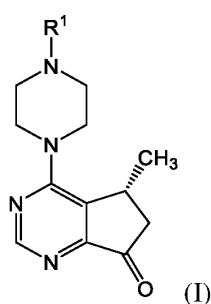
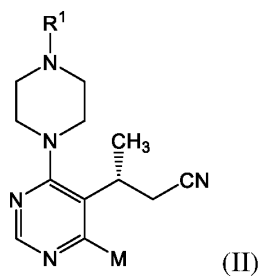


Claims

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



wherein the process comprises a continuous flow reaction, which continuous flow reaction comprises cyclization of a compound of formula (II):



or a pharmaceutically acceptable salt thereof,

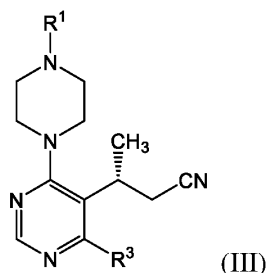
wherein:

R¹ is an amino protecting group; and

M is MgX wherein X is Br.

2. The process according to claim 1, wherein the continuous flow reaction comprises:
- (a) contacting a compound of formula (III) or a pharmaceutically acceptable salt thereof

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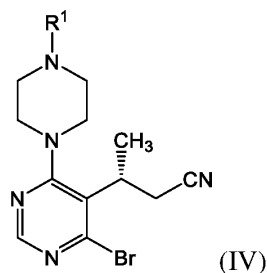
wherein:

R^1 is an amino protecting group; and

R^3 is bromo;

with a Mg metalating agent to form a compound of formula (I).

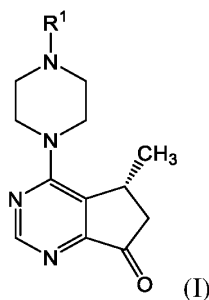
3. The process of claim 2, wherein the compound of formula (III) is a compound of formula (IV) or a pharmaceutically acceptable salt thereof



wherein R^1 is an amino protecting group.

4. The process of claim 3, wherein the metalating agent is $iPrMgBr$.
5. The process of any one of claims 1-4, wherein said continuous flow reaction is conducted in a coordinating ethereal solvent or a non-coordinating apolar solvent, or a mixture thereof.
6. The process of any one of claims 1-5, wherein said continuous flow reaction is conducted in a coordinating ethereal solvent.
7. The process of any one of claims 1-5, wherein said continuous flow reaction is conducted in a non-coordinating apolar solvent.
8. The process of claim 6, wherein the coordinating ethereal solvent is EtOEt, MeOtBu, $iPrOiPr$, dioxane, cPentylOMe, THF, MeTHF or a mixture thereof.

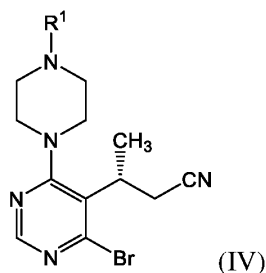
9. The process of claim 7, wherein the non-coordinating apolar solvent is hexane, heptane, toluene, or xylene, or a mixture thereof.
10. The process of any one of claims 4-9, wherein the $i\text{PrMgBr}$ is in MeTHF.
11. The process of any one of claims 3-10, wherein the compound of formula (IV) is in EtOEt, MeOtBu, $i\text{PrOiPr}$, dioxane, cPentylOMe, THF, MeTHF, hexane, heptane, toluene, or xylene, or a mixture thereof.
12. The process of claim 13, wherein the compound of formula (IV) is in a mixture comprising MeTHF and toluene.
13. The process of any one of claims 4-12, wherein the $i\text{PrMgBr}$ is added to the compound of formula (IV).
14. The process of any one of claims 2-13, wherein in step (a) the compound of formula (III) is transferred to the compound of formula (II) and the compound of formula (II) is transferred to a Mg-imine complex;
and R^1 is hydrogen or an amino protecting group 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.
15. The process of claim 14, wherein the Mg-imine complex is a solid in suspension.
16. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



the process comprising the steps of:

- (a) solubilizing a compound of formula (IV)

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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).

17. The process of any one of claims 4-16, wherein the molar ratio of iPrMgBr to compound of formula (IV) is about 1:1 to about 1.5:1.

18. The process of claim 7, wherein the molar ratio of iPrMgBr to compound of formula (IV) is about 1.3 to about 1.

19. The process of claim 17 or claim 18, wherein the molar ratio of iPrMgBr to compound of formula (IV) is about 1:1.

20. The process of any one of claims 4-19, wherein the iPrMgBr is added to the compound of formula (IV) in one or more steps.

21. The process of any one of claims 14-20, wherein the aqueous acid salt is selected from the group consisting of acetic acid, HCl, H₂SO₄, NaHSO₄, H₃PO₄, NaH₂PO₄, Na₂HPO₄, NaH₂Citrate, NH₄Cl, or oxalic acid, or a mixture thereof.

22. The process of claim 21, wherein the aqueous acid salt is NaHSO₄.

23. The process of any one of claims 1-22, wherein the compound of formula (I) is optionally (a) washed; (b) distilled; (c) precipitated; and (d) dried.

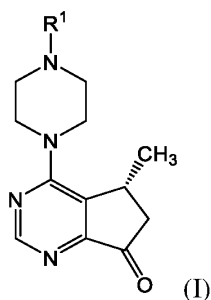
24. The process of any one of claims 1-23, wherein the process does not require a re-crystallization step.

25. The process of any one of claims 1-24, wherein the process is performed in one or more continuous stirred tank reactors (CSTR).
26. The process of claim 25, wherein the process is performed using 1, 2, 3, 4, 5, 6, or 7 CSTRs.
27. The process of claim 25 or claim 26, wherein the process is performed using 5 CSTRs.
28. The process of any one of claims 25-27, 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.
29. The process of claim 28, wherein the compound of formula (IV) is in a mixture of MeTHF and toluene.
30. The process of claim 28 or claim 29, wherein to the solution of the compound of formula (IV) in the first CSTR is added iPrMgBr in MeTHF.
31. The process of claim 30 wherein the molar ratio of iPrMgBr to the compound of formula (IV) is about 1:1.
32. The process of any one of claims 25-31, 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.
33. The process of claim 32, wherein the contents of the first CSTR are transferred to the second CSTR.
34. The process of any one of claims 25-33, further comprising a third CSTR, wherein the contents of the second CSTR are transferred to the third CSTR and stirred in the third CSTR.
35. The process of any one of claims 25-34, 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.
36. The process of any one of claims 25-35, comprising a fourth CSTR to which aqueous NaHSO₄ is added.

37. The process of claim 36, wherein pH of a biphasic mixture after addition of the aqueous NaHSO_4 in the fourth CSTR is about 1 to about 3.
38. The process of claim 37 wherein the pH of the biphasic mixture in the fourth CSTR is about 2.
39. The process of any one of claims 25-38, wherein the contents of the third CSTR are added to the fourth CSTR, thereby forming the compound of formula (I).
40. The process of any one of claims 25-33 and claims 35-39, further comprising a fourth CSTR, wherein the contents of the second CSTR are transferred to the fourth CSTR.
41. The process of any one of claims 25-40, comprising a fifth CSTR to which a solution of a base in water is added.
42. The process of claim 41, where as a base in water NaOH in water is added.
43. The process of claim 42, wherein the pH of a biphasic mixture in the fifth CSTR after addition of NaOH is about 4 to about 7.
44. The process of claim 43, wherein the pH of the biphasic mixture in the fifth CSTR after addition of NaOH is about 4.6 ± 0.2 .
45. The process of any one of claims 25-44 further comprising a first separation vessel.
46. The process of claim 46, wherein the contents of the fifth CSTR are transferred to the first separation vessel, thereby separating organic and aqueous phases.
47. The process of claim 46, 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).
48. The process of any of claims 25-47, further comprising a sixth CSTR to which water is added.
49. The process of claim 48, wherein the organic phase after separation is transferred to the sixth CSTR.
50. The process of claim 49, further comprising a second separation vessel.

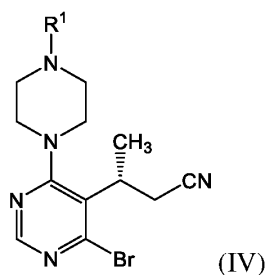
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51. The process of claim 50, wherein the contents of the sixth CSTR are transferred to the second separation vessel, thereby separating organic and aqueous phases.
52. The process of claim 51, wherein the organic phase is: (i) distilled; (ii) precipitated; and (iii) dried to isolate the compound of formula (I).
53. The process of any one of claims 1-52 substantially performed according to Figure 1.
54. The process of any one of claims 1-52 substantially performed according to Figure 2.
55. A process of any one of claims 1-54, wherein R¹ is tert-butyloxycarbonyl.
56. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



the process comprising the steps of:

- (a) solubilizing a compound of formula (IV)



in a mixture of toluene and MeTHF in a first continuous stirred tank reactor (CSTR);

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

(c) transferring the contents of the first CSTR to a second CSTR to which iPrMgBr in MeTHF is added, thereby forming a Mg-imine complex as a solid;

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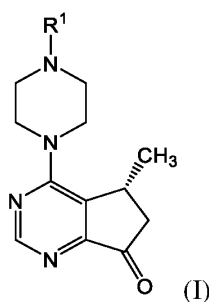
(d) transferring the contents of the second CSTR to a third CSTR to which toluene is added, thereby forming a Mg-imine complex as a solid;

(e) transferring the contents of the third CSTR to a fourth CSTR to which aqueous NaHSO_4 is added to set a pH about 2, thereby forming the compound of formula (I) and allowing the reaction to proceed;

(f) transferring the contents of the fourth CSTR to a fifth CSTR to which NaOH in water is added to set a pH of about 5 and allowing the reaction to proceed; and

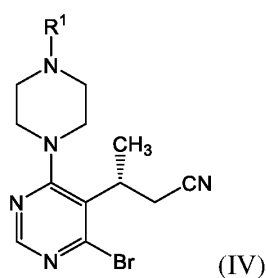
(g) transferring the contents of the fifth CSTR to a first separation vessel to separate the compound of formula (I) in the organic phase.

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



the process comprising the steps of:

(a) solubilizing a compound of formula (IV)



in a mixture of toluene and MeTHF in a first continuous stirred tank reactor (CSTR);

(b) adding $i\text{PrMgBr}$ in MeTHF to the solubilized compound of step (a) in the first CSTR and wherein the first CSTR has a residence time of about 15 min, thereby forming a Mg-imine complex as a solid;

(c) transferring the contents of the first CSTR to a second CSTR to which $i\text{PrMgBr}$ in MeTHF is added wherein the second CSTR has a residence time of about 15 min, thereby forming a Mg-imine complex as a solid;

(d) transferring the contents of the second CSTR to a third CSTR to which toluene is added wherein the third CSTR has a residence time of about 15 min, thereby forming a Mg-imine complex as a solid;

(e) transferring the contents of the third CSTR to a fourth CSTR to which aqueous NaHSO_4 is added to set a pH about 2, thereby forming the compound of formula (I) and allowing the reaction to proceed for about 4.45 min;

(f) transferring the contents of the fourth CSTR to a fifth CSTR to which NaOH in water is added to set a pH of about 5 and allowing the reaction to proceed for about 4.45 min; and

(g) transferring the contents of the fifth CSTR to a first separation vessel to separate the compound of formula (I) in the organic phase.

58. The process of claim 56 or claim 57, wherein the Mg-imine complex is formed as solid in suspension.

59. The process of any one of claim 56 to 58, wherein the product containing organic phase is: (i) washed with water; (ii) distilled; (iii) precipitated; and (iv) dried.

60. The process of claim 58, further comprising a sixth CSTR to which water is added.

61. The process of claim 60, wherein the organic phase after separation is transferred to the sixth CSTR.

62. The process of claim 61, further comprising a second separation vessel.

63. The process of claim 62, wherein the contents of the sixth CSTR are transferred to the second separation vessel, thereby separating organic and aqueous phases.

64. The process of claim 63, wherein the organic phase is: (i) distilled; (ii) precipitated; and (iii) dried.