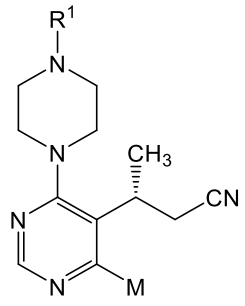
In certain examples, the continuous flow reaction described above comprises cyclizing a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof,

wherein:

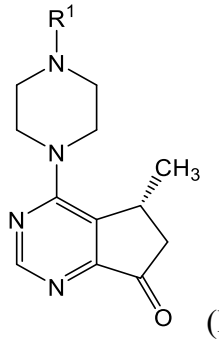
R^1 an amino protecting group; and

M is MgBr.

In one example, the continuous flow reaction comprises iPrMgBr as metalating reagent.

The iPrMgBr permits continuous mode processing with a very fast reaction, reduced levels of dimerization by-products (amongst others), and easily isolated final products.

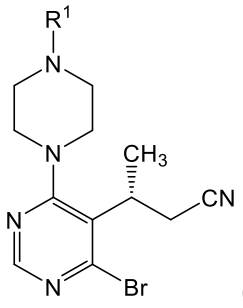
In one aspect, the present disclosure provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

the process comprising the steps of:

(a) solubilizing a compound of formula (IV)



(IV)

in a mixture of toluene and MeTHF;

(b) adding iPrMgBr in MeTHF to the solubilized compound of step (a) thereby forming a Mg-imine complex as a solid in suspension;

(c) adding an aqueous acid salt;

(d) adding a base in water; and

(e) isolating the compound of formula (I),

wherein the process is performed in one or more continuous stirred tank reactors (CSTR).

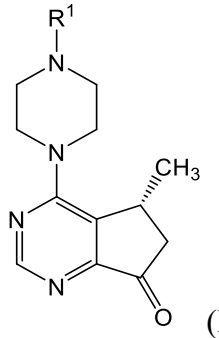
Provided herein is a process as exemplified by Figure 1.

Provided herein is a process as exemplified by Figure 2.

Provided herein is a process for the preparation of a compound of formula (I) as described herein or a pharmaceutically acceptable salt thereof the process comprising a continuous flow reaction wherein in step (a) the compound of formula (III) or a pharmaceutically acceptable salt thereof, wherein R^1 is as defined above, and R^3 is iodo or bromo, in a coordinating ethereal solvent or a non-coordinating apolar solvent, or a mixture of such solvents, is reacted with iPrMgBr in MeTHF to form a solid Mg-imine complex and wherein in step (b) an aqueous acid salt is added to the mixture obtained from step (a), thereby forming the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Claims

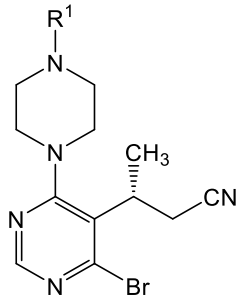
1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

the process comprising the steps of:

(a) solubilizing a compound of formula (IV)



(IV)

in a mixture of toluene and MeTHF;

(b) adding iPrMgBr in MeTHF to the solubilized compound of step (a) thereby forming a Mg-imine complex as a solid in suspension;

(c) adding an aqueous acid salt;

(d) adding a base in water; and

(e) isolating the compound of formula (I),

wherein the process is performed in one or more continuous stirred tank reactors (CSTR).

2. The process of claim 1, wherein the aqueous acid salt is selected from the group consisting of acetic acid, HCl, H_2SO_4, $NaHSO_4$, H_3PO_4, NaH_2PO_4, Na_2HPO_4, NaH_2Citrate, NH_4Cl, or oxalic acid, or a mixture thereof.

3. The process of claim 2, wherein the aqueous acid salt is $NaHSO_4$.

4. The process of any one of claims 1-3, wherein the process is performed using 1, 2, 3, 4, 5, 6, or 7 CSTRs.

5. The process of claim 4, wherein the process is performed using 5 CSTRs.

6. The process of claim 4 or 5, comprising a first CSTR containing a solution of the compound of formula (IV) in an organic solvent, the organic solvent comprising one or more components such as EtOEt, MeOtBu, iPrOiPr, dioxane, cPentylOMe, THF, MeTHF, hexane, heptane, toluene, or xylene, or a mixture thereof.

7. The process of claim 6, wherein the compound of formula (IV) is in a mixture of MeTHF and toluene.

8. The process of claim 6 or 7, wherein to the solution of the compound of formula (IV) in the first CSTR is added iPrMgBr in MeTHF.

9. The process of any one of claims 4-8, comprising a second CSTR comprising a mixture of the compounds of formula (IV) and the Mg-imine complex in a suspension of MeTHF and toluene wherein to this mixture about 0.3 equivalents of iPrMgBr in MeTHF are added.

10. The process of claim 9, wherein the contents of the first CSTR are transferred to the second CSTR.

11. The process of any one of claims 4-10, further comprising a third CSTR, wherein the contents of the second CSTR are transferred to the third CSTR and stirred in the third CSTR.

12. The process of any one of claims 4-11, wherein the Mg-imine complex is formed as a solid in suspension by reacting the compound of formula (IV) with iPrMgBr and is transferred as a suspension between CSTRs.

13. The process of any one of claims 4-12, comprising a fourth CSTR to which aqueous $NaHSO_4$ is added.

14. The process of any one of claims 4-13, wherein the contents of the third CSTR are added to the fourth CSTR, thereby forming the compound of formula (I).

15. The process of any one of claims 4-10 and claims 12-14, further comprising a fourth CSTR, wherein the contents of the second CSTR are transferred to the fourth CSTR.

16. The process of any one of claims 4-15, comprising a fifth CSTR to which a solution of a base in water is added.

17. The process of claim 16, where as a base in water NaOH in water is added.

18. The process of claim 17, wherein the pH of a biphasic mixture in the fifth CSTR after addition of NaOH is 4 to 7.

19. The process of any one of claims 4-18 further comprising a first separation vessel.

20. The process of claim 19, wherein the contents of the fifth CSTR are transferred to the first separation vessel, thereby separating organic and aqueous phases.

21. The process of claim 20, wherein the product containing organic phase is: (a) washed with water; (b) distilled; (c) precipitated; and (d) dried to isolate the compound of formula (I).

22. The process of any of claims 4-21, further comprising a sixth CSTR to which water is added.

23. The process of claim 22, wherein the organic phase after separation is transferred to the sixth CSTR.

24. The process of claim 23, further comprising a second separation vessel.

25. The process of claim 24, wherein the contents of the sixth CSTR are transferred to the second separation vessel, thereby separating organic and aqueous phases.

26. The process of claim 25, wherein the organic phase is: (i) distilled; (ii) precipitated; and (iii) dried to isolate the compound of formula (I).