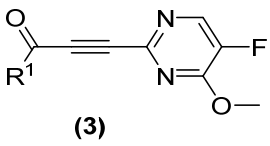
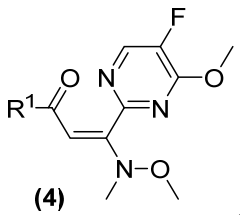
[0007g] In another aspect of the present disclosure, there is provided a compound of formula **(3)** or **(4)**:



(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.

[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:

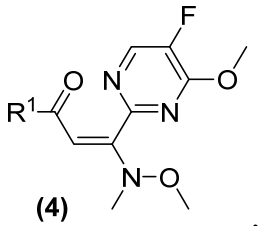
R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O;

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

CLAIMS

What is claimed is:

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

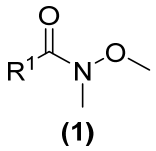


(4)

,

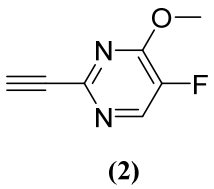
comprising the steps of:

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



(1)

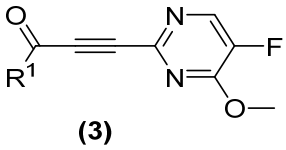
with a pyrimidine compound of formula **(2):**



(2)

,

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



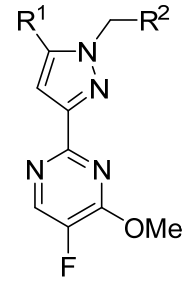
(3)

, 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.

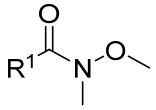
2. A process for preparing a compound of Formula II:



Formula II ,

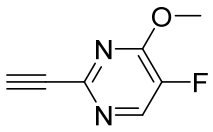
comprising the steps of:

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



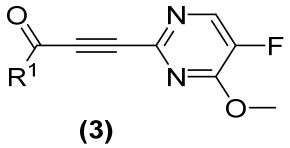
(1)

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



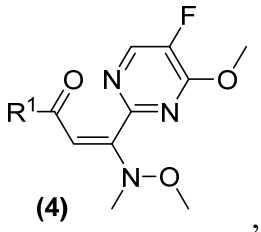
(2) ,

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

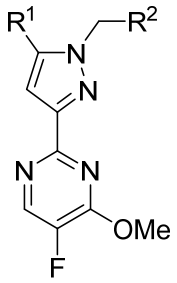
iii) condensing the compound of formula **(4)** with a hydrazine of formula R^2-CH_2-NH-NH_2 or a salt thereof, optionally in the presence of a base, to form the compound of Formula II, wherein:

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.

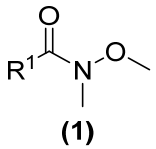
3. A process of preparing a compound of Formula II:



Formula II ,

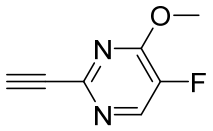
comprising the steps of:

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



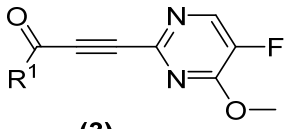
(1)

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



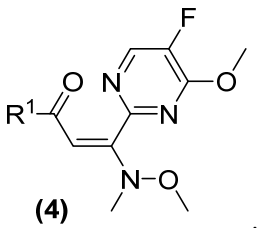
(2) ,

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



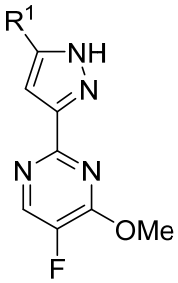
(3) ,

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)**:



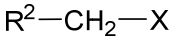
(4) ,

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:

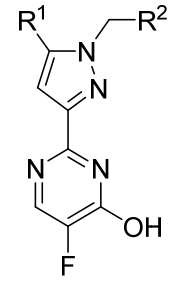
R^1 is phenyl, or a 5 to 6-membered heteroaryl ring; optionally substituted with up to three instances independently selected from the group consisting of halogen or methyl; wherein said 5 or 6-membered heteroaryl ring contains up to 3 ring atoms selected from the group consisting of N, S or O; and

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;

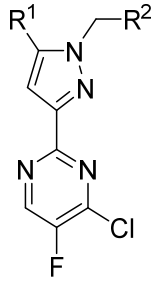
X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

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**):



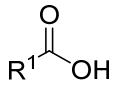
Compound (**9**).

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.

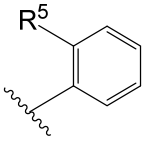
6. The process of any one of claims 1-5, wherein the compound of formula **(1)** is prepared by reacting a carboxylic acid of formula **(8)**



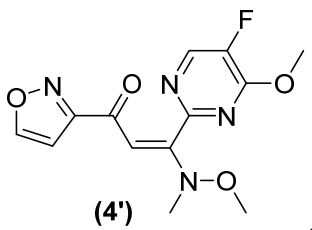
(8)

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

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.

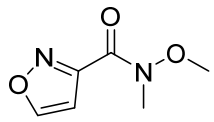
9. A process of preparing a compound of formula **(4')**:



(4') ,

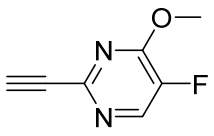
comprising the steps of:

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



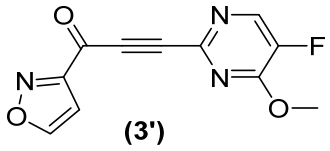
(1')

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



(2) ,

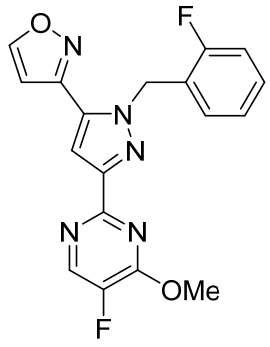
in an aprotic organic solvent in the presence of a base, to form, after quenching with acid, an intermediate of formula **(3')**:



(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')**.

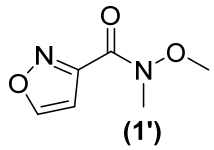
10. A process of preparing a compound of Formula V:



Formula V ,

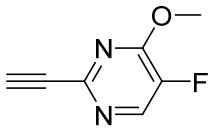
comprising the steps of:

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



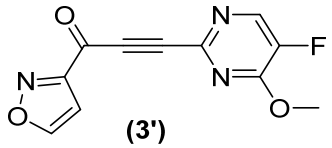
(1')

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



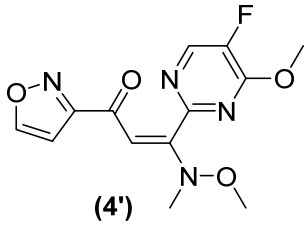
(2) ,

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



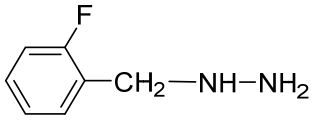
(3') ,

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')**:



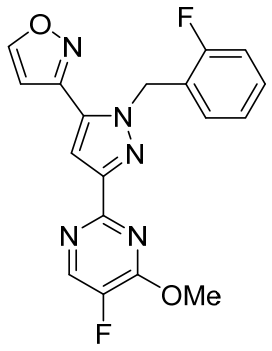
(4') , and

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.

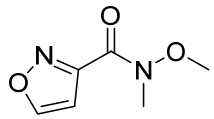
11. A process of preparing a compound of Formula V:



Formula V ,

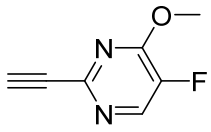
comprising the steps of:

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



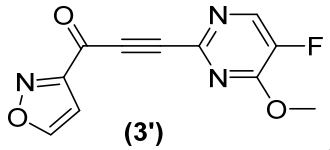
(1')

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



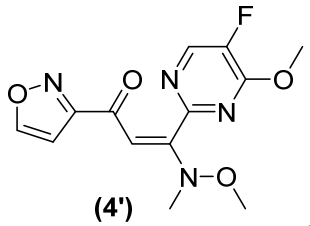
(2) ,

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



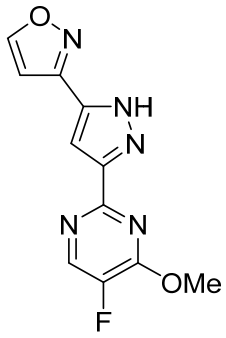
(3') ,

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')**:



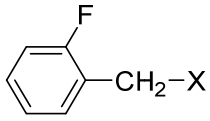
(4') ,

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



(24') ; and

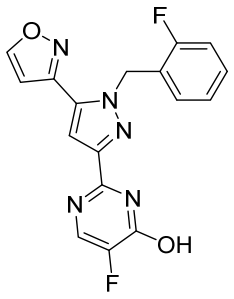
iiib) alkylating intermediate of formula (**24'**) with an alkylating agent of formula (**23A**) to provide the compound of Formula V:



(23A) ,

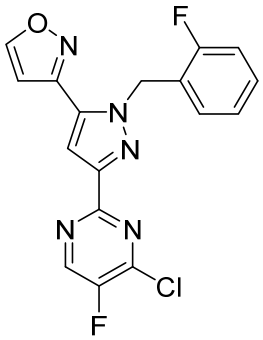
wherein X is a leaving group selected from –Br, -I, -Cl, -F, and a sulfonate ester (e.g., mesylate, tosylate or triflate).

12. The process of claim 10 or 11, further comprising step iv) de-methylating the compound of Formula V to form an alcohol Compound (**9'**):



(9')

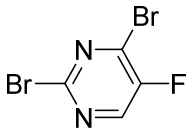
13. The process of claim 12, further comprising step v) chlorinating the alcohol compound of formula **(9')** with phosphoryl chloride to form the compound of Formula VI:



Formula VI

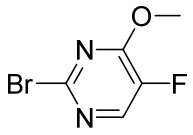
14. The process of any one of claims 1-13, wherein the compound of formula **(2)** is prepared by a process comprising the steps of:

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



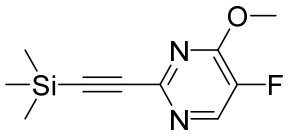
(5)

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



(6) ,

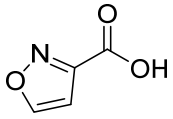
b) coupling the bromopyrimidine compound of formula **(6)** with ethynyltrimethylsilane, in an aprotic organic solvent in the presence of a base and a Pd catalyst, and optionally in the presence of a Cu(I) catalyst, to form a compound of formula **(7)**:



(7) , and

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

15. The process of any one of claims 9-13, wherein 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 thereof, in the presence of a base to form the amide of formula **(1').**

16. The process of any one of claims 1-15, wherein the base in step i) is n-butyllithium.

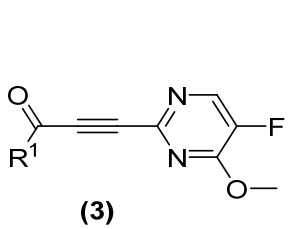
17. The process of any one of claims 1-16, wherein the process comprises contacting the reaction product of the reaction between the amide of formula (**1**) or (**1'**) and the pyrimidine compound of formula (**2**) with a solution comprising *N,O*-dimethylhydroxylamine or a salt thereof and an acid to form the compound of formula (**4**) or (**4'**).

18. The process of claim 17, wherein the solution comprises *N,O*-dimethylhydroxylamine hydrochloride.

19. The process of claim 17 or 18, wherein (i) the acid is an aqueous acid; (ii) the acid is hydrochloric acid; or (iii) the acid is glacial acetic acid.

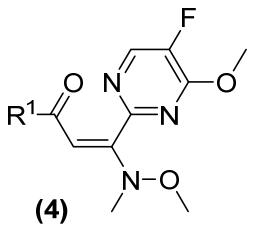
20. The process of any one of claims 3, 11 and 13-16, wherein X is –Br.

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



(3)

; or



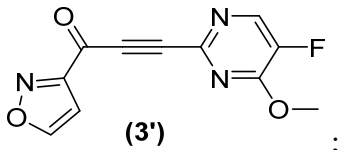
(4)

,

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.

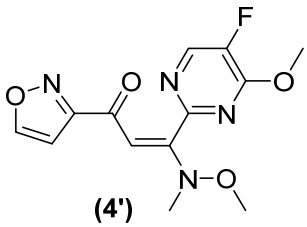
22. The compound of claim 21, wherein (i) R^1 is a 5-membered heteroaryl ring or (ii) R^1 is an unsubstituted 5-membered heteroaryl ring containing up to 2 ring heteroatoms selected from the group consisting of N and O.

23. The compound of claim 22, wherein the compound is represented by formula **(3')** or **(4'):**



(3')

; or



(4')

.