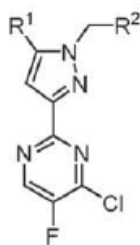


[0005] NO-independent, heme-dependent sGC stimulators displayed several important differentiating characteristics when compared with NO-independent, heme-independent sGC activators. These include crucial dependency on the presence of the reduced prosthetic heme moiety for their activity, strong synergistic enzyme activation when combined with NO and stimulation of the synthesis of cGMP by direct stimulation of sGC, independent of NO. The benzylindazole compound YC-1 was the first sGC stimulator to be identified. Additional sGC stimulators with improved potency and specificity for sGC have since been developed.

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

SUMMARY

[0006a] In one aspect of the present disclosure, there is provided a process for preparing a compound of Formula II:



Formula II

wherein:

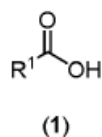
R¹ is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three ring heteroatoms independently selected from N, O or S;

R² is phenyl or a 6-membered heteroaryl, both optionally substituted with up to three instances of R⁵; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; and

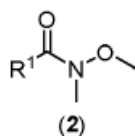
each R⁵ is independently selected from C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen;

said process comprising the steps of:

i) amidating starting material **(1)**

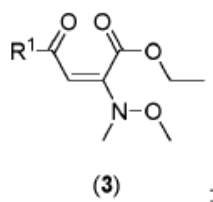


by reacting it with an appropriate amount of oxalyl chloride or an equivalent reagent, in a suitable mixture of water and an aprotic organic solvent, at a suitable temperature, in the presence of an appropriate amount of a suitable catalyst; followed by an appropriate amount of N,O-dimethylhydroxylamine hydrochloride, in the presence of an appropriate excess of a suitable base, at a suitable temperature, in a suitable mixture of water and an aprotic organic solvent to afford amide **(2)**;

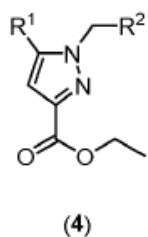


wherein R¹ is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three ring heteroatoms independently selected from N, O or S;

ii) alkylating intermediate amide **(2)** with an appropriate amount of ethyl propiolate, in a suitable aprotic organic solvent, at a suitable temperature, in the presence of an appropriate amount of a suitable base, to afford β-enaminoketoester **(3)**;

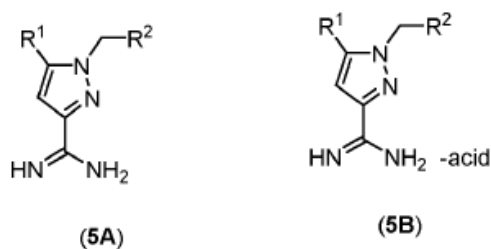


iii) condensing β-enaminoketoester **(3)** with an appropriate amount of a hydrazine of formula R²-CH₂-NH-NH₂ or its HCl salt, optionally in the presence of an appropriate amount of a suitable base, in a suitable protic solvent, at a suitable temperature, affording pyrazole ester intermediate **(4)**

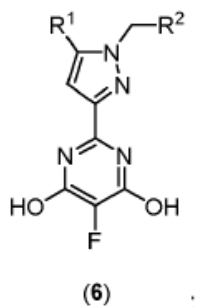


wherein R^2 is phenyl or a 6-membered heteroaryl, both optionally substituted with up to three instances of R^5 ; wherein the 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

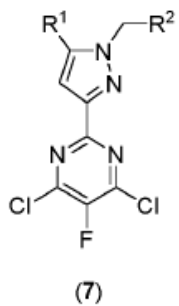
iv) aminating pyrazole ester intermediate **(4)** with an appropriate amount of ammonium chloride, in the presence of an appropriate amount of trimethylaluminum, in a suitable aprotic organic solvent, at a suitable temperature, affording amidine **(5A)** or, after treatment with a suitable aqueous mineral acid, amidine salt **(5B)**:



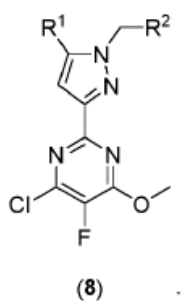
v) condensing amidine **(5A)** or amidine salt **(5B)** and an appropriate amount of fluoromalonate, optionally in the presence of an appropriate amount of a suitable base, in a suitable protic solvent, at a suitable temperature to afford, after treatment with an appropriate amount of a suitable mineral acid, diol **(6)**



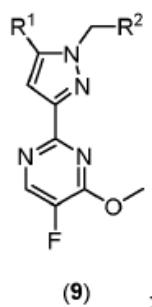
vi) chlorinating diol **(6)** with an appropriate amount of phosphoryl chloride, at a suitable temperature, in a suitable aprotic organic solvent, optionally in the presence of an appropriate amount of a suitable base, to afford dichloropyrimidine **(7)**



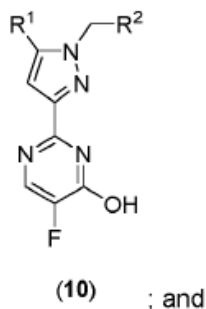
vii) mono-methoxylating dichloropyrimidine (**7**) with an appropriate amount of sodium methoxide, at a suitable temperature, in an appropriate protic solvent, to afford methoxypyrimidine (**8**)



viii) de-chlorinating methoxypyrimidine (**8**) with hydrogen gas or a transfer hydrogenation reagent and, optionally, an appropriate amount of a suitable metal catalyst, in the presence of an appropriate amount of a suitable base, at a suitable temperature, in an appropriate organic solvent, to provide fluoromethoxypyrimidine (**9**)

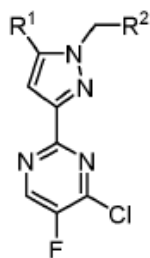


ix) de-methylating fluoromethoxypyrimidine (**9**) by reacting it with an appropriate amount of an aqueous acid in an appropriate protic solvent, at a suitable temperature, to afford alcohol (**10**)



x) chlorinating alcohol (**10**) with an appropriate amount of phosphoryl chloride and optionally an appropriate amount of a suitable base, at a suitable temperature, in a suitable aprotic organic solvent.

[0006b] In another aspect of the present disclosure, there is provided a process for preparing a compound of Formula II:



Formula II

wherein:

R^1 is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three

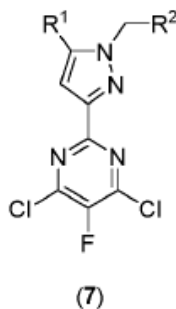
ring heteroatoms independently selected from N, O or S;

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

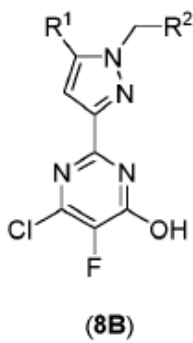
each R^5 is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

said process comprising the steps of:

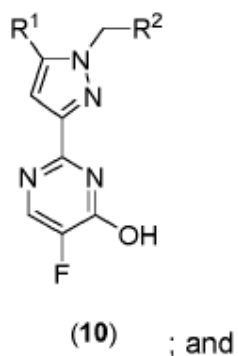
1) mono-hydroxylating a dichloropyrimidine **(7)**



with an appropriate amount of sodium hydroxide, at a suitable temperature, in a suitable mixture of an aprotic and a protic solvent, in the presence of an appropriate amount of a suitable phase transfer catalyst, to afford hydroxypyrimidine **(8B)**;

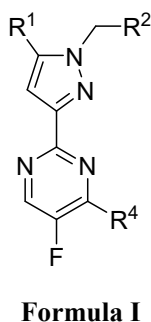


2) de-chlorinating hydroxypyrimidine **(8B)** with hydrogen gas or a transfer hydrogenation reagent and, optionally, an appropriate amount of a suitable metal catalyst, in the presence of an appropriate amount of a suitable base, at a suitable temperature, in a suitable organic solvent, to provide fluorohydroxypyrimidine **(10)**;



3) chlorinating the alcohol of fluorohydroxypyrimidine **(10)** with an appropriate amount of phosphoryl chloride and optionally an appropriate amount of a suitable base, at a suitable temperature, in a suitable aprotic organic solvent.

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



[0008] Some compounds of Formula I and their pharmaceutically acceptable salts are sGC stimulators that are useful for treating diseases or disorders that benefit from sGC stimulation or from an increase in the concentration of NO and/or cGMP. Other compounds of Formula I are useful as intermediates in the synthesis of other sGC stimulators, including other compounds of Formula I.

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

R^1 is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three ring heteroatoms independently selected from N, O or S;

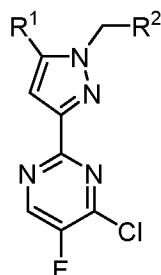
R^2 is phenyl or 6-membered heteroaryl, both optionally substituted with up to three instances of R^5 ; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms;

R^4 is halogen or $-NR^6R^7$;

each R^5 is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

CLAIMS

1. A process for preparing a compound of **Formula II**:



Formula II

wherein:

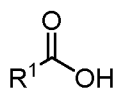
R¹ is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three ring heteroatoms independently selected from N, O or S;

R² is phenyl or a 6-membered heteroaryl, both optionally substituted with up to three instances of R⁵; wherein said 6-membered heteroaryl ring contains up to 2 nitrogen ring atoms; and

each R⁵ is independently selected from C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen;

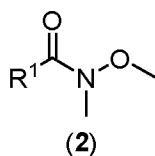
said process comprising the steps of:

i) amidating starting material **(1)**



(1)

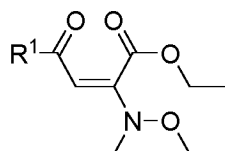
by reacting it with an appropriate amount of oxalyl chloride or an equivalent reagent, in a suitable mixture of water and an aprotic organic solvent, at a suitable temperature, in the presence of an appropriate amount of a suitable catalyst; followed by an appropriate amount of N,O-dimethylhydroxylamine hydrochloride, in the presence of an appropriate excess of a suitable base, at a suitable temperature, in a suitable mixture of water and an aprotic organic solvent to afford amide **(2)**;



(2)

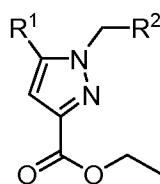
wherein R^1 is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three ring heteroatoms independently selected from N, O or S;

ii) alkylating intermediate amide **(2)** with an appropriate amount of ethyl propiolate, in a suitable aprotic organic solvent, at a suitable temperature, in the presence of an appropriate amount of a suitable base, to afford β -enaminoketoester **(3)**;



(3) ;

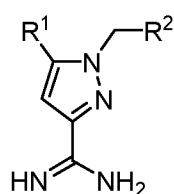
iii) condensing β -enaminoketoester **(3)** with an appropriate amount of a hydrazine of formula $R^2\text{-CH}_2\text{-NH-NH}_2$ or its HCl salt, optionally in the presence of an appropriate amount of a suitable base, in a suitable protic solvent, at a suitable temperature, affording pyrazole ester intermediate **(4)**



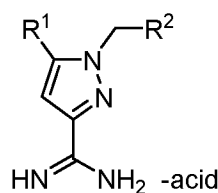
(4) ,

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

iv) aminating pyrazole ester intermediate **(4)** with an appropriate amount of ammonium chloride, in the presence of an appropriate amount of trimethylaluminum, in a suitable aprotic organic solvent, at a suitable temperature, affording amidine **(5A)** or, after treatment with a suitable aqueous mineral acid, amidine salt **(5B)**:

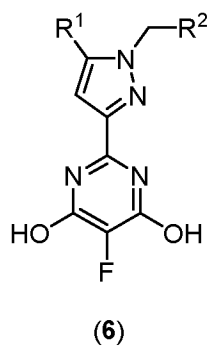


(5A)

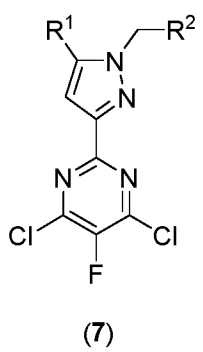


(5B) ;

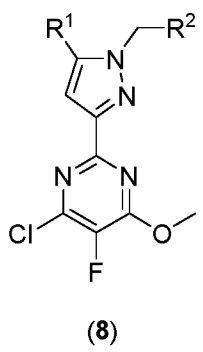
v) condensing amidine (**5A**) or amidine salt (**5B**) and an appropriate amount of fluoromalonate, optionally in the presence of an appropriate amount of a suitable base, in a suitable protic solvent, at a suitable temperature to afford, after treatment with an appropriate amount of a suitable mineral acid, diol (**6**)



vi) chlorinating diol (**6**) with an appropriate amount of phosphoryl chloride, at a suitable temperature, in a suitable aprotic organic solvent, optionally in the presence of an appropriate amount of a suitable base, to afford dichloropyrimidine (**7**)

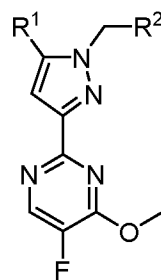


vii) mono-methoxylating dichloropyrimidine (**7**) with an appropriate amount of sodium methoxide, at a suitable temperature, in an appropriate protic solvent, to afford methoxypyrimidine (**8**)



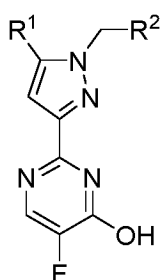
viii) de-chlorinating methoxypyrimidine (**8**) with hydrogen gas or a transfer hydrogenation reagent and, optionally, an appropriate amount of a suitable metal catalyst, in

the presence of an appropriate amount of a suitable base, at a suitable temperature, in an appropriate organic solvent, to provide fluoromethoxypyrimidine **(9)**



(9) ;

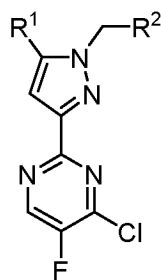
ix) de-methylating fluoromethoxypyrimidine **(9)** by reacting it with an appropriate amount of an aqueous acid in an appropriate protic solvent, at a suitable temperature, to afford alcohol **(10)**



(10) ; and

x) chlorinating alcohol **(10)** with an appropriate amount of phosphoryl chloride and optionally an appropriate amount of a suitable base, at a suitable temperature, in a suitable aprotic organic solvent.

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



Formula II

wherein:

R¹ is unsubstituted phenyl or 5 to 6-membered heteroaryl ring containing up to three

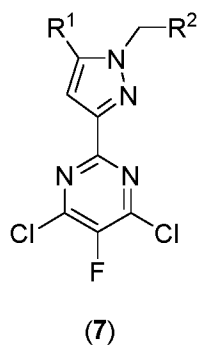
ring heteroatoms independently selected from N, O or S;

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

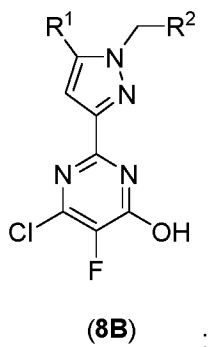
each R^5 is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy or halogen;

said process comprising the steps of:

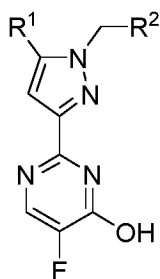
1) mono-hydroxylating a dichloropyrimidine (**7**)



with an appropriate amount of sodium hydroxide, at a suitable temperature, in a suitable mixture of an aprotic and a protic solvent, in the presence of an appropriate amount of a suitable phase transfer catalyst, to afford hydroxypyrimidine (**8B**);



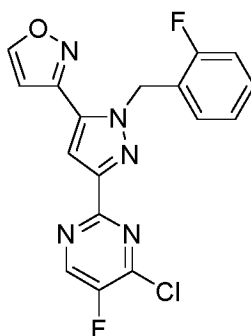
2) de-chlorinating hydroxypyrimidine (**8B**) with hydrogen gas or a transfer hydrogenation reagent and, optionally, an appropriate amount of a suitable metal catalyst, in the presence of an appropriate amount of a suitable base, at a suitable temperature, in a suitable organic solvent, to provide fluorohydroxypyrimidine (**10**);



(10) ; and

3) chlorinating the alcohol of fluorohydroxypyrimidine **(10)** with an appropriate amount of phosphoryl chloride and optionally an appropriate amount of a suitable base, at a suitable temperature, in a suitable aprotic organic solvent.

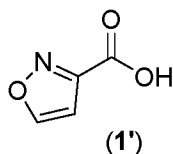
3. The process of claim 1 for preparing a compound of **Formula IV**



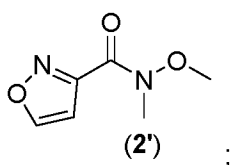
Formula IV

wherein said process comprises the steps of:

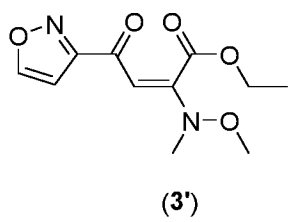
i) amidating starting material **(1')**



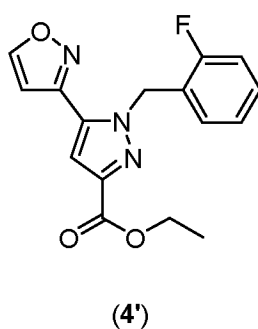
by reacting it with an appropriate amount of oxalyl chloride or an equivalent reagent, in a suitable aprotic organic solvent, at a suitable temperature, in the presence of an appropriate amount of a suitable catalyst; followed by an appropriate amount of N,O-dimethylhydroxylamine hydrochloride, in the presence of an appropriate excess of a suitable base, at a suitable temperature, in a suitable mixture of water and an aprotic organic solvent to afford amide **(2')**



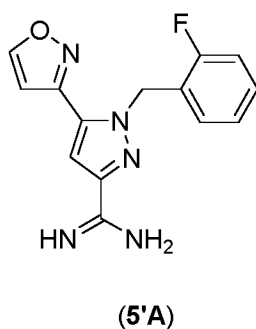
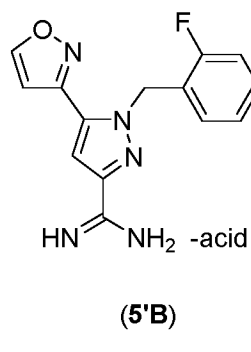
ii) alkylating intermediate amide **(2')** with an appropriate amount of ethyl propiolate, in a suitable aprotic organic solvent, at a suitable temperature, in the presence of an appropriate amount of a suitable base, to afford β -enaminoketoester **(3')**



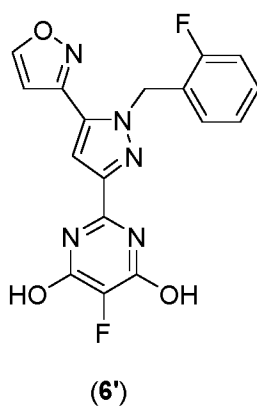
iii) condensing β -enaminoketoester **(3')** with an appropriate amount of a hydrazine of formula $\text{NH}_2\text{NH}-\text{CH}_2-(2\text{-fluorophenyl})$ or its HCl salt, optionally in the presence of an appropriate amount of a suitable base, in a suitable protic solvent, at a suitable temperature, affording a pyrazole ester intermediate **(4')**



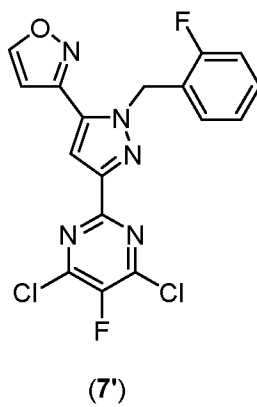
iv) aminating pyrazole ester intermediate **(4')** with an appropriate amount of ammonium chloride, in the presence of an appropriate amount of trimethylaluminum, in a suitable aprotic organic solvent, at a suitable temperature, affording amidine **(5'A)** or, after treatment with a suitable aqueous mineral acid, amidine salt **(5'B)**;



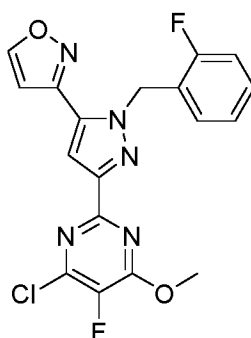
v) condensing amidine (**5'A**) or amidine salt (**5'B**) and an appropriate amount of fluoromalonate, optionally in the presence of an appropriate amount of a suitable base, in a suitable protic solvent, at a suitable temperature to afford, after treatment with an appropriate amount of a suitable mineral acid, diol (**6'**);



vi) chlorinating diol (**6'**) with an appropriate amount of phosphoryl chloride, at a suitable temperature, in a suitable aprotic organic solvent, optionally in the presence of an appropriate amount of a suitable base, to afford dichloropyrimidine (**7'**);

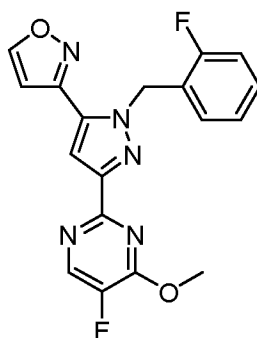


vii) mono-methoxylating dichloropyrimidine (**7'**) with an appropriate amount of sodium methoxide, at a suitable temperature, in an appropriate protic solvent, to afford methoxypyrimidine (**8'**);



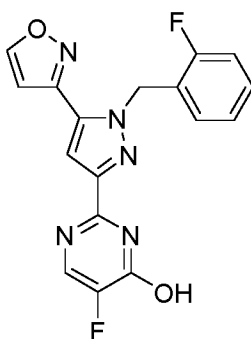
(8') ;

viii) dechlorinating methoxypyrimidine (8') with hydrogen gas or a transfer hydrogenation reagent and, optionally, an appropriate amount of a suitable metal catalyst, in the presence of an appropriate amount of a suitable base, at a suitable temperature, in an appropriate organic solvent, to provide fluoromethoxypyrimidine (9');



(9') ;

ix) de-methylating fluoromethoxypyrimidine (9') by reacting it with an appropriate amount of an aqueous acid, in an appropriate protic solvent, at a suitable temperature, to afford alcohol (10');

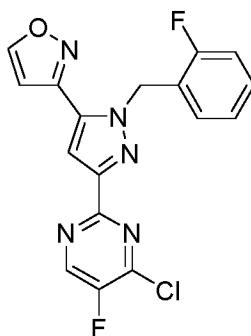


(10') ; and

x) chlorinating alcohol (10') with an appropriate amount of phosphoryl chloride and, optionally, an appropriate amount of a suitable base, at a suitable temperature, in a suitable

aprotic organic solvent.

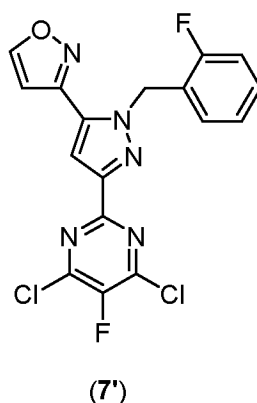
4. The process of claim 2, for preparing a compound of Formula IV



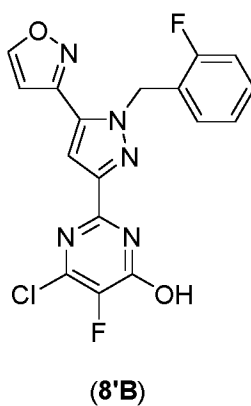
Formula IV

wherein said process comprises the steps of

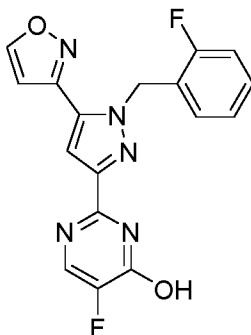
- 1) mono-hydroxylating a dichloropyrimidine (**7'**)



with an appropriate amount of sodium hydroxide, at a suitable temperature, in a suitable mixture of an aprotic and a protic solvent, in the presence of an appropriate amount of a suitable phase transfer catalyst, to afford hydroxypyrimidine (**8'B**);



2) de-chlorinating hydroxypyrimidine (**8'B**) with hydrogen gas or a transfer hydrogenation reagent and, optionally, an appropriate amount of a suitable metal catalyst, in the presence of an appropriate amount of a suitable base, at a suitable temperature, in a suitable organic solvent, to provide fluorohydroxypyrimidine (**10'**);



(**10'**) ; and

3) chlorinating alcohol (**10'**) with an appropriate amount of phosphoryl chloride and optionally an appropriate amount of a suitable base, at a suitable temperature, in a suitable aprotic organic solvent.

5. The process according to claim 1 or 2, wherein R^1 is a 5-membered heteroaryl ring containing up to three heteroatoms independently selected from N, O or S.
6. The process according to claim 5, wherein R^1 is isoxazolyl.
7. The process according to claim 5, wherein R^1 is 3-isoxazolyl.
8. The process according to claim 1 or 2, wherein R^2 is phenyl optionally substituted with up to three instances of R^5 .
9. The process according to claim 8, wherein R^2 is phenyl substituted with one instance of R^5 , wherein R^5 is halogen.
10. The process according to claim 9, wherein R^5 is fluoro.
11. The process according to claim 8, wherein R^2 is phenyl substituted with two instances of R^5 ; wherein each instance of R^5 is independently selected from halogen.
12. The process according to claim 11, wherein each instance of R^5 is fluoro.