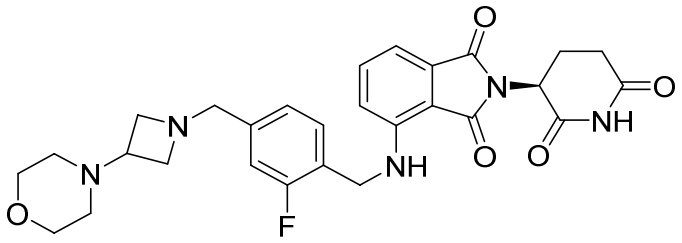
CLAIMS

What is claimed is:

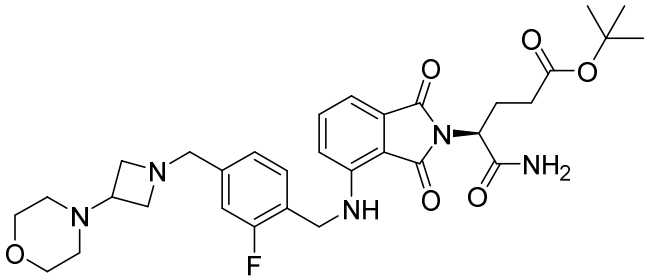
1. A process for preparing a compound of Formula (I):



(I)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, comprising:

(step 1.0) cyclizing a compound of Formula (II):



(II)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, to provide a compound of Formula (I), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof; and

(step 1.1) optionally converting the compound of Formula (I), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, to a salt of the compound.

2. The process of claim 1, wherein step 1.0 occurs in the presence of an acid.

3. The process of claim 2, wherein the acid is benzenesulfonic acid.

4. The process of claim 3, wherein the compound of Formula (I), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, prepared in step 1.0 is a besylate salt.

5. The process of any one of claims 1 to 4, wherein step 1.0 occurs in a solvent of acetonitrile, methyltetrahydrofuran, water, or a combination thereof.

6. The process of any one of claims 1 to 5, wherein in step 1.1 the compound of Formula (I), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is converted to a hydrochloride salt of the compound.

7. The process of claim 6, wherein in step 1.1 a salt of the compound of Formula (I) is contacted with a basic aqueous solution and is subsequently acidified.

8. The process of claim 7, wherein the basic aqueous solution is a bicarbonate solution.

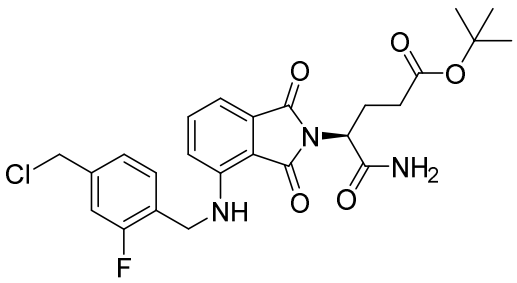
9. The process of claim 7 or 8, wherein acidification comprises addition of hydrochloric acid.

10. The process of any one of claims 6 to 9, wherein step 1.1 occurs in a biphasic mixture comprising an aqueous solution and an organic solvent.

11. The process of any one of claims 6 to 10, wherein step 1.1 occurs in a solvent of ethyl acetate (EtOAc), isopropanol (IPA), or water.

12. The process of any one of claims 1 to 11, wherein the compound of Formula (II), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 2.a) reacting a compound of Formula (II-A):

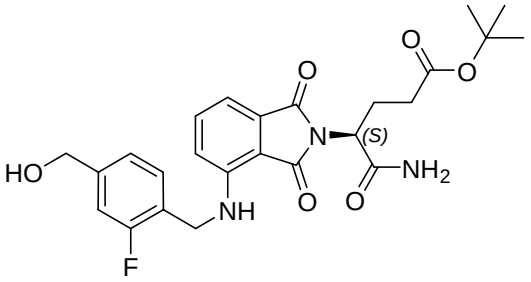


(II-A)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, with 4-(azetidin-3-yl)morpholine, or a salt thereof, optionally in the presence of a base.

13. The process of claim 12, wherein the compound of Formula (II-A), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 2.b) chlorinating a compound of Formula (II-B):

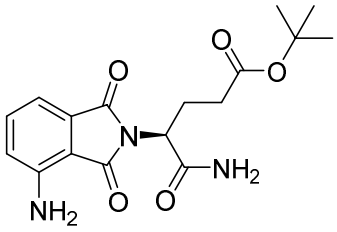


(II-B)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, optionally in the presence of mesyl chloride (MsCl) and/or base.

14. The process of claim 13, wherein the compound of Formula (II-B), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 2.c) reacting a compound of Formula (V):

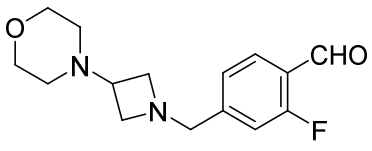


(V)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, with 2-fluoro-4-(hydroxymethyl)benzaldehyde, optionally in the presence of a reducing agent and/or acid, particularly wherein the reducing agent is a borohydride reagent and/or the acid is trifluoroacetic acid.

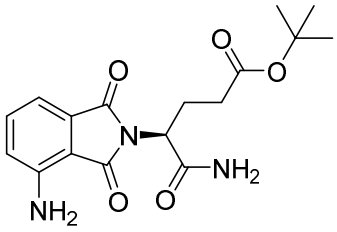
15. The process of any one of claims 1 to 11, wherein the compound of Formula (II), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 2.0) reacting a compound of Formula (III):



(III)

or a salt, solvate, hydrate, or isotopologue thereof, optionally a bis-hydrochloride or bis-oxalic acid salt of the compound of Formula (III), with a compound of Formula (V):

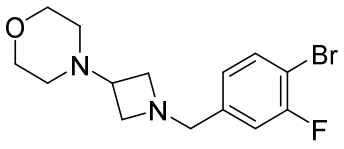


(V)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, optionally in the presence of a reducing agent and/or acid, particularly wherein the reducing agent is a borohydride reagent and/or the acid is trifluoroacetic acid.

16. The process of claim 15, wherein the compound of Formula (III), or a salt, solvate, hydrate, or isotopologue thereof, is prepared by a process comprising:

(step 3.0) reacting a compound of Formula (IV):



(IV)

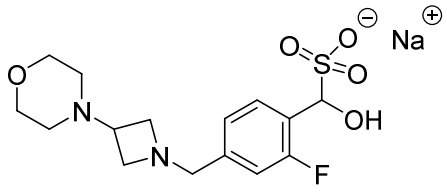
or a salt, solvate, hydrate, or isotopologue thereof, with a formaldehyde source, particularly dimethylformamide (DMF),

optionally wherein step 3.0 occurs in the presence of an organomagnesium reagent, particularly wherein the organomagnesium reagent is iPrMgCl·LiCl, and

optionally wherein in step 3.0 the compound of Formula (III), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is converted to a bis-hydrochloride salt of the compound.

17. The process of claim 16, further comprising:

(step 3.a) reacting the compound of Formula (III), or a salt, solvate, hydrate, or isotopologue thereof, prepared in step 3.0, with $Na_2S_2O_5$ to provide a sodium sulfonate compound of the Formula:



;

or a salt, solvate, hydrate, or isotopologue thereof, and

(step 3.b) converting the sodium sulfonate compound to the compound of Formula (III), or a salt, solvate, hydrate, or isotopologue thereof, particularly a bis-oxalic acid salt of the compound.

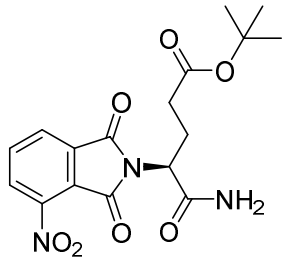
18. The process of claim 16 or 17, wherein the compound of Formula (IV), or a salt, solvate, hydrate, or isotopologue thereof, is prepared by a process comprising:

(step 4.0) reacting 4-(azetidin-3-yl)morpholine, or a salt thereof, particularly a hydrochloride salt of 4-(azetidin-3-yl)morpholine, with 4-bromo-3-fluorobenzaldehyde, optionally in the presence of a reducing agent, particularly wherein the reducing agent is a borohydride reagent, and

optionally wherein in step 4.0 the compound of Formula (IV), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is converted to a methanesulfonic acid salt of the compound.

19. The process of claim 15, wherein the compound of Formula (V), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 5.0) reducing a compound of Formula (VI):

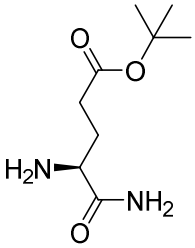


(VI)

or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, optionally wherein step 5.0 occurs by hydrogenation, particularly using hydrogen gas, and optionally wherein step 5.0 occurs in the presence of a catalyst, particularly wherein the catalyst is palladium on carbon.

20. The process of claim 19, wherein the compound of Formula (VI), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

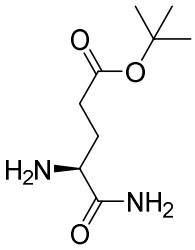
(step 6.0) reacting (*S*)-tert-butyl 4,5-diamino-5-oxopentanoate of the Formula:



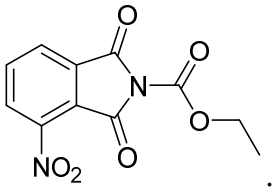
or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, with 3-nitrophthalic anhydride, optionally in the presence of base and/or an activating reagent;

or

(step 6.a) reacting (*S*)-tert-butyl 4,5-diamino-5-oxopentanoate of the Formula:



or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, with ethyl 4-nitro-1,3-dioxoisoindoline-2-carboxylate of the Formula, optionally in the presence of base:



21. The process of claim 1, wherein a compound of Formula I, or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 1.0) cyclizing a compound of Formula (II), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, to provide a compound of Formula (I), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof; and

(step 1.1) optionally converting the compound of Formula (I), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, to a salt of the compound;

wherein the compound of Formula (II), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 2.0) reacting a compound of Formula (III), or a salt, solvate, hydrate, or isotopologue thereof, with a compound of Formula (V) or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof;

wherein the compound of Formula (III), or a salt, solvate, hydrate, or isotopologue thereof, is prepared by a process comprising:

(step 3.0) reacting a compound of Formula (IV), or a salt, solvate, hydrate, or isotopologue thereof, with a formaldehyde source;

wherein the compound of Formula (IV), or a salt, solvate, hydrate, or isotopologue thereof, is prepared by a process comprising:

(step 4.0) reacting 4-(azetidin-3-yl)morpholine, or a salt thereof, with 4-bromo-3-fluorobenzaldehyde;

wherein the compound of Formula (V), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 5.0) reducing a compound of Formula (VI), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof; and

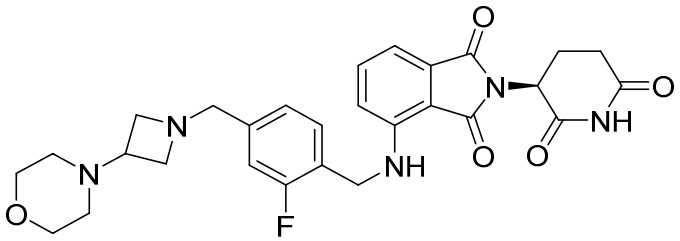
wherein the compound of Formula (VI), or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, is prepared by a process comprising:

(step 6.0) reacting (*S*)-tert-butyl 4,5-diamino-5-oxopentanoate or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof, with 3-nitrophthalic anhydride.

22. A bis-besylate salt of Compound 1;

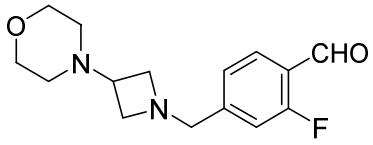
a compound, which is Compound 2, Compound 2-a, Compound 2-b, Compound 3, Compound 4, Compound 5, or Compound 6, or a salt, solvate, hydrate, enantiomer, mixture of enantiomers, or isotopologue thereof;

a solid form comprising a besylate salt of Compound 1:



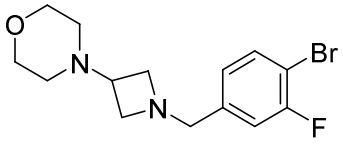
1;

a solid form comprising a hydrochloride salt of Compound 3:



3; or

a solid form comprising a methanesulfonic acid salt of Compound 4:



4.