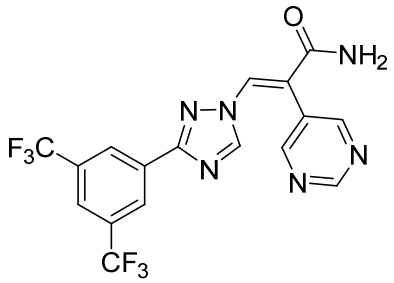
CLAIMS

1. A crystalline form of the compound represented by the following Structural Formula (VII):



(VII),

wherein
the crystalline form is Form I characterized by x-ray powder diffraction peaks at 2θ angles 4.6°, 22.8°, 23.2°, and 24.4°.

2. The crystalline form of claim 1, wherein the crystalline form is by at least four x-ray powder diffraction peaks at 2θ angles selected from 4.6°, 20.0°, 22.8°, 23.2°, and 24.4°.

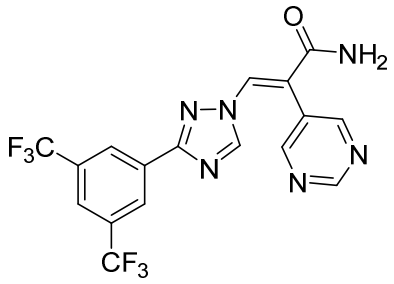
3. The crystalline form of claim 1 or 2, wherein the crystalline form is characterized by at least five x-ray powder diffraction peaks at 2θ angles selected from 4.6°, 19.0°, 20.0°, 22.8°, 23.2°, 23.7°, 24.4°, and 27.9°.

4. The crystalline form of any one of claims 1-3, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially in accordance with that depicted in FIG. 20.

5. The crystalline form of any one of claims 1-4, wherein the crystalline form is characterized by a DSC thermogram having an endothermic event at about 226 °C.

6. The crystalline form of any one of claims 1-5, wherein the crystalline form is characterized by a DSC thermogram substantially in accordance with that depicted in FIG. 21.

7. A crystalline form of the compound represented by Structural Formula (VII):



(VII),

wherein

the crystalline form is Form II characterized by x-ray powder diffraction peaks at 2θ angles 9.9°, 19.2°, 22.4°, and 24.4°.

8. The crystalline form of claim 7, wherein the crystalline form is by at least four x-ray powder diffraction peaks at 2θ angles selected from 9.9°, 19.2°, 22.4°, 23.5°, and 24.4°.

9. The crystalline form of claim 7 or 8, wherein the crystalline form is characterized by at least five x-ray powder diffraction peaks at 2θ angles selected from 9.9°, 19.2°, 21.3°, 21.9°, 22.4°, 23.5°, 24.4°, and 29.2°.

10. The crystalline form of any one of claims 7-9, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially in accordance with that depicted in FIG. 24.

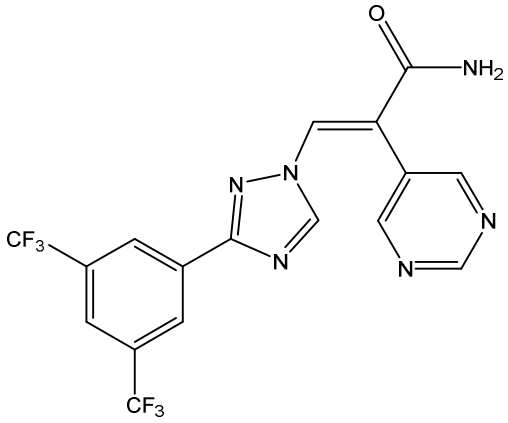
11. The crystalline form of any one of claims 7-10, wherein the crystalline form is characterized by a DSC thermogram having two endothermic events at about 112 °C and at about 225 °C.

12. The crystalline form of any one of claims 7-11, wherein the crystalline form is characterized by a DSC thermogram substantially in accordance with that depicted in FIG. 25.

13. The crystalline form of any one of claims 7-12, wherein the compound of Structural Formula (VII) is in the form of a solvate.

14. The crystalline form of any one of claims 4-13, wherein the form is a methanol solvate.

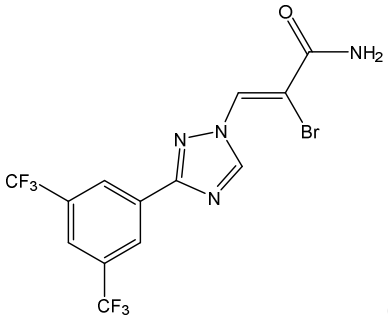
15. A method of preparing a compound represented by structural formula (VII),



(VII),

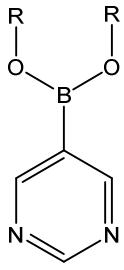
comprising:

reacting a compound represented by structural formula (II),



(II),

with a compound represented by structural formula (III),



(III),

in a first solvent, in the presence of a Pd catalyst and one or more inorganic bases under conditions suitable to prepare a compound represented by structural formula (VII), wherein:

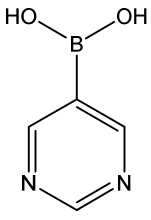
each R is hydrogen, a C_1-C_4 alkyl, or two groups R, taken together with the oxygen atoms to which they are attached, form a 5-7 member cyclic acetal moiety,

and thereby obtaining the compound represented by structural formula (VII).

16. The method of Claim 15, wherein the one or more inorganic base is selected from a quaternary ammonium, sodium, potassium, or cesium carbonate, bicarbonate, acetate, or hydroxide.

17. The method of Claim 15 or 16, wherein the Pd catalyst is selected from chloro{[4-(N,N-dimethylamino)phenyl]di-t-butylphosphino}(2'-amino-1,1'-biphenyl-2-yl)palladium(II) or chloro(crotyl)[di-tert-butyl(4-dimethylaminophenyl)phosphine]palladium(II).

18. The method of any one of Claims 15-17, wherein the compound represented by structural formula (III) is a compound represented by structural formula (IIIB):



(IIIB).

19. The method of any one of Claims 15-18, wherein the inorganic base is Cs_2CO_3 or CsOH.

20. The method of any one of Claims 15-19, wherein the inorganic base is Cs_2CO_3.

21. The method of any one of Claims 15-20, wherein the Pd catalyst is chloro{[4-(N,N-dimethylamino)phenyl]di-t-butylphosphino}(2'-amino-1,1'-biphenyl-2-yl)palladium(II).

22. The method of any one of Claims 15-21, wherein the first solvent is an ether solvent, a C1-C4 alcohol, or a combination thereof.

23. The method of any one of Claims 15-22, wherein the first solvent is MTBE, CPME, THF, dioxane, MeTHF, methanol, either alone or in combination with water or ethanol.

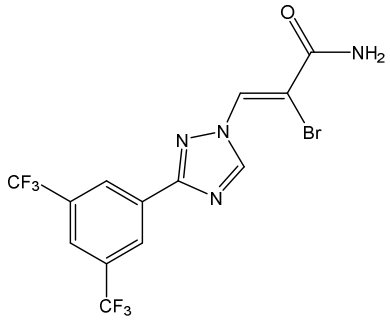
24. The method of any one of Claims 15-23, wherein a Pd catalyst load is from 0.5 % to mol% to 10 mol%.

25. The method of any one of Claims 15-24, wherein an amount of the inorganic base is from 0.5 to 2 molar equivalents of base with respect to the compound represented by structural formula (II).

26. The method of any one of Claims 15-25, wherein the conditions suitable to prepare the compound represented by structural formula (VII) comprise:

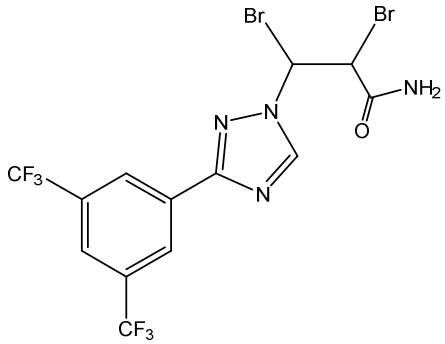
- the Pd catalyst load from 0.5 mol% to 3 mol%;
- an amount of the compound represented by structural formula (III) of from 1.0 to 2.2 molar equivalents with respect to the compound represented by structural formula (II);
- an amount of the inorganic base of 0.8-1.2 total molar equivalents of base with respect to the compound represented by structural formula (II);
- the first solvent comprises from 16 parts to 21 parts of dioxane and from 2 parts to 3 parts of water;
- a reaction temperature from about 55 °C to about 60 °C; and
- a reaction time of about 7-8 hours.

27. The method of any one of Claims 15-26, further comprising a step of preparing the compound represented by structural formula (II),



(II),

by dehydrobrominating a compound represented by structural formula (IV),



(IV),

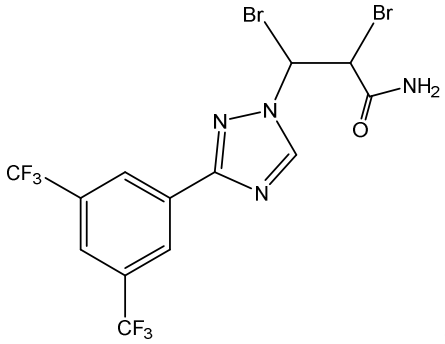
in a second solvent, in the presence of an organic base, under conditions suitable for producing the compound represented by structural formula (II).

28. The method of any one of Claims 15-27, wherein the organic base is triethylamine or diisopropylethylamine (DIPEA).

29. The method of any one of Claims 15-28, wherein the second solvent comprises acetonitrile (ACN).

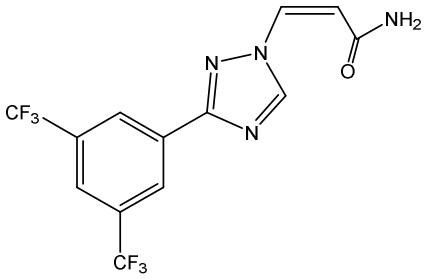
30. The method of any one of Claims 15-29, wherein the second solvent is 80% ACN/20% water.

31. The method of any one of Claims 15-30, further comprising a step of preparing the compound represented by structural formula (IV),



(IV),

by reacting a compound represented by structural formula (V),



(V),

with bromine (Br_2) in a third solvent, in the presence of a bromide salt, under conditions suitable to prepare the compound represented by structural formula (IV).

32. The method of Claim 31, wherein the third solvent comprises water and the bromide salt is sodium bromide.

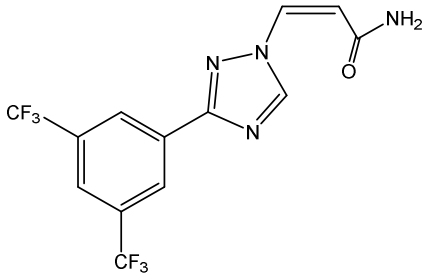
33. The method of any one of Claims 27-30, wherein the second solvent comprises about 11 parts of ACN and about 4 parts of H_2O with respect to the compound represented by structural formula (IV), the organic base is DIPEA, and wherein the conditions suitable for preparing the compound represented by structural formula (II) comprise:

- an amount of DIPEA of about 1 molar equivalent with respect to the compound represented by structural formula (IV);
- a reaction temperature of from 20 °C to 25 °C; and
- a reaction time from 2 to 3 hours.

34. The method of any one of Claims 15-33, wherein the third solvent is acetic acid.

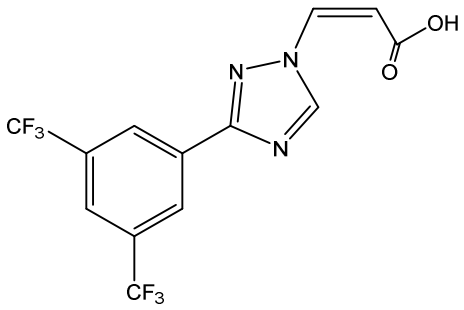
35. The method of any one of Claims 15-34, wherein reacting the compound represented by structural formula (V) with Br_2 is performed at a temperature of from 20 °C to 30 °C, for a time of from 12 hours to 16 hours.

36. The method of any one of Claims 15-35, further comprising a step of preparing a compound represented by structural formula (V),



(V),

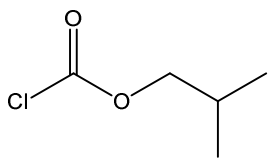
by amidating a compound represented by structural formula (VI),



(VI),

in a fourth solvent, with an amidating agent, in the presence of a tertiary amine organic base and a chloroformate, under conditions suitable for producing the compound represented by structural formula (V).

37. The method of any one of Claims 15-36, wherein the amidating agent is ammonium hydroxide, the tertiary amine organic base is N-methylmorpholine (NMM) and the chloroformate is isobutyl chloroformate represented by the following structural formula



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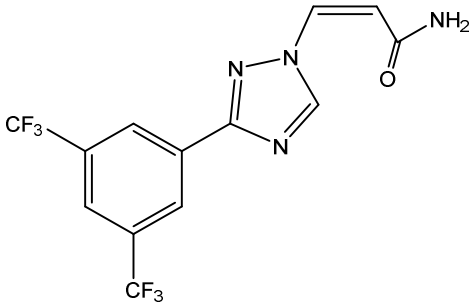
38. The method of any one of Claims 15-37, wherein the fourth solvent is tetrahydrofuran (THF) or 2-methyltetrahydrofuran (MeTHF).

39. The method of any one of Claims 15-38 wherein the fourth solvent is MeTHF, and wherein amidating the compound represented by structural formula (VI) is performed at a temperature from 0 °C to 5 °C and for a time from 3 hours to 4 hours.

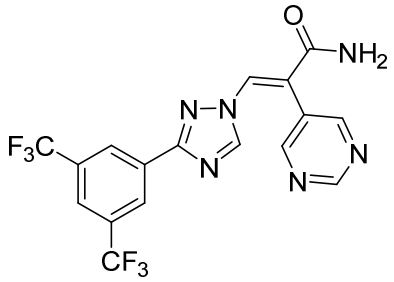
40. A compound represented by structural formula (V)



(V)

or a salt thereof.

41. A method of preparing crystalline Form I of the compound represented by Structural Formula (VII)



(VII),

the method comprising:

(a) contacting crystalline Form II of the compound represented by Structural Formula (VII) with about 18 volumes of 4-methyl-2-pentanone (MIBK) to form a mixture;

(b) heating the mixture of step (a) to about 80-85 °C to form a heated mixture;

(c) optionally adding to the heated mixture of step (b) SiDMT;

(d) maintaining the heated mixture at a temperature of about 80-85 °C for about 4.5 hours;

(e) filtering the heated mixture to obtain a filtrate;

(f) adding MIBK at a temperature of about 80-85 °C to the filtrate;

(g) inducing nucleation of Form I in the filtrate by cooling the filtrate to about 20-25 °C;

(h) crystallizing Form I by a controlled cooling crystallization of the filtrate with a final temperature of 0-5 °C; and

(i) isolating crystalline Form I from the filtrate.

42. Use of crystalline Form I of the compound represented by Structural Formula VII, in the manufacture of a medicament for treating a CRM1 associated disease or disorder.

43. A pharmaceutical composition comprising crystalline Form I of the compound represented by Structural Formula (VII) and a pharmaceutically acceptable carrier.

44. Crystalline Form I of the compound represented by Structural Formula VII, for use in therapy.