the 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, and 21st specific examples, the compound of formula **(2)** is prepared by a process comprising the steps of:

(a) reacting dibromopyrimidine compound of formula **(5):**



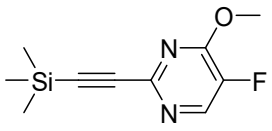
(5)

with a base in methanol or a methoxide salt in an aprotic solvent to form a bromopyrimidine compound of formula **(6)**:



(6) ,

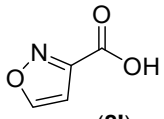
b) coupling the bromopyrimidine compound of formula **(6)** with ethynyltrimethylsilane, in an aprotic organic solvent in the presence of a base and a Pd catalyst, optionally in the presence of a Cu(I) catalyst, to form a compound of formula **(7)**:



(7) , and

c) de-silylating the compound of formula **(7)** to form the pyrimidine compound of **(2)**.

[0040] In a 23rd specific example, for the process of the 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, 21st, and 22nd specific examples, the compound of formula **(1')** is prepared by reacting a carboxylic acid of formula **(8')**:



(**8'**)

with oxalyl chloride or an equivalent amide coupling reagent, followed by *N,O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, in the presence of a base to form the amide of formula **(1')**.

[0041] In certain examples, for the process of the 20th, 21st, 22nd or 23rd specific example, R^6 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8. In some examples, R^6 is hydrogen.

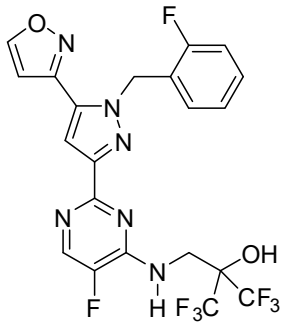
[0042] In certain examples, for the process of the 20th, 21st, 22nd or 23rd specific example, R^7 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8. In some examples, R^7 is C_{1-2} alkyl substituted with 3 instances of R^8.

[0043] In certain examples, for the process of the 20th, 21st, 22nd or 23rd specific example, R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

[0044] In certain examples, for the process of the 20th, 21st, 22nd or 23rd specific

example, R^6 is hydrogen; R^7 is C_{1-2} alkyl substituted with 3 instances of R^8 and each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

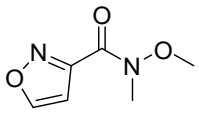
[0045] In a 24th specific example, the present disclosure provides a process of preparing a compound of Formula IA:



Formula IA ,

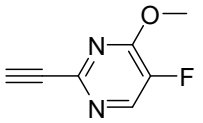
comprising the step of:

i) coupling an amide of formula **(1')**:



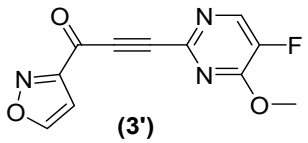
(1')

with a pyrimidine compound of formula **(2)**:



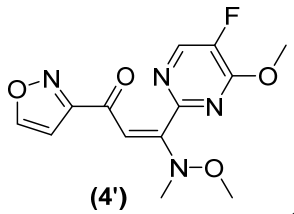
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



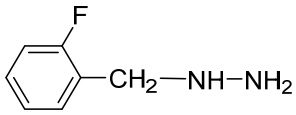
(3') ,

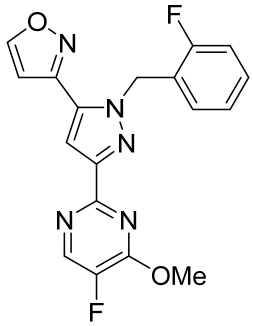
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4') ,

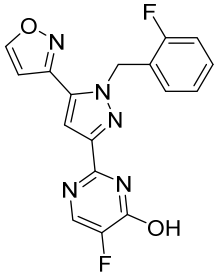
iii) condensing the compound of formula **(4')** with a hydrazine of formula

 or a salt (*e.g.* HCl salt) thereof, optionally in the presence of a base, to form a compound of Formula V:



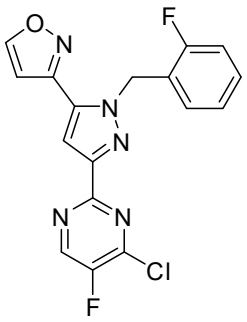
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



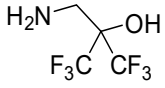
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride o form a compound of Formula VI:



Formula VI , and

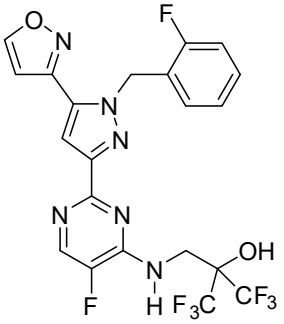
vi) reacting an amine of formula **(17)**:



(**17**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IA.

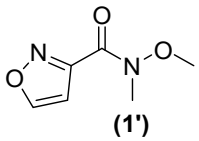
[0046] In a 25th specific example, the present disclosure provides a process of preparing a compound of Formula IA:



Formula IA ,

comprising the step of:

i) coupling an amide of formula **(1')**:



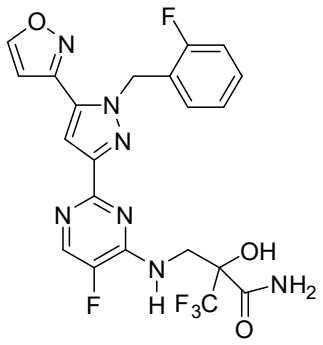
(1')

with a pyrimidine compound of formula **(2)**:

(e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

[0047] In one example, the processes of the 24th and 25th specific examples further comprise recrystallization of the compound of Formula IA. In one example, the process further comprises recrystallization of the compound of Formula IA in a mixture of methanol and water. In one example, the recrystallization comprises the steps of: A') dissolving the compound of Formula IA in methanol at a temperature between 30 °C and 65 °C to obtain a methanol solution of the compound of Formula IA; B') filtering the methanol solution of the compound of Formula IA from step A') to form a filtered methanol solution of the compound of Formula IA; C') adding water to the filtered methanol solution of the compound of Formula IA at a temperature between 50 °C and 60 °C to yield a slurry; D') cooling the slurry of step C') to yield a recrystallized compound of Formula IA; and E') filtering and drying the recrystallized compound of Formula IA.

[0048] In a 26th specific example, the present disclosure provides a process of preparing a compound of Formula IB:

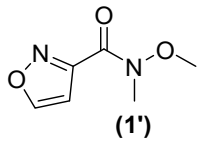


Formula IB

,

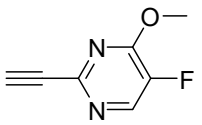
comprising the step of:

i) coupling an amide of formula **(1')**:



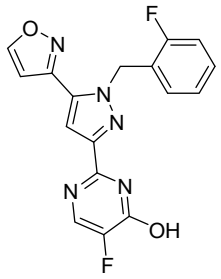
(1')

with a pyrimidine compound of formula **(2)**:



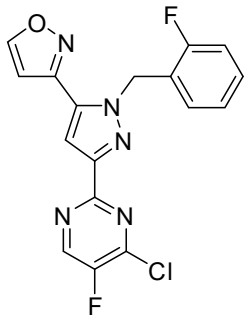
(2)

,



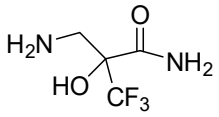
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI , and

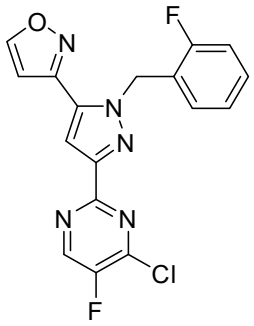
vi) reacting an amine of formula **(13)**:



(**13**)

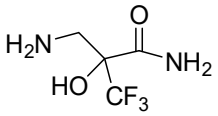
with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IB.

[0049] In a 27th specific example, the present disclosure provides a process of preparing a compound of Formula IB:



Formula VI , and

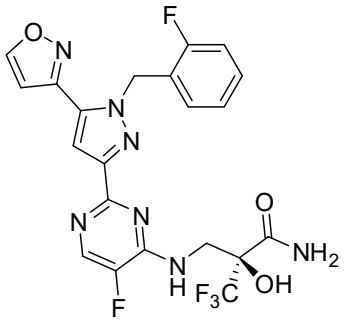
vi) reacting an amine of formula **(13)**:



(**13**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IB, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

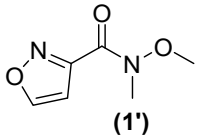
[0050] In a 28th specific example, the present disclosure provides a process of preparing a compound of Formula IC:



Formula IC ,

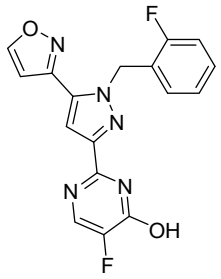
comprising the steps of:

i) coupling an amide of formula **(1')**:



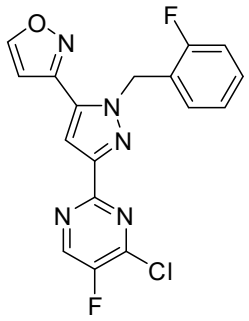
(1')

with a pyrimidine compound of formula **(2)**:



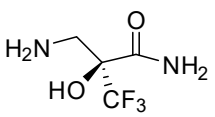
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

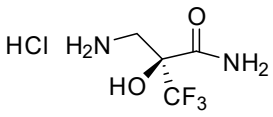


Formula VI , and

vi) reacting an amine of formula **(19A)** or its HCl salt of formula **(19)**:



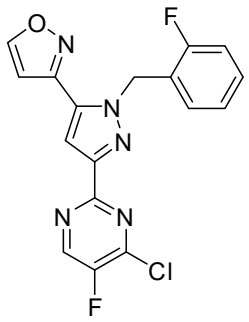
(**19A**)



(**19**)

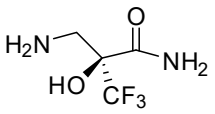
with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC.

[0051] In a 29th specific example, the present disclosure provides a process of preparing a compound of Formula IC:

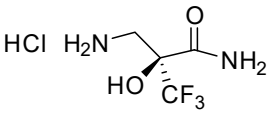


Formula VI , and

vi) reacting an amine of formula **(19A)** or its HCl salt of formula **(19)**:



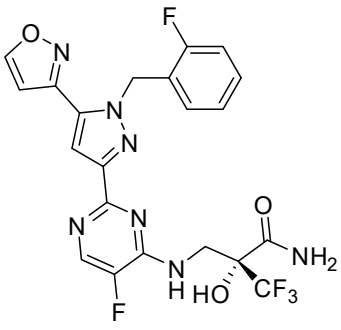
(**19A**)



(**19**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

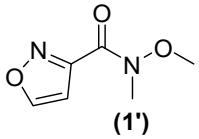
[0052] In a 30th specific example, the present disclosure provides a process of preparing a compound of Formula ID:



Formula ID ,

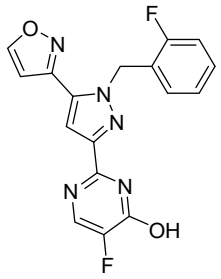
comprising the steps of:

i) coupling an amide of formula **(1')**:



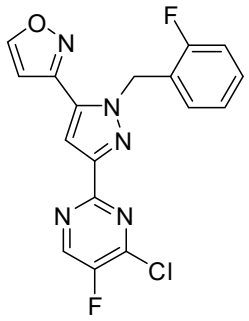
(1')

with a pyrimidine compound of formula **(2)**:



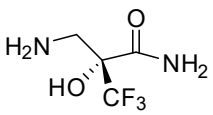
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

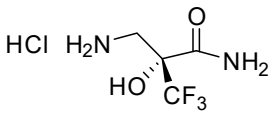


Formula VI , and

vi) reacting an amine of formula **(15A)** or its HCl salt of formula **(15)**:



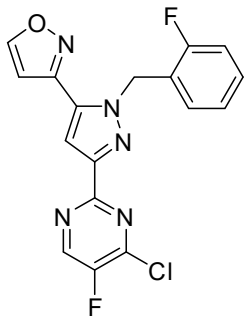
(**15A**)



(**15**)

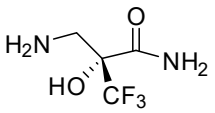
with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID.

[0053] In a 31st specific example, the present disclosure provides a process of preparing a compound of Formula ID:

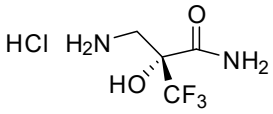


Formula VI , and

vi) reacting an amine of formula **(15A)** or its HCl salt of formula **(15)**:



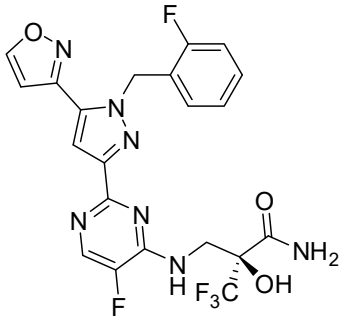
(**15A**)



(**15**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

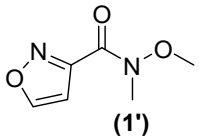
[0054] In a 32nd specific example, the present disclosure provides a process of preparing a compound of Formula IC:



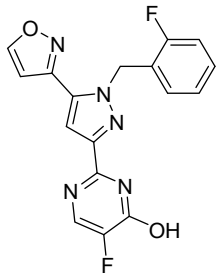
Formula IC ,

comprising the steps of:

i) coupling an amide of formula **(1')**:

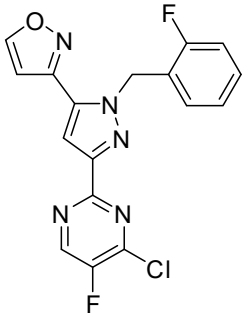


(1')



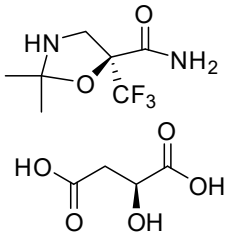
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

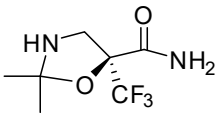


Formula VI , and

vi) reacting an (*L*)-malic acid salt of an amine **(21)** represented by formula **(18)**:



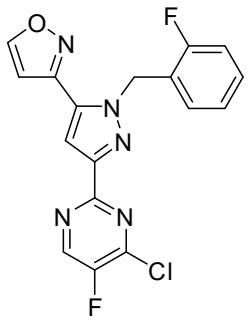
(**18**)



(**21**)

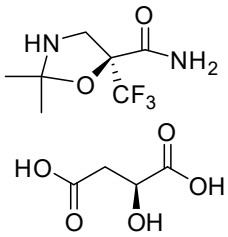
with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC.

[0055] In a 33rd specific example, the present disclosure provides a process of preparing a compound of Formula IC:

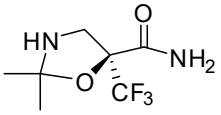


Formula VI , and

vi) reacting an (*L*)-malic acid salt of an amine **(21**) represented by formula **(18)**:



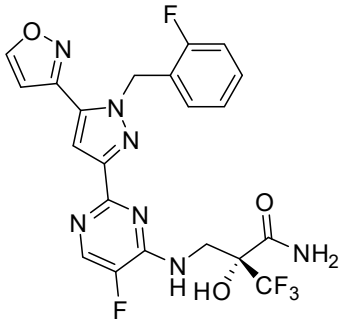
(**18**)



(**21**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

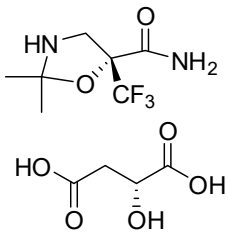
[0056] In a 34th specific example, the present disclosure provides a process of preparing a compound of Formula ID:



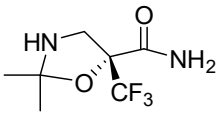
Formula ID ,

comprising the steps of:

i) coupling an amide of formula **(1')**:



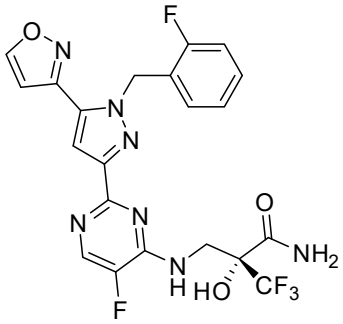
(**14**)



(**20**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID.

[0057] In a 35th specific example, the present disclosure provides a process of preparing a compound of Formula ID:

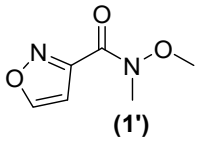


Formula ID

,

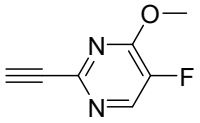
comprising the steps of:

i) coupling an amide of formula **(1')**:



(1')

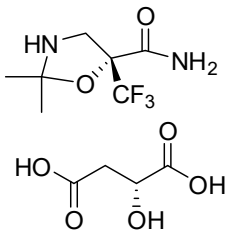
with a pyrimidine compound of formula **(2)**:



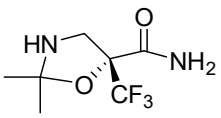
(2)

,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(**14**)



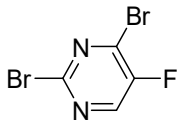
(**20**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate). In a more specific example, X is –Br.

[0058] In one example, the processes of the 34th and 35th specific examples further comprise a step of recrystallization of the compound of Formula ID to yield crystalline Form B of the compound of Formula ID. In one example, the recrystallization comprises the steps of: A") dissolving the compound of Formula ID in acetonitrile and water at a temperature between 70 °C and 75 °C to form a solution of the compound; B") filtering the solution of step A") to form a filtered solution of the compound; C") heating the filtered solution at a temperature between 65 °C and 75 °C and adding water to yield a slurry; D") cooling the slurry of step C") to a temperature between 0 to 5 °C to yield crystalline Form B of the compound of Formula ID; and E") filtering, washing with a mixture of acetonitrile and water, and drying the crystalline Form B of the compound of Formula ID.

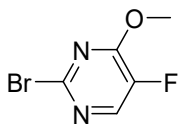
[0059] In a 36th specific example, for the process described in the 24th, 25st, 26th, 27th, 28th, 29th, 30th, 31st, 32nd, 33rd 34th and 35th specific examples, the compound of formula **(2)** is prepared by a process comprising the steps of:

a) reacting dibromopyrimidine compound of formula **(5):**



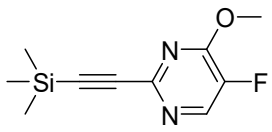
(5)

with a base in methanol or a methoxide salt in an aprotic solvent to form a bromopyrimidine compound of formula **(6)**:



(6) ,

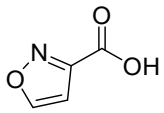
b) coupling the bromopyrimidine compound of formula **(6)** with ethynyltrimethylsilane, in an aprotic organic solvent in the presence of a base and a Pd catalyst, optionally in the presence of a Cu(I) catalyst, to form a compound of formula **(7)**:



(7) , and

c) de-silylating the compound of formula **(7)** to form the pyrimidine compound of **(2).**

[0060] In a 37th specific example, for the process described in the 24th, 25st, 26th, 27th, 28th, 29th, 30th, 31st, 32nd, 33rd 34th, 35th and 36th specific example, the compound of formula **(1')** is prepared by reacting a carboxylic acid of formula **(8')**:



(**8'**)

with oxalyl chloride or an equivalent amide coupling reagent, followed by *N,O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, in the presence of a base to form the amide of formula **(1').**

[0061] In a 38th specific example, for steps i) and ii) of the process described in the 13th to 37th specific examples, the process comprises contacting the reaction product of the reaction between the amide of formula (**1'**) and the pyrimidine compound of formula (**2**) with a solution comprising *N,O*-dimethylhydroxylamine or a salt thereof and an acid to form the compound of formula (**4'**). In one example, the acid is an aqueous acid. More specifically, the acid is hydrochloric acid. In another example, the acid is a non-aqueous acid. More specifically, the acid is glacial acetic acid.

[0062] In some examples, for the process of the 1st to 38th specific example, *N,O*-dimethylhydroxylamine or a salt (*e.g.*, hydrochloride salt) thereof is added in step ii).

[0063] In one examples, for the process of the 1st to 11th and 13th to 37th specific

example, the intermediate of formula **(3)** or **(3')** formed in step i) is isolated and then reacted with *N*,*O*-dimethylhydroxylamine or a salt (*e.g.*, hydrochloride salt) thereof at a pH >5 to form the compound of formula (**4**) or **(4')** respectively.

[0064] In some examples, for the process of the 1st to 38th specific examples, the base in step i) is n-butyllithium.

[0065] In some examples, for the process of the 1st to 38th specific example, the aprotic solvent in step i) is THF, hexane or a mixture of THF and hexane.

[0066] In some examples, for the process of the 1st to 38th specific examples, 0.5 or 0.6 equivalents of *N*,*O*-dimethylhydroxylamine hydrochloride for every one equivalent of the pyrimidine compound formula **(2)** is used in the reaction of step ii).

[0067] In some examples, for the process of the 2nd, 4th, 6th, 8th, 10th,11th, 12th, 14th, 16th, 18th, 20th, 22th, 23th, 24th, 26th, 28th, 30th, 32nd, 34th, 36th, 37th and 38th specific examples, a base is present in the reaction of step iii). In one example, the base is potassium carbonate.

[0068] In some examples, for the process of the 3rd, 5th, 7th, 9th, 10th, 11th, 12th, 15th, 17th, 19th, 21st, 22nd, 23rd, 25th, 27th, 29th, 31st, 33rd, 35th, 36th, 37th and 38th specific examples, a base is present in the reaction of step iiia). In one example, the base is potassium carbonate.

[0069] In some examples, for the process of the 3rd, 5th, 7th, 9th, 10th, 11th, 12th, 15th, 17th, 19th, 21st, 22nd, 23rd, 25th, 27th, 29th, 31st, 33rd, 35th, 36th, 37th and 38th specific examples, no base is added for the reaction of step iiia).

[0070] In some examples, for the process of the 3rd, 5th, 7th, 9th, 10th, 11th, 12th, 15th, 17th, 19th, 21st, 22nd, 23rd, 25th, 27th, 29th, 31st, 33rd, 35th, 36th, 37th and 38th specific examples, hydrazine hydrate is used in the reaction of step iiia).

[0071] In some examples, for the process of the 3rd, 5th, 7th, 9th, 10th, 11th, 12th, 15th, 17th, 19th, 21st, 22nd, 23rd, 25th, 27th, 29th, 31st, 33rd, 35th, 36th, 37th and 38th specific examples, a base is present in the reaction of step iiib). In one example, the base is an alkoxide. In another example, the base is lithim tert-butoxide (LTB), potassium tert-butoxide (KTB), or sodium tert-butoxide (STB). In yet another example, the base is lithium tert-butoxide. In another example, the base is bis(trimethylsilylyl)amine (HMDS), sodium bis(trimethylsilyl)amide (NaHMDS), lithium bis(trimethylsilyl)amide (LiHMDS), potassium bis(trimethylsilyl)amide (KHMDS), NaH or lithium diisopropylamide (LDA). In one example, the base is NaHMDS, LiHMDS or KHMDS.

[0072] In some examples, for the process of the 4th to 12th, 16th to 38th specific examples, de-methylation in step iv) is carried out using an aqueous acid and the aqueous acid is HCl.

[0073] In some examples, for the process of the 8th to 12th and 20th to 38th specific examples, a base is present in the reaction of step vi). In one example, the base is Hunig's base.

[0074] In some examples, for the process of the 8th to 12th and 20th to 38th specific examples, a base is not present in the reaction of step vi).

[0075] In some examples, for the process of the 10th, 11th, 12th, 22nd, 23rd, 36th, 37th and 38th specific examples, the methoxide salt in step a) is MeONa, MeOLi, MeOK or MeOCs. In one example, the base is MeONa.

[0076] In some examples, for the process of the 10th, 11th, 12th, 22nd, 23rd, 36th, 37th and 38th specific examples, the aprotic organic solvent in step b) is an ether. In one example, the ether is methyl-*tert*-butyl ether.

[0077] In some examples, for the process of the 10th, 11th, 12th, 22nd, 23rd, 36th, 37th and 38th specific examples, the base in step c) is triethylamine, Hunig's base, Et_2NH, iPr_2NH, piperidine, pyrrolidine, K_2CO_3, Na_2CO_3, Cs_2CO_3, or K_3PO_4. In one example, the base is triethylamine.

[0078] In some examples, for the process of the 10th, 11th, 12th, 22nd, 23rd, 36th, 37th and 38th specific examples, a Cu(I) catalyst and a Pd catalyst are present in the reaction of step c). In one example, the Cu(I) catalyst is CuCl, CuBr, CuI or CuOTf. In one example, the Cu(I) catalyst is CuI. In another example, the Pd catalyst is $PdCl_2(PPh_3)_2$.

[0079] In some examples, for the process of the 10th, 11th, 12th, 22nd, 23rd, 36th, 37th and 38th specific examples, de-silylation in step c) is carried out using a fluoride reactant. In some examples, the fluoride reactant is KF.

[0080] In some examples, for the process of the 11th, 12th, 23rd, 37th and 38th specific examples, oxalyl chloride is reacted with the compound of formula **(8)** or **(8')**, followed by *N,O*-dimethylhydroxylamine hydrochloride in the presence of a base. In one example, the base is K_2CO_3.

[0081] Also provided by the present disclosure are compounds prepared by the processes of the present disclosure. In one example, the present disclosure is directed to a compound of

formula **(3)**, **(4), (3'), (4'), (14), (18), (15), (19), (20)** or **(21)**. In one example, for compound of formula **(3)** or **(4)**, R^1 is a 5-membered heteroaryl ring. In another example, for compound of formula **(3)** or **(4)**, R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O.

[0082] In one example, the present disclosure provides crystalline Form A of the compound of Formula IA. In one example, Form A is characterized by XRPD pattern substantially similar to that shown in FIG. 1. In another example, Form A has the XRPD pattern as shown in FIG. 1. In another example, Form A has at least one, two, three, four, five, six, seven or eight major peaks in an x-ray powder diffraction (XRPD) pattern selected from 4.2, 9.1, 9.8, 17.2, 17.7, 18.2, 27.5, and 36.0 degree 2θ angles.

[0083] In one example, Form A has an endothermic onset (*i.e.*, melting point) at a temperature between 155 °C and 170 °C, between 160 °C and 165 °C, between 162 °C and 164 °C, or between 162.5 °C and 163.5 °C in a differential scanning calorimetry (DSC) profile. In another example, Form A has an endothermic onset at 163.1 °C.

[0084] In some examples, a composition of compound of formula IA has at least 70%, 80%, 90%, 95%, 98%, 99%, 99.5%, or 99.9% by weight of the compound is the crystalline Form A of the compound.

DESCRIPTION OF THE DRAWINGS

[0085] FIG. 1 shows an XRPD pattern of crystalline Form A of the compound of Formula IA.

[0086] FIG. 2 shows a DSC profile of crystalline Form A of the compound of Formula IA.

[0087] FIG. 3A shows an XRPD pattern of crystalline Form B of the compound of Formula ID in the 2θ angle range of 5 to 45 degrees.

[0088] FIG. 3B shows an XRPD pattern of crystalline Form B of the compound of Formula ID before and after storage for 14 months.

[0089] FIG. 3C shows an XRPD pattern of crystalline Form B of the Compound of Formula ID in the 2θ angle range of 3 to 40 degrees.

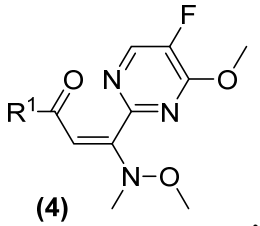
DETAILED DESCRIPTION OF THE INVENTION

[0090] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulae. While the invention will

CLAIMS

What is claimed is:

1. A process for preparing a compound of formula (**4**):

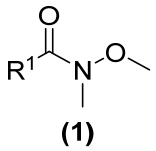


(4)

,

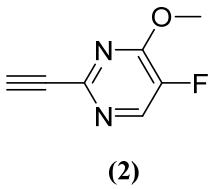
comprising the steps of:

i) coupling an amide of formula **(1)**:



(1)

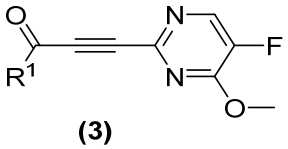
with a pyrimidine compound of formula **(2):**



(2)

,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**



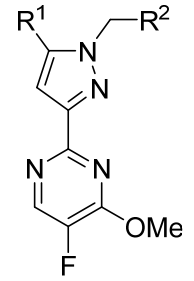
(3)

, and

ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4)**, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O.

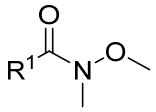
2. A process for preparing a compound of Formula II:



Formula II ,

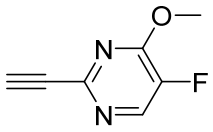
comprising the steps of:

i) coupling an amide of formula **(1)**:



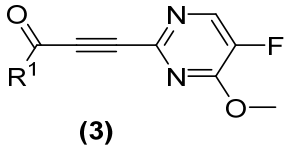
(1)

with a pyrimidine compound of formula **(2)**:



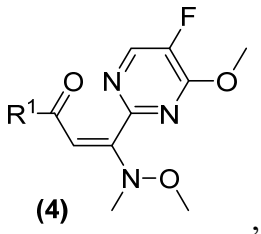
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3)**:



(3) ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4)**:



(4) , and

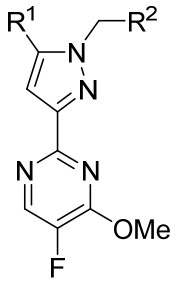
iii) condensing the compound of formula **(4)** with a hydrazine of formula R^2-CH_2-NH-NH_2 or a salt thereof, optionally in the presence of a base, to form the compound of Formula II, wherein:

R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; and

each R^5 is independently methyl, methoxy or halogen.

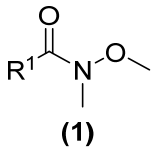
3. A process of preparing a compound of Formula II:



Formula II ,

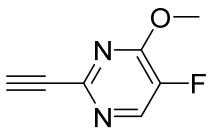
comprising the steps of:

i) coupling an amide of formula **(1)**:



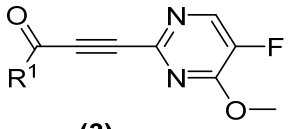
(1)

with a pyrimidine compound of formula **(2):**



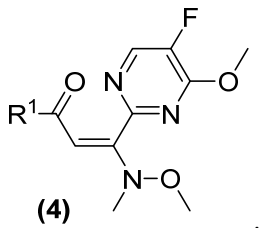
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3)**:



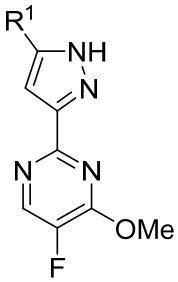
(3) ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4)**:



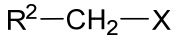
(4) ,

iiia) condensing the compound of formula **(4)** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24**):



(24) ; and

iiib) alkylating intermediate of formula (**24**) with an alkylating agent of formula (**22**) to provide the compound of Formula II



(22) ;

wherein:

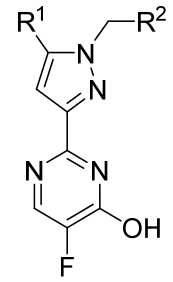
R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

R^2 is phenyl or a 6-membered heteroaryl, optionally substituted with up to three instances of R^5; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

each R^5 is independently methyl, methoxy or halogen;

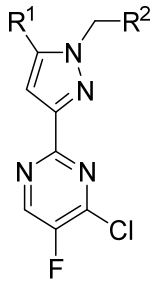
X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

4. The process of claim 2 or 3, further comprising step iv) de-methylating the compound of Formula II to form an alcohol Compound (**9**):



Compound (**9**)~~; wherein~~

5. The process of claim 4, further comprising step v) chlorinating the alcohol compound of formula **(9)** with phosphoryl chloride, to form the compound of Formula III:



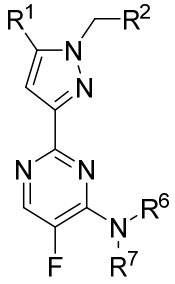
Formula III

6. The process of claim 5, further comprising step vi) reacting with an amine compound of formula **(10)**:



(**10**)

with the compound of Formula III, optionally in the presence of a base, to yield the compound of Formula IV:



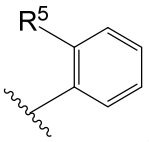
Formula IV , wherein:

R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$.

7. The process of any one of claims 1-6, wherein R^1 is a 5-membered heteroaryl ring or R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O.

8. The process of any one of claims 2-7, wherein: (i) R^2 is phenyl optionally substituted with up to two instances of R^5; (ii) R^2 is phenyl optionally substituted with one instance of R^5; (iii) R^2 is represented by formula  ; or (iv) R^2 is a 6-membered heteroaryl, optionally substituted with up to two instances of R^5; and wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; optionally wherein (i) each R^5 is independently methyl or halogen; (ii) each R^5 is independently halogen; or (iii) each R^5 is fluoro.

9. The process of any one of claims 6-8, wherein (i) R^6 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8 or R^6 is hydrogen; and/or (ii) R^7 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8 or R^7 is C_{1-2} alkyl substituted with 3 instances of R^8; optionally each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

10. The process of any one of claims 1-6, wherein:

(i) R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O;

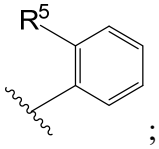
R^2 is phenyl, optionally substituted with one or two instances of R^5;

each R^5 is fluoro;

R^6 is hydrogen;

R^7 is C_{1-2} alkyl substituted with 3 instances of R^8 and each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$; or

(ii) R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O;

R^2 is 

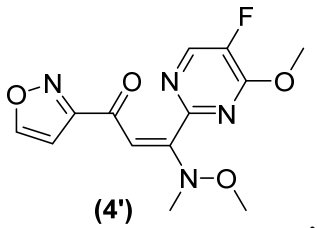
;

each R^5 is fluoro;

R^6 is hydrogen;

R^7 is C_{1-2} alkyl substituted with 3 instances of R^8 and each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

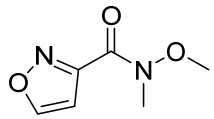
11. A process of preparing a compound of formula **(4')**:



(4') ,

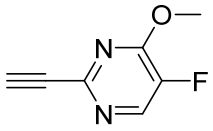
comprising the steps of:

i) coupling an amide of formula **(1')**:



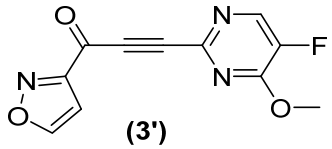
(1')

with a pyrimidine compound of formula **(2)**:



(2) ,

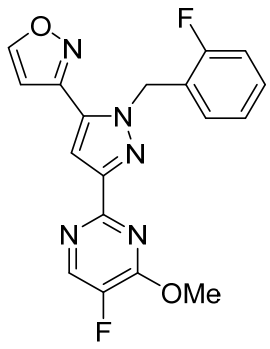
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3') , and

ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**.

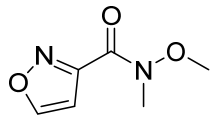
12. A process of preparing a compound of Formula V:



Formula V ,

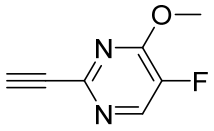
comprising the steps of:

i) coupling an amide of formula **(1')**:



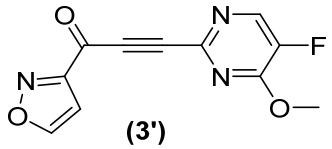
(1')

with a pyrimidine compound of formula **(2)**:



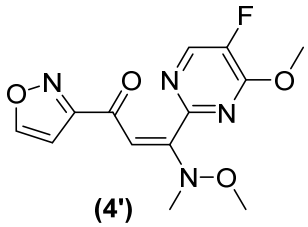
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



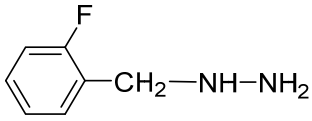
(3') ,

ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



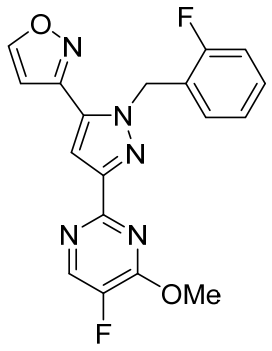
(4') , and

iii) condensing the compound of formula **(4')** with a hydrazine of formula



or a salt thereof, optionally in the presence of a base, to form the compound of Formula V.

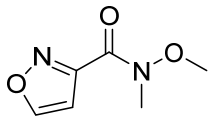
13. A process of preparing a compound of Formula V:



Formula V ,

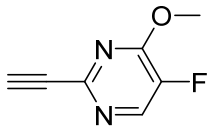
comprising the steps of:

i) coupling an amide of formula **(1')**:



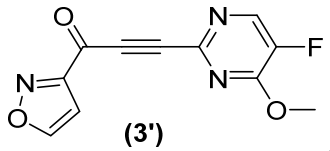
(1')

with a pyrimidine compound of formula **(2)**:



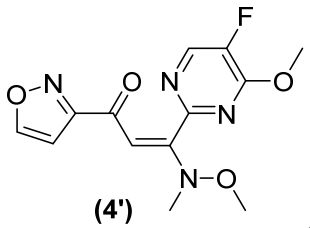
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



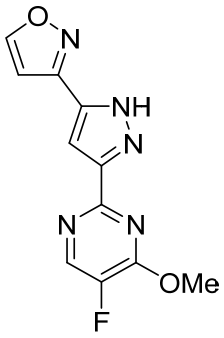
(3') ,

ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



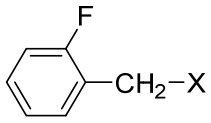
(4') ,

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



(24') ; and

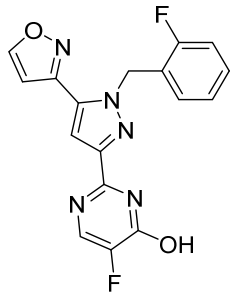
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) ,

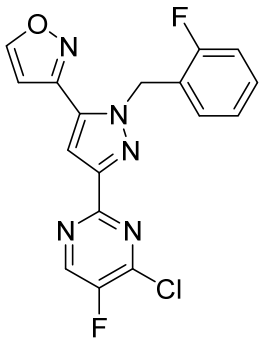
wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

14. The process of claim 12 or 13, further comprising step iv) de-methylating the compound of Formula V to form an alcohol Compound (**9'**):



(9') .

15. The process of claim 14, further comprising step v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form the compound of Formula VI:



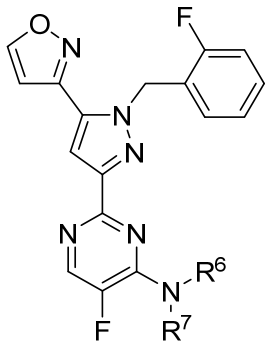
Formula VI .

16. The process of claim 15, further comprising step vi) reacting an amine compound of formula **(10):**



(**10**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula VII:



Formula VII , wherein:

R^6 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8;

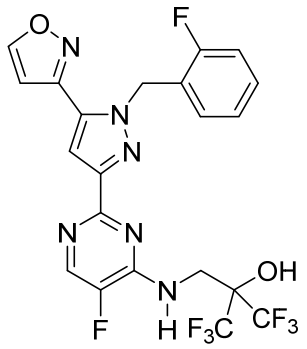
R^7 is hydrogen or C_{1-4} alkyl substituted with 0 to 3 instances of R^8; and

each R^8 is independently –OH, C_{1-3} haloalkyl, halogen or $–C(O)NH_2$.

17. The process of any one of claims 14-16, wherein (i) R^6 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8 or R^6 is hydrogen; and/or (ii) R^7 is hydrogen or C_{1-2} alkyl substituted with 0 to 3 instances of R^8 or (ii) R^7 is C_{1-2} alkyl substituted with 3 instances of R^8, optionally wherein each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

18. The process of any one of claims 14-16, wherein R^6 is hydrogen; R^7 is C_{1-2} alkyl substituted with 3 instances of R^8 and each R^8 is independently –OH, trifluoromethyl, or $–C(O)NH_2$.

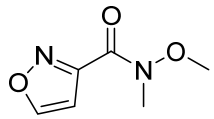
19. A process of preparing a compound of Formula IA:



Formula IA ,

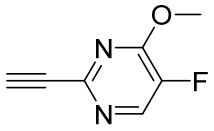
comprising the step of:

i) coupling an amide of formula **(1')**:



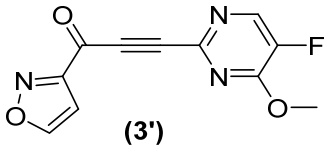
(1')

with a pyrimidine compound of formula **(2)**:



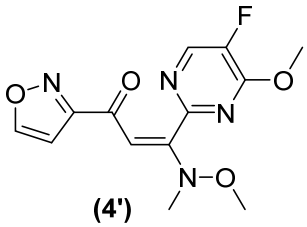
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



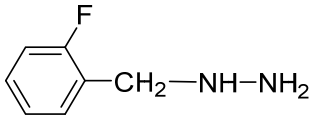
(3') ,

ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:

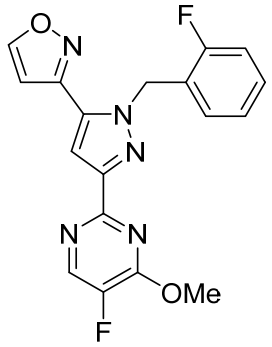


(4') ,

iii) condensing the compound of formula **(4')** with a hydrazine of formula

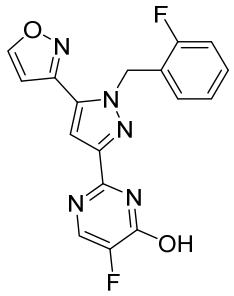


or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



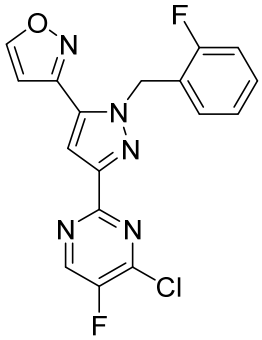
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



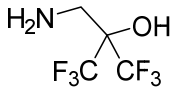
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI ,

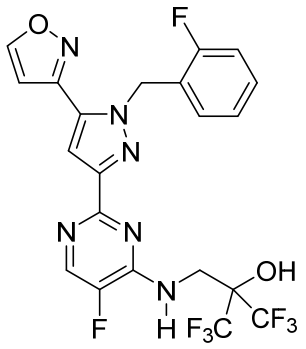
vi) reacting an amine of formula **(17)**:



(**17**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IA.

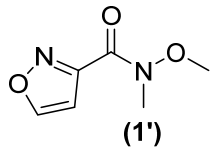
20. A process of preparing a compound of Formula IA:



Formula IA ,

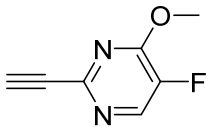
comprising the step of:

i) coupling an amide of formula **(1')**:



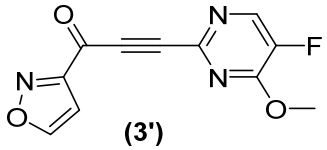
(1')

with a pyrimidine compound of formula **(2)**:



(2) ,

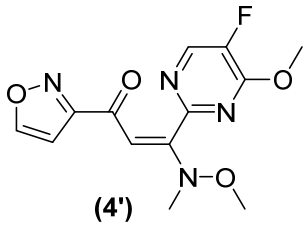
in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



(3')

, and

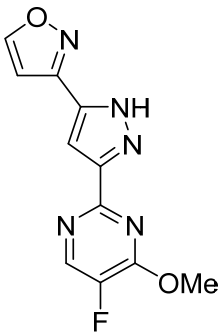
ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4')

;

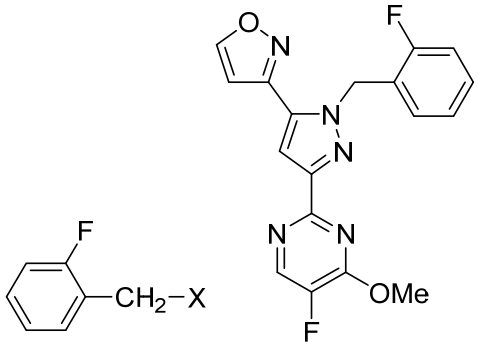
iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



(24')

;

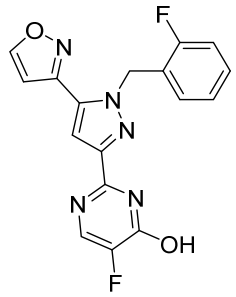
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) Formula V

,

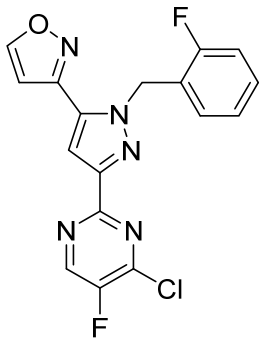
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9')

,

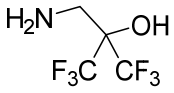
v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride o form a compound of Formula VI:



Formula VI

, and

vi) reacting an amine of formula **(17)**:



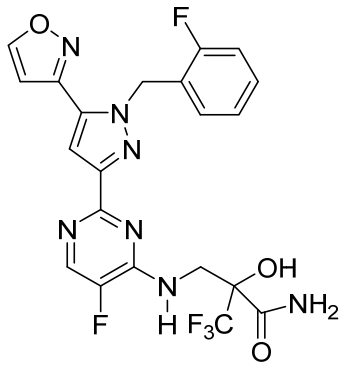
(**17**)

with the compound of Formula VIA, optionally in the presence of a base, to yield the compound of Formula IA, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

21. The process of claim 19 or 20, wherein the process further comprises re-crystalization of the compound of Formula IA in a mixture of methanol and water; optionally wherein the re-crystallization comprises the steps of: A') dissolving the compound of Formula IA in methanol at a temperature between 30 °C and 65 °C to obtain a methanol solution of the compound of

Formula IA; B') filtering the methanol solution of the compound of Formula IA from step A') to form a filtered methanol solution of the compound of Formula IA; C') adding water to the filtered methanol solution of the compound of Formula IA at a temperature between 50 °C and 60 °C to yield a slurry; D') cooling the slurry of step 3) to yield a recrystallized compound of Formula IA; and E') filtering and drying the recrystallized compound of Formula IA.

22. A process of preparing a compound of Formula IB:

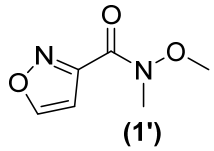


Formula IB

,

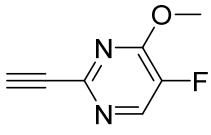
comprising the step of:

i) coupling an amide for formula **(1')**:



(1')

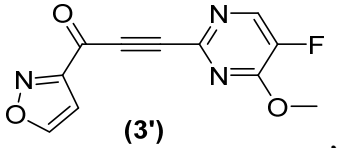
with a pyrimidine compound of formula **(2)**:



(2)

,

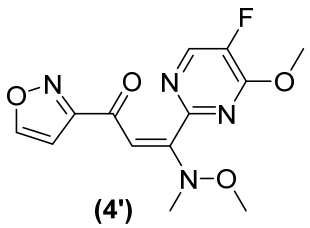
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3')

,

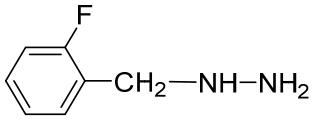
ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



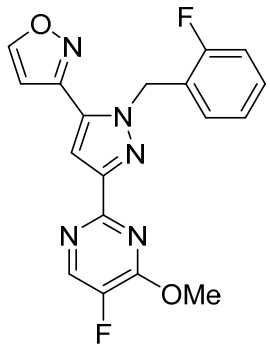
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



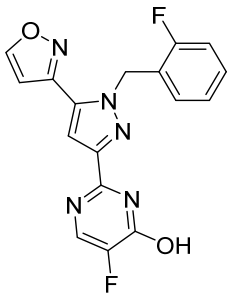
or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



Formula V

,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:

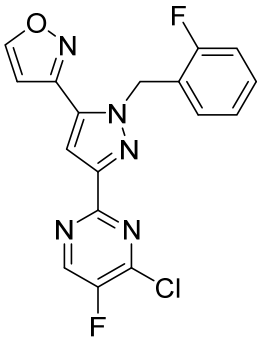


(9')

,

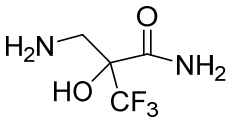
v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a

compound of Formula VI:



Formula VI , and

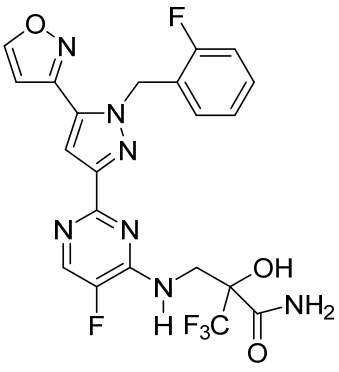
vi) reacting an amine of formula **(13)**:



(**13**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IB.

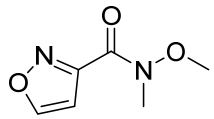
23. A process of preparing a compound of Formula IB:



Formula IB ,

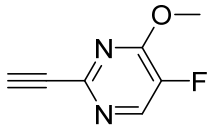
comprising the step of:

i) coupling an amide of formula **(1')**:



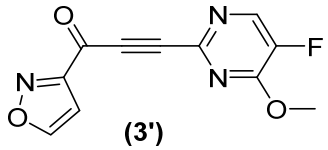
(1')

with a pyrimidine compound of formula **(2)**:



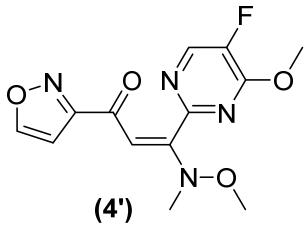
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



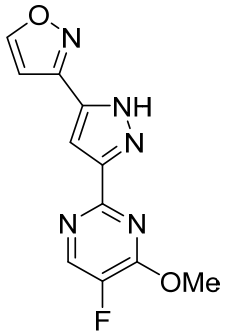
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



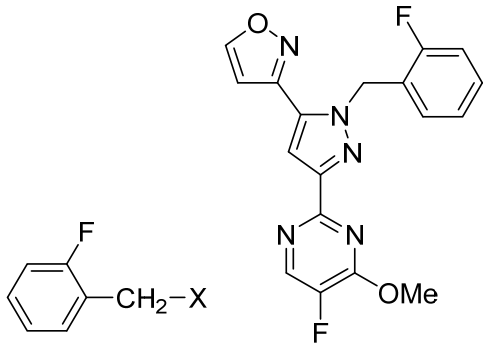
(4') ,

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



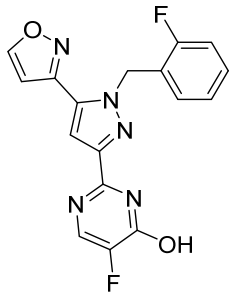
(24') ;

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



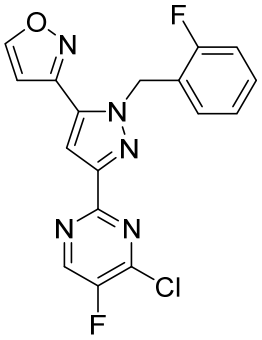
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



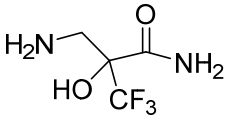
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI , and

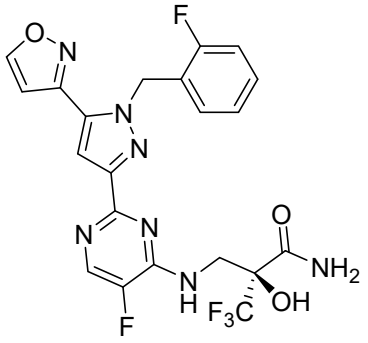
vi) reacting an amine of formula **(13)**:



(**13**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IB, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

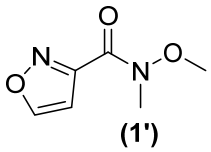
24. A process of preparing a compound of Formula IC:



Formla IC ,

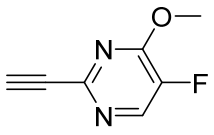
comprising the steps of:

i) coupling an amide for formula **(1')**:



(1')

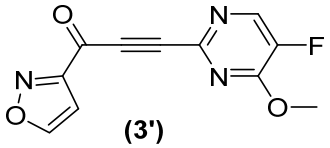
with a pyrimidine compound of formula **(2)**:



(2)

,

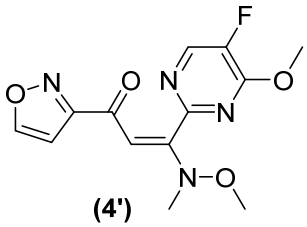
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3')

,

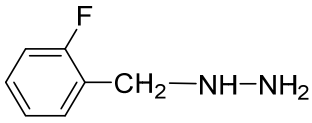
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



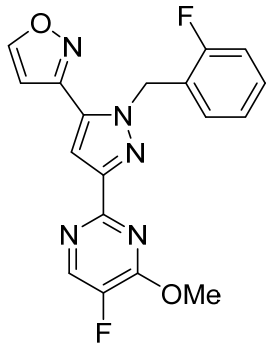
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



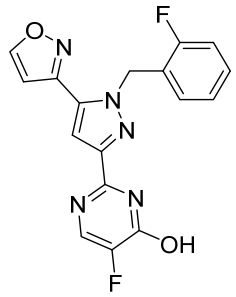
or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



Formula V

,

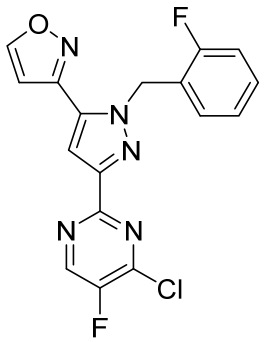
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9')

,

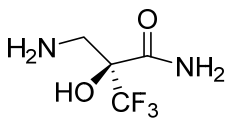
v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



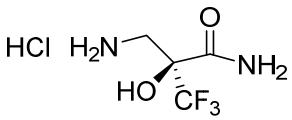
Formula VI

, and

vi) reacting an amine of formula **(19A)** or its HCl salt of formula **(19)**:



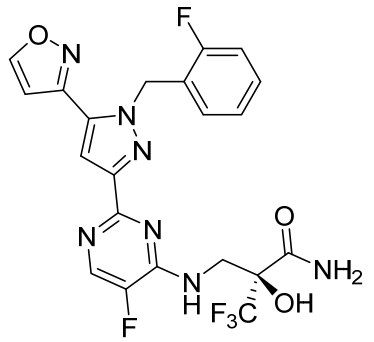
(**19A**)



(**19**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC.

25. A process of preparing a compound of Formula IC:

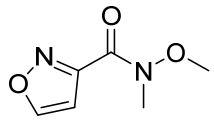


Formula IC

,

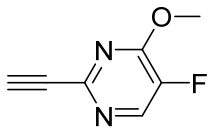
comprising the steps of:

i) coupling an amide of formula **(1')**:



(1')

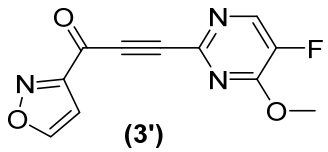
with a pyrimidine compound of formula **(2)**:



(2)

,

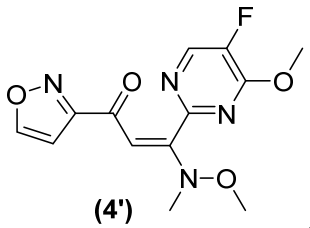
in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



(3')

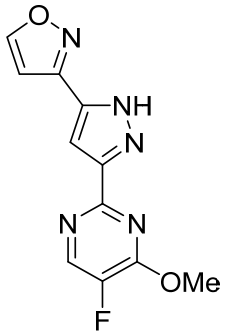
,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



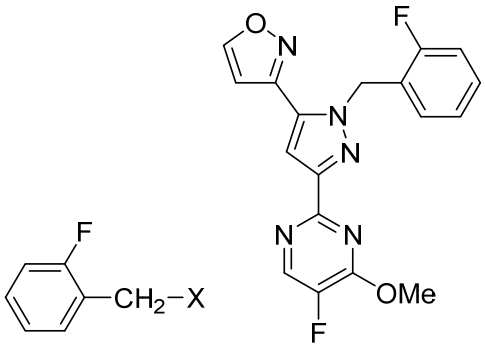
(4') ,

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



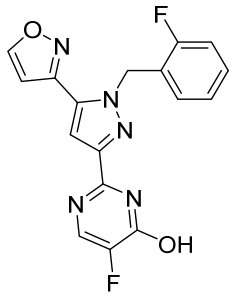
(24') ;

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



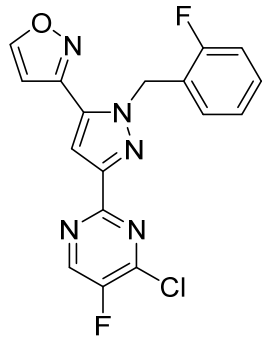
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



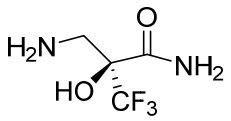
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

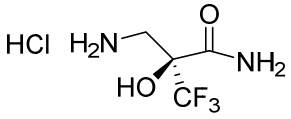


Formula VI , and

vi) reacting an amine of formula **(19A)** or its HCl salt of formula **(19)**:



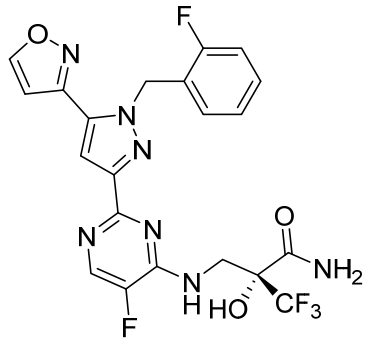
(19A)



(19)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

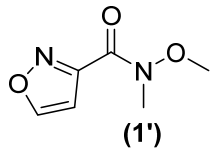
26. A process of preparing a compound of Formula ID:



Formula ID ,

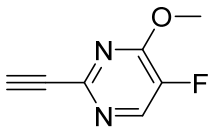
comprises the steps of:

i) coupling an amide for formula **(1')**:



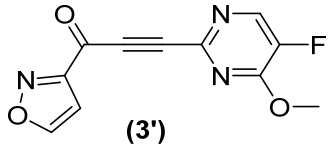
(1')

with a pyrimidine compound of formula **(2)**:



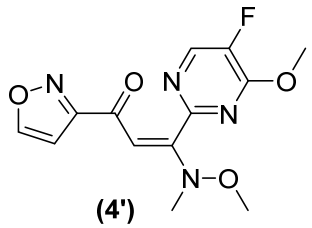
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



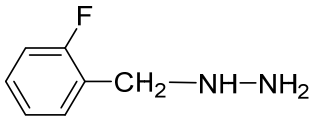
(3') ,

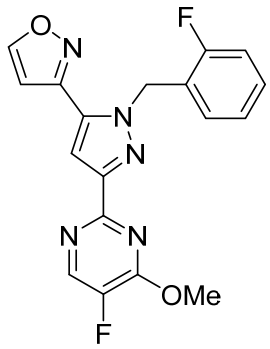
ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4') ,

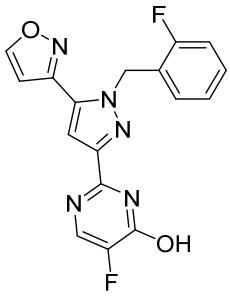
iii) condensing the compound of formula **(4')** with a hydrazine of formula

 or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



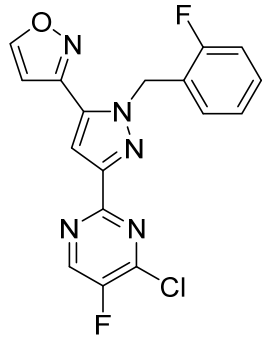
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



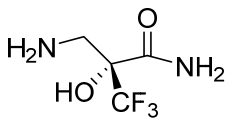
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

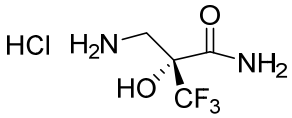


Formula VI , and

vi) reacting an amine of formula **(15A)** or its HCl salt of formula **(15)**:



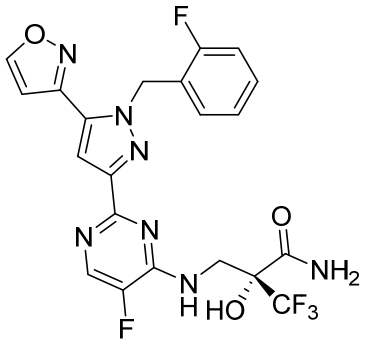
(**15A**)



(**15**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID.

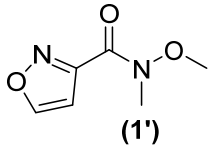
27. A process of preparing a compound of Formula ID:



Formula ID ,

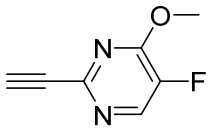
comprising the steps of:

i) coupling an amide of formula **(1')**:



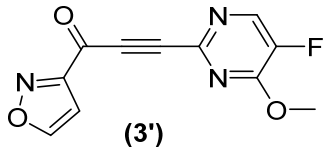
(**1'**)

with a pyrimidine compound of formula **(2)**:



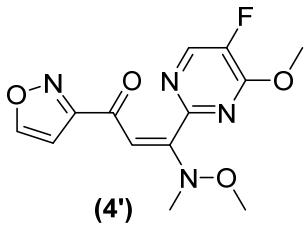
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



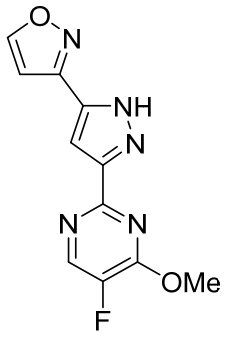
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



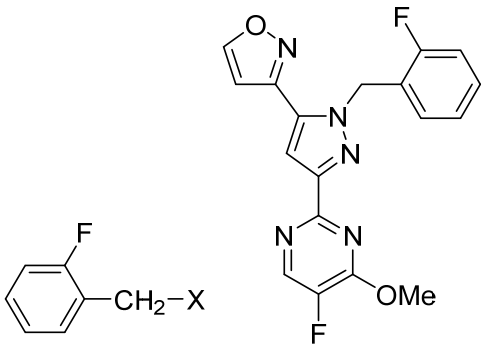
(4') ,

iiia) condensing the compound of formula **(4')** with hydrazine (*e.g.*, hydrazine hydrate) to form the compound of formula (**24'**):



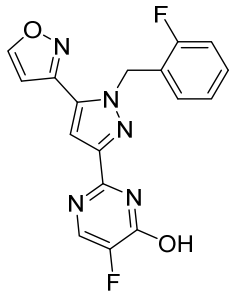
(24') ,

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



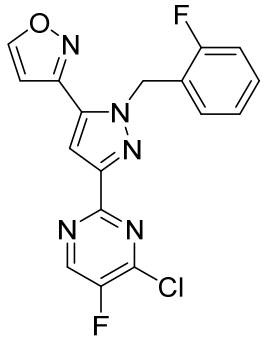
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



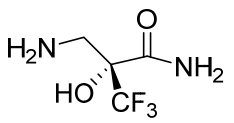
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

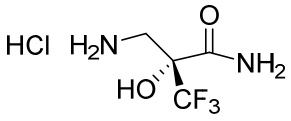


Formula VI , and

vi) reacting an amine of formula **(15A)** or its HCl salt of formula **(15)**:



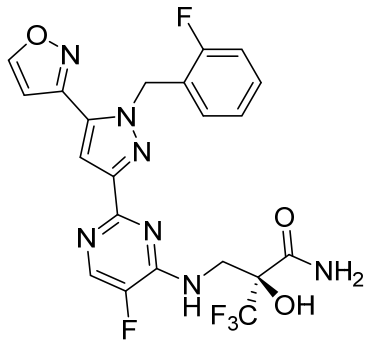
(**15A**)



(**15**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (*e.g.*, mesylate, tosylate or triflate).

28. A process of preparing a compound of Formula IC:

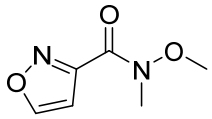


Formula IC

,

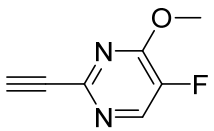
comprises the steps of:

i) coupling an amide for formula **(1')**:



(1')

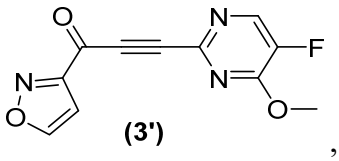
with a pyrimidine compound of formula **(2)**:



(2)

,

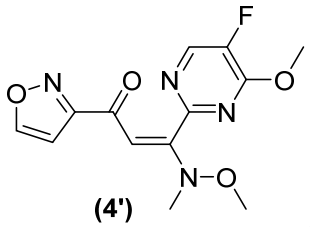
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(3')

,

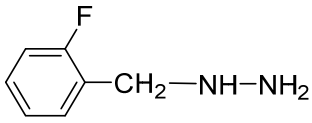
ii) at a pH >5, optionally in the presence of added *N,O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



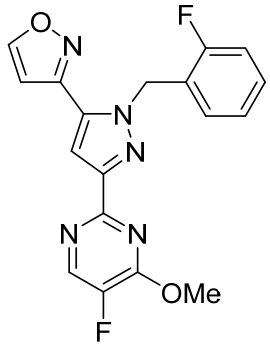
(4')

,

iii) condensing the compound of formula **(4')** with a hydrazine of formula



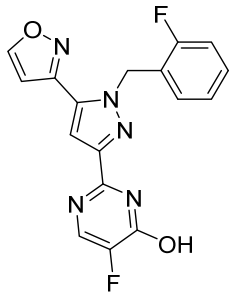
or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



Formula V

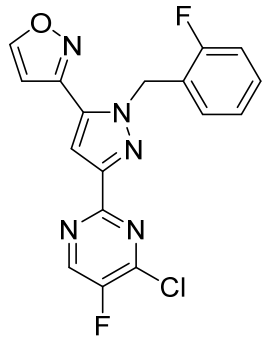
,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



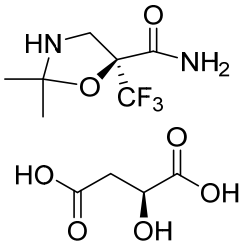
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

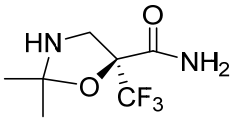


Formula VI ; and

vi) reacting an (*L*)-malic acid salt of an amine **(21**) represented by formula **(18)**:



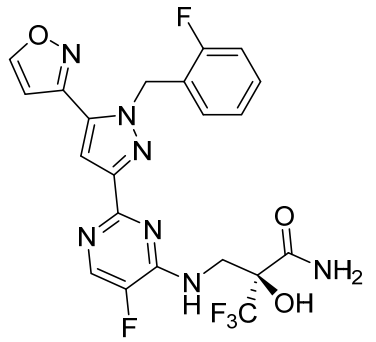
(**18**)



(**21**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC.

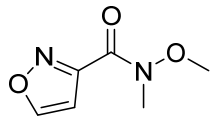
29. A process of preparing a compound of Formula IC:



Formula IC ,

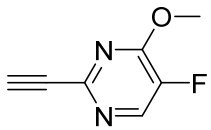
comprising the steps of:

i) coupling an amide of formula **(1')**:



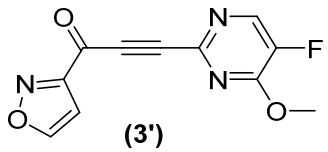
(1')

with a pyrimidine compound of formula **(2)**:



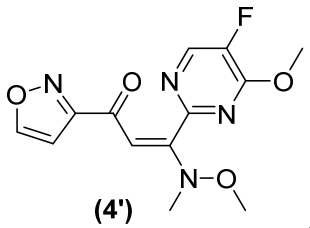
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**:



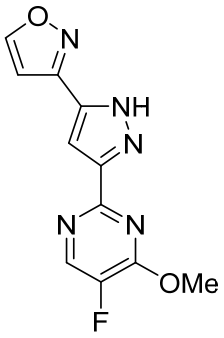
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



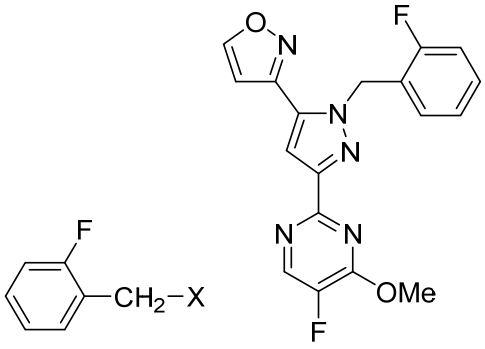
(4') ,

iiia) condensing the compound of formula **(4')** with a hydrazine (*e.g.*, hydrazine hydrate) to form a compound of formula (**24'**):



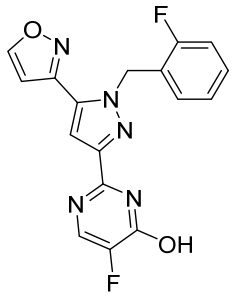
(24') ,

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



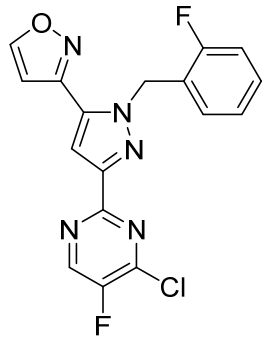
(23A) Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



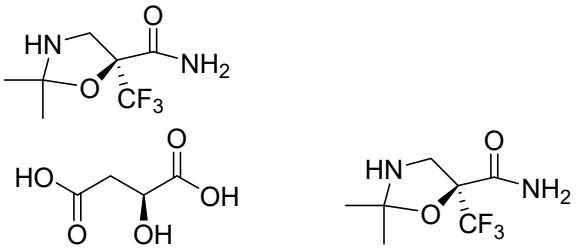
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:



Formula VI , and

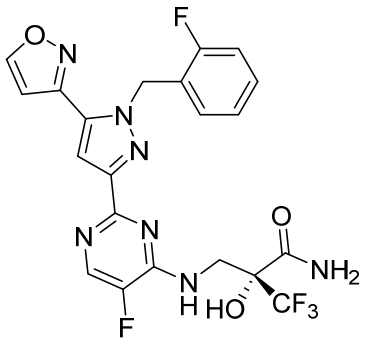
vi) reacting an (*L*)-malic acid salt of an amine **(21**) represented by formula **(18)**:



(**18**) (**21**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula IC, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

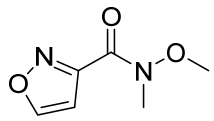
30. A process of preparing a compound of Formula ID:



Formula ID

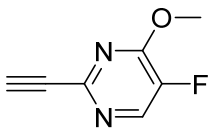
comprising the steps of:

i) coupling an amide of formula **(1')**:



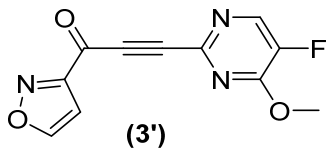
(1')

with a pyrimidine compound of formula **(2)**:



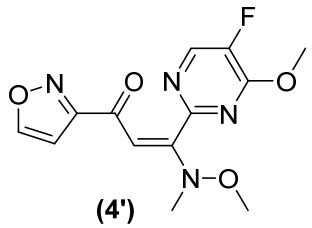
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with an acid, an intermediate of formula **(3')**



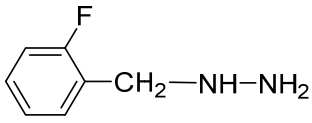
(3') ,

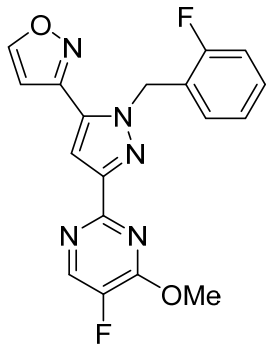
ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt thereof, allowing the mixture to react to form the compound of formula **(4')**:



(4') ,

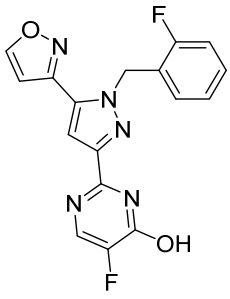
iii) condensing the compound of formula **(4')** with a hydrazine of formula

 or a salt thereof, optionally in the presence of a base, to form a compound of Formula V:



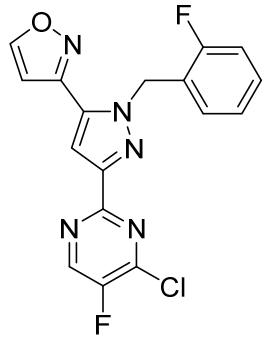
Formula V ,

iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



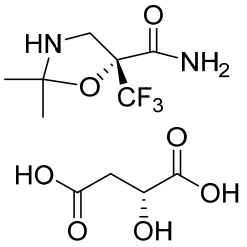
(9') ,

v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a compound of Formula VI:

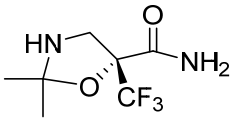


Formula VI , and

vi) reacting a (*D*)-malic acid salt of an amine (**20**) represented by formula (**14**):



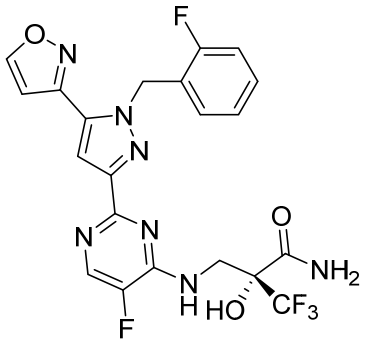
(**14**)



(**20**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID.

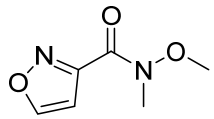
31. A process of preparing a compound of Formula ID:



Formula ID ,

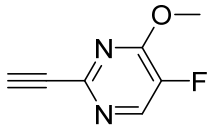
comprising the steps of:

i) coupling an amide of formula **(1')**:



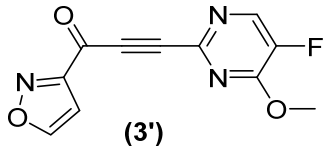
(1')

with a pyrimidine compound of formula **(2)**:



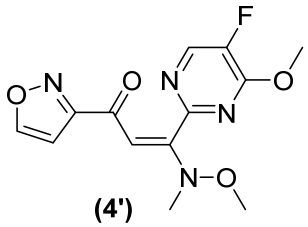
(2) ,

in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



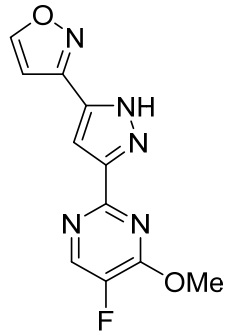
(3') ,

ii) at a pH >5, optionally in the presence of added *N*,*O*-dimethylhydroxylamine or a salt (*e.g.* HCl salt) thereof, allowing the mixture to react to form the compound of formula **(4')**:



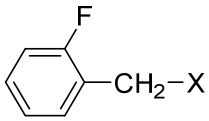
(4') ,

iiia) condensing the compound of formula **(4')** with a hydrazine (*e.g.*, hydrazine hydrate) to form a compound of formula (**24'**):

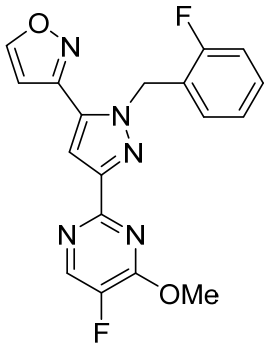


(24') ,

iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**)

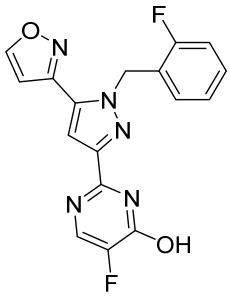


(23A) to provide the compound of Formula V:



Formula V ,

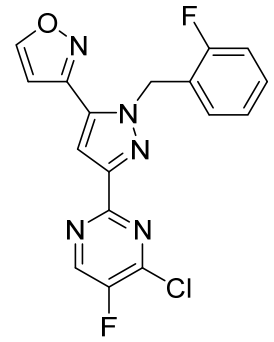
iv) de-methylating the compound of Formula V to form an alcohol compound of formula **(9')**:



(9') ,

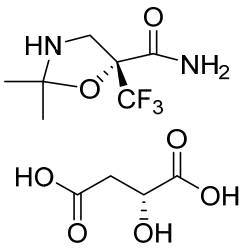
v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form a

compound of Formula VI:

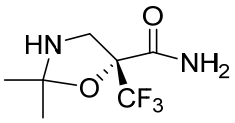


Formula VI , and

vi) reacting a (*D*)-malic acid salt of an amine (**20**) represented by formula (**14**):



(**14**)



(**20**)

with the compound of Formula VI, optionally in the presence of a base, to yield the compound of Formula ID, wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

32. The process of claim 30 or 31, further comprising the step of crystallization of the compound of Formula ID to yield Form B of the compound, optionally wherein the crystallization comprises the steps of: A) dissolving the compound of Formula ID in acetonitrile and water at between a temperature between 40 °C and 80 °C to form a solution of the compound; B) filtering the solution of step A) to form a filtered solution of the compound; C) heating the filtered solution at a temperature between 40 °C and 80 °C and adding water to yield a slurry; D) cooling the slurry of step C) to yield crystalline Form B of the compound of Formula ID; and E) filtering and drying the crystalline Form B of the compound of Formula ID.

33. The process of any one of claims 1-32, wherein the base in step i) is n-butyllithium.

34. The process of any one of claims 1-33, wherein the process comprises contacting the

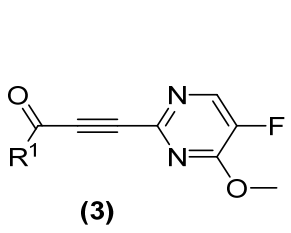
reaction product of the reaction between the amide of formula (**1**) or (**1'**) and the pyrimidine compound of formula (**2**) with a solution comprising *N,O*-dimethylhydroxylamine or a salt thereof and an acid to form the compound of formula (**4**) or (**4'**).

35. The process of claim 34, wherein the solution comprises *N,O*-dimethylhydroxylamine hydrochloride.

36. The process of claim 34 or 35, wherein (i) the acid is an aqueous acid; (ii) the acid is hydrochloric acid; or (iii) the acid is glacial acetic acid.

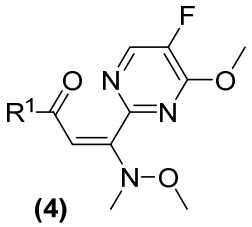
37. The process of any one of claims 3, 13, 20, 23, 25, 27, 29 and 31-36, wherein X is –Br.

38. A compound of formula **(3)** or **(4)**:



(3)

; or



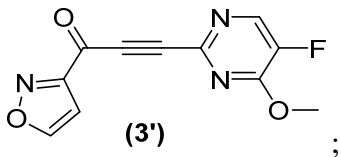
(4)

,

wherein R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O.

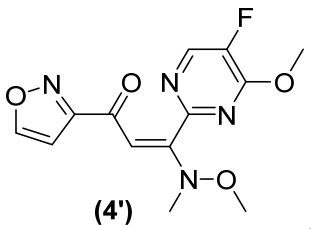
39. The compound of claim 38, wherein (i) R^1 is a 5-membered heteroaryl ring or (ii) R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O.

40. The compound of claim 39, wherein the compound is represented by formula **(3')** or **(4'):**



(3')

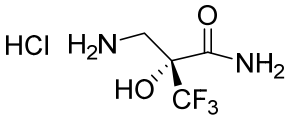
; or



(4')

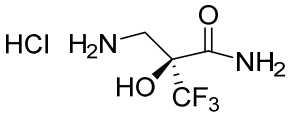
.

41. A compound represented by any one of the following formulae:



(**15**)

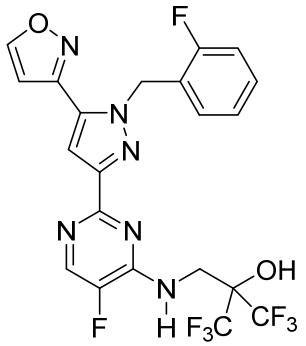
; and



(**19**)

.

42. Crystalline Form A of the compound of Formula IA:



Formula IA

,

having at least one, two, three, four, five, six, seven or eight major peaks in an x-ray powder diffraction (XRPD) pattern selected from selected from 4.2, 9.1, 9.8, 17.2, 17.7, 18.2, 27.5, and 36.0 degree 2θ angles; optionally the crystalline Form A has (i) the XRPD pattern of FIG. 1; (ii) an endothermic onset at a temperature between 160 °C and 165 °C in a differential scanning calorimetry (DSC) profile; and/or (iii) an endothermic onset at 163.1 °C; and optionallyat least 70%, 80%, 90%, 95%, 98%, 99%, 99.5%, or 99.9% of the compound is the crystalline Form A of the compound.