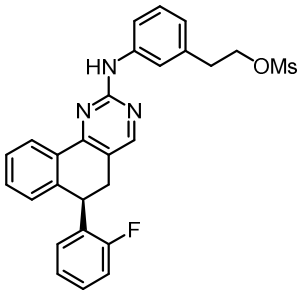


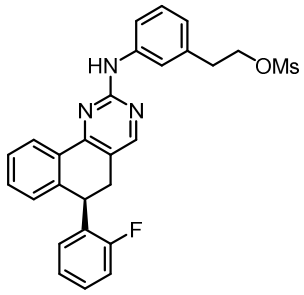
(4),

with methanesulfonyl chloride (MsCl) to form Compound 5:



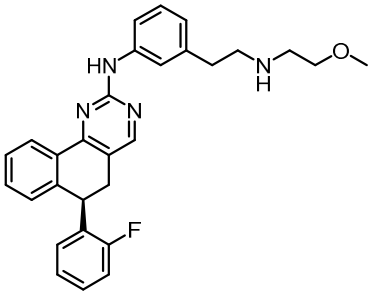
(5); and

Step 4: reacting Compound 5:



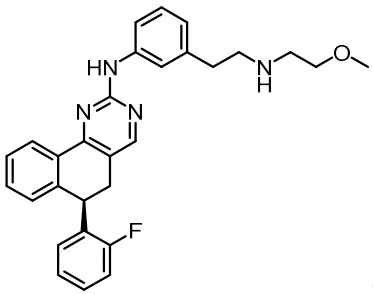
(5),

with methoxyethylamine to form Compound A:



(A).

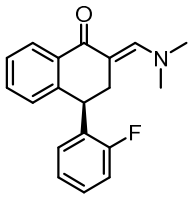
In one aspect, the present disclosure refers to a method of making Compound A:



(A),

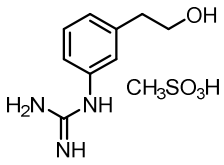
or a salt thereof, comprising

Step 2: reacting Compound 2:



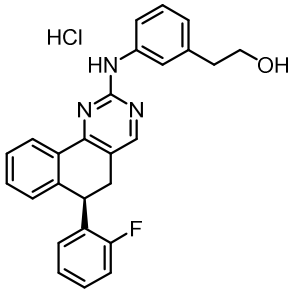
(2),

with Compound 3:



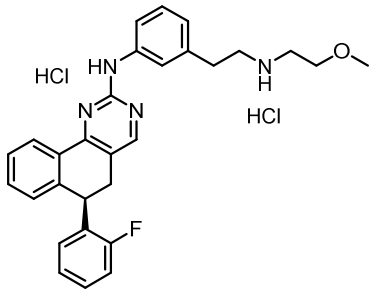
(3),

to form Compound 4:



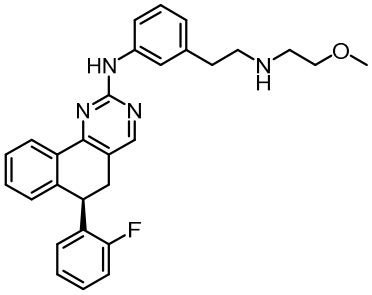
(4).

The present application also relates to a method of making a polymorph of Compound A dihydrochloride salt:



,

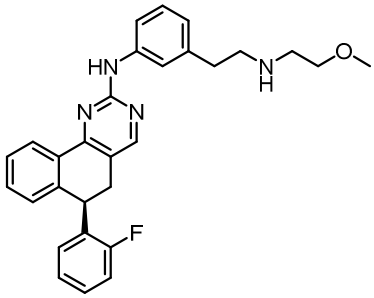
comprising reacting Compound A:



(A),

with HCl to form the polymorph; and optionally recrystallizing the polymorph.

In another aspect, the present disclosure refers to a method of making a pharmaceutical composition comprising Compound A:



(A),

or a salt thereof, comprising the step of making Compound A or a salt thereof as disclosed herein, and a step of combining Compound A or a salt thereof with at least one pharmaceutically acceptable excipient or carrier.

The present application also provides a pharmaceuitcal composition comprising Compound A or a salt thereof or a polymorph of Compound A dihydrochloride salt prepared by the methods of the present application, and a pharmaceutically acceptable carrier or excipient.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising Compound A or a salt thereof prepared according to the method as disclosed herein.

The present application also provides a method of treating a cell proliferative disorder, comprising administering, to a subject in need thereof, a therapeutically effective amount of a composition comprising Compound A or a salt thereof or a polymorph of Compound A dihydrochloride salt prepared by the methods of the present application.

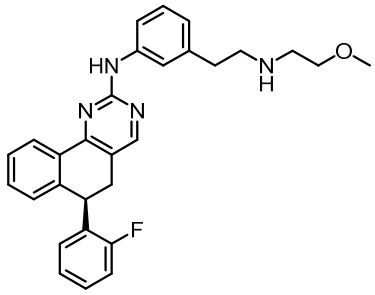
The present application also provides Compound A or a salt thereof or a polymorph of Compound A dihydrochloride salt prepared by the methods of the present application for use in the manufacture of a medicament for treating a cell proliferative disorder in a subject in need thereof.

The present application also provides use of Compound A or a salt thereof or a polymorph of Compound A dihydrochloride salt prepared by the methods of the present application in treating a cell proliferative disorder in a subject in need thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly

CLAIMS

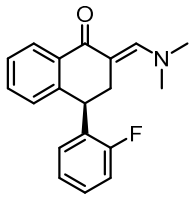
1. A method of making Compound A:



(A),

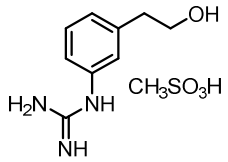
or a salt thereof, comprising

Step 2: reacting Compound 2:



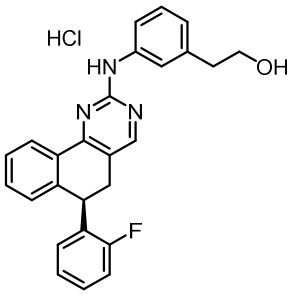
(2),

with Compound 3:



(3),

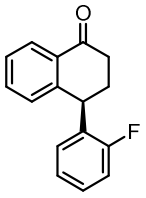
to form Compound 4:



(4).

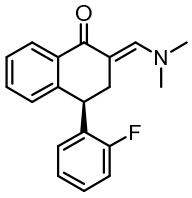
2. The method of claim 1, further comprising one or more steps selected from:

Step 1: reacting Compound 1:



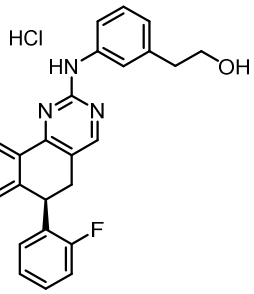
(1),

with N,N-dimethylformamide dimethyl acetal (DMF-DMA), to form Compound 2:



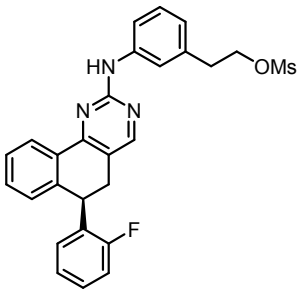
(2);

Step3: reacting Compound 4:



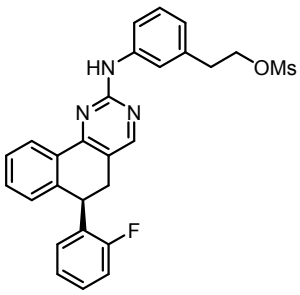
(4),

with methanesulfonyl chloride (MsCl) to form Compound 5:



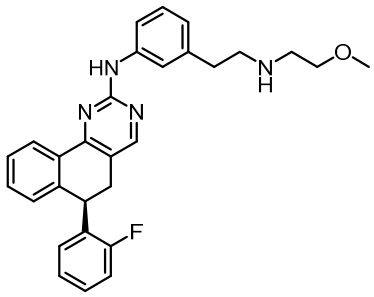
(5); and

Step 4: reacting Compound 5:



(5),

with methoxyethylamine to form Compound A:



(A).

3. The method of claim 2, wherein Step 1 comprises:

1a. adding DMF-DMA, optionally together with a protic solvent to Compound 1; and

1b. reacting Compound 1 with DMF-DMA, optionally in the presence of a protic solvent at a temperature below 100 ^{o}C.

4. The method of claim 3, further comprising:

1c. cooling the reaction between Compound 1 and DMF-DMA; and

1d. adding a hydrocarbon solvent to the reaction to generate a slurry.

5. The method of claim 4, further comprising one or more steps selected from:

1e. stirring the slurry from 1d;

1f. adding a hydrocarbon solvent to the slurry from 1d or 1e;

1g. cooling the slurry from 1d, 1e, or 1f, optionally followed by stirring the slurry;

1h. further cooling the slurry from 1g, optionally followed by stirring the slurry; and

1i. filtering the slurry from 1d, 1e, 1f, 1g, or 1h to produce solid Compound 2.

6. The method of claim 1, wherein Step 2 comprises:

2a. adding Compound 2 to Compound 3, optionally preceded by the addition of 2-MeTHF and a base to Compound 3;

2b. reacting Compound 2 and Compound 3 at a temperature between about 75 ^{o}C and about 80 ^{o}C;

2c. adding HCl after the reaction between Compound 2 and Compound 3; and

2d. optionally adding a seed Compound 4 to generate a slurry.

7. The method of claim 6, further comprising, after 2b and before 2c, one or more steps selected from:

2ab1. cooling the reaction between Compound 2 and Compound 3, and optionally washing the reaction with a NaCl solution after the cooling;

2ab2. distilling the organic phase generated in the reaction between Compound 2 and Compound 3;

2ab3. adding 2-MeTHF to the organic phase and distilling the organic phase to generate a dried 2-MeTHF solution; and

2ab4. adding water to the dried 2-MeTHF solution, and optionally heating the solution.

8. The method of claim 6, further comprising, after 2d, one or more steps selected from:

2e. stirring the slurry from 2d;

2f. adding HCl to the slurry from 2d or 2e;

2g. cooling the slurry from 2d, 2e, or 2f;

2h. stirring the slurry from 2g; and

2i. filtering the slurry from 2d, 2e, 2f, 2g, or 2h to produce solid Compound 4.

9. The method of claim 2, wherein Step 3 comprises:

3a. adding a base to Compound 4, optionally preceded by forming a Compound 4 slurry in 2-MeTHF;

3b. adding triethylamine, and optionally cooling the mixture; and

3c. adding MsCl, and optionally heating the mixture.

10. The method of claim 9, further comprising, after 3a and before 3b, one or more steps selected from:

3ab1. after adding the base to Compound 4, stirring the resulting mixture;

3ab2. after the stirring, removing the aqueous phase and keeping the organic phase; and

3ab3. concentrating the organic phase, and adding 2-MeTHF to and distilling the organic phase.

11. The method of claim 9, further comprising, after 3c, one or more steps selected from:

3d. adding additional triethylamine and MsCl to the mixture, for once, twice, or more times, and after each additional addition of triethylamine and MsCl, optionally stirring the mixture;

3e. after the reaction between Compound 4 and MsCl, adding water to the reaction mixture, optionally stirring the mixture, and collecting the aqueous phase; and

3f. extracting the aqueous phase with 2-MeTHF, and collecting the organic phase.

12. The method of claim 2, wherein Step 4 comprises adding methoxyethylamine to Compound 5 and heating the mixture.

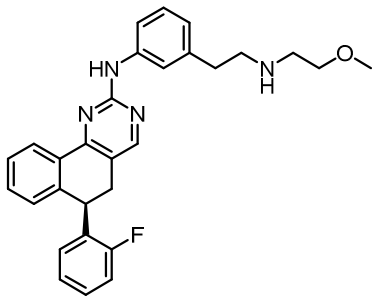
13. The method of claim 12, wherein the mixture is heated to a temperature below 90 ^{o}C.

14. The method of claim 12, further comprising one or more steps selected from:
adding a solvent and water to the reaction mixture;
collecting the aqueous phase;
extracting the aqueous phase with a solvent;
collecting the organic phase; and
distilling the organic phase to form a slurry.

15. The method of claim 14, further comprising one or more steps selected from:
adding a non-polar hydrocarbon solvent to the slurry;
stirring the slurry; and
filtering the slurry.

16. A pharmaceutical composition comprising Compound A or a salt thereof prepared according to the method of claim 1.

17. A method of making a pharmaceutical composition comprising Compound A:



(A),

or a salt thereof, comprising the step of making Compound A or a salt thereof of claim 1, and a step of combining Compound A or a salt thereof with at least one pharmaceutically acceptable excipient or carrier.