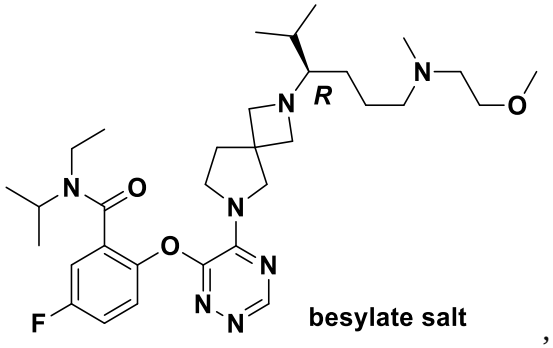
Several references describe inhibitors targeting the menin-MLL interaction: WO2011029054, J Med Chem 2016, 59, 892-913 describe the preparation of thienopyrimidine and benzodiazepine derivatives; WO2014164543 describes thienopyrimidine and thienopyridine derivatives; *Nature Chemical Biology* March 2012, *8*, 277-284 and Ren, J.; *et al*. *Bioorg Med Chem Lett* (2016), *26(18)*, 4472-4476 describe thienopyrimidine derivatives; *J Med Chem* 2014, *57*, 1543-1556 describes hydroxy- and aminomethylpiperidine derivatives; *Future Med Chem* 2014, *6*, 447-462 reviews small molecule and peptidomimetic compounds; WO2016195776 describes furo[2,3-d]pyrimidine, 9H-purine, [1,3]oxazolo[5,4-d]pyrimidine, [1,3]oxazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-d]pyrimidine, thieno[2,3-b]pyridine and thieno[2,3-d]pyrimidine derivatives; WO2016197027 describes 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine, 5,6,7,8-tetrahydropyrido]4,3-d]pyrimidine, pyrido[2,3-d]pyrimidine and quinoline derivatives; and WO2016040330 describes thienopyrimidine and thienopyridine compounds. WO2017192543 describes piperidines as Menin inhibitors. WO2017112768, WO2017207387, WO2017214367, WO2018053267 and WO2018024602 describe inhibitors of the menin-MLL interaction. WO2017161002 and WO2017161028 describe inhibitors of menin-MLL. WO2018050686, WO2018050684 and WO2018109088 describe inhibitors of the menin-MLL interaction. WO2018226976 describes methods and compositions for inhibiting the interaction of menin with MLL proteins. WO2018175746 provides methods of treatment for hematological malignancies and Ewing's sarcoma. WO2018106818 and WO2018106820 provide methods of promoting proliferation of a pancreatic cell. WO2018153312 discloses azaspiro compounds relating to the field of medicinal chemistry. WO2017132398 discloses methods comprising contacting a leukemia cell exhibiting an NPM1 mutation with a pharmacologic inhibitor of interaction between MLL and Menin. WO2019060365 describes substituted inhibitors of menin-MLL. WO2020069027 describes the treatment of hematological malignancies with inhibitors of menin. Krivtsov et al., Cancer Cell 2019. No.6 Vol.36, 660-673 describes a menin-MLL inhibitor.

SUMMARY

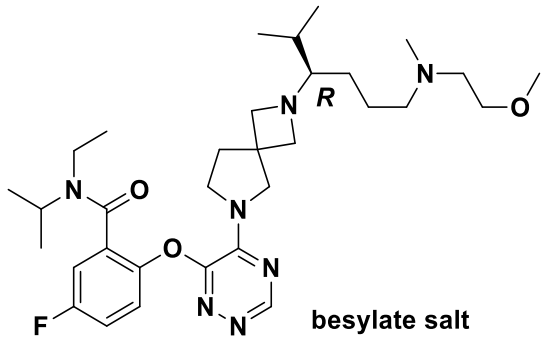
The present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt (benzenesulfonate salt):



,

and solvates thereof.

In one aspect, there is provided (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt



,

or a solvate thereof.

A skilled person will understand that the 'and solvates thereof' or 'or a solvate thereof' refer to the besylate salt of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide. Thus the present disclosure covers the besylate salt of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide, and also the solvates of the besylate salt of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt or hydrates thereof.

In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof.

In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or hydrates thereof.

In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 0.5-2.0 equivalents hydrate.

In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 2.0 equivalents hydrate.

More in particular the present disclosure is directed to a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate.

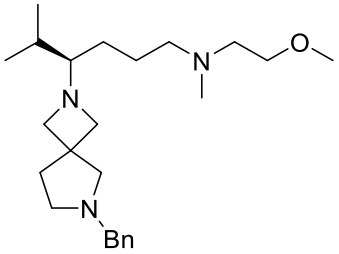
More in particular the present disclosure is directed to a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 0.5-2.0 equivalents hydrate.

More in particular the present disclosure is directed to a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 2.0 equivalents hydrate.

The besylate salt of (*R*)-N-ethyl-5-fluoro-N-isopropyl-

2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide or a solvate thereof is superior with respect to its chemical/physical stability, its physical properties and the fact that it can be isolated as a stable crystalline solid.

In another aspect, there is provided a crystalline form of



citric acid salt,

wherein the crystalline form produces an X-ray powder diffraction pattern comprising peaks at 5.82, 10.09 and 18.42 degrees two theta ± 0.2 degrees two theta.

An example of the present disclosure is directed to a pharmaceutical composition comprising (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.

The present disclosure also provides a pharmaceutical composition comprising, consisting of and/or consisting essentially of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent and (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof.

Also provided are processes for making a pharmaceutical composition comprising, consisting of, and/or consisting essentially of admixing (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof, and a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent.

In another aspect, there is provided a process for preparing a pharmaceutical composition as defined herein comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound as defined herein.

In another aspect, there is provided a compound as defined herein or a pharmaceutical composition as defined herein for use as a medicament.

The present disclosure further provides methods for treating or ameliorating diseases such as cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes, using (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof.

The present disclosure is also directed to the use of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof in the preparation of a medicament wherein the medicament is prepared for treating a disease such as cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

In another aspect, there is provided use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for the prevention or treatment of cancer,

In another aspect, there is provided use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for the prevention or treatment of leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN).

In particular, the compound according to the present disclosure and the pharmaceutical compositions thereof may be useful in the treatment or prevention of leukemias, in particular nucleophosmin (NPM1)-mutated leukemias, e.g. NPM1c.

In an example, the compound according to the present disclosure, may have improved metabolic stability properties.

In an example, the compound according to the present disclosure, may have extended in

vivo half-life (T1/2).

In an example, the compound according to the present disclosure , may have improved oral bioavailability.

In an example, the compound according to the present disclosure , may reduce tumor growth e.g., tumours harbouring MLL (KMT2A) gene rearrangements/alterations and/or NPM1 mutations.

In an example, the compound according to the present disclosure , may have improved PD properties *in vivo* during a prolonged period of time, e.g. inhibition of target gene expression such as MEIS1 and upregulation of differentiation marker over a period of at least 16 hours.

In an example, the compound according to the present disclosure , may have an improved safety profile (e.g. reduced hERG inhibition; improved cardiovascular safety).

In an example, the compound according to the present disclosure , may be suitable for Q.D. dosing (once daily).

The disclosure also relates to the use of the compound according to the present disclosure , in combination with an additional pharmaceutical agent for use in the treatment or prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

Furthermore, the disclosure relates to a process for preparing a pharmaceutical composition according to the disclosure, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of the compound according to the present disclosure.

The disclosure also relates to a product comprising the compound according to the present disclosure, and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of cancer, including but not limited to leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN); and diabetes.

Additionally, the disclosure relates to a method of treating or preventing a cell proliferative disease in a warm-blooded animal which comprises administering to the said animal an effective amount of the compound according to the present disclosure, as defined herein, or a pharmaceutical composition or combination as defined herein.

In another example, the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt and solvates thereof for use as a medicament.

In another example, the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-

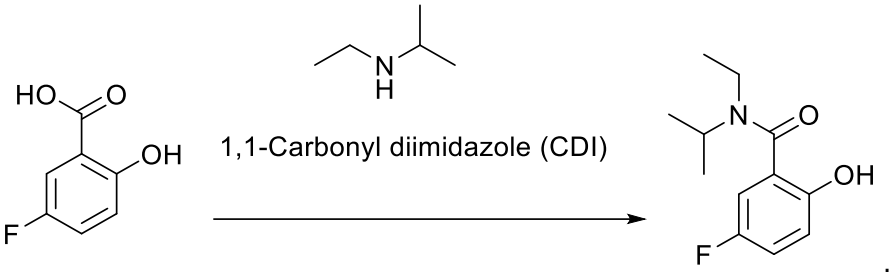
2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt and solvates thereof for use as a medicament.

In another example, the present disclosure is directed to a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt hydrate for use as a medicament.

In another example, the present disclosure is directed to a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate for use as a medicament.

The present disclosure is also directed to the preparation of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt and solvates thereof.

In another aspect, there is provided a method to provide N-ethyl-5-fluoro-2-hydroxy-N-isopropylbenzamide via a one step reaction by reacting 5-fluoro-2-hydroxy-benzoic acid in the presence of the coupling agent CDI, in a suitable solvent:



The present disclosure is also directed to the preparation of a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate thereof.

In another aspect, there is provided a process for preparing the crystalline form as defined herein, comprising the step of recrystallising Compound A, wherein the recrystallisation comprises the steps of: a) adding Compound A, or a hydrate or solvate thereof, to a mixture of suitable solvents, in the presence of benzenesulfonic acid, and adjusting to a temperature in the range of from about 20 °C to solvent reflux temperature; b) seeding with crystalline form A; c) yielding a precipitate of the crystalline form as defined herein.

BRIEF DESCRIPTION OF THE DRAWINGS

The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings exemplary embodiments of the invention; however, the invention is not limited to the specific disclosure of the drawings. In the drawings:

Figure 1 is an X-ray powder diffraction (XRPD) pattern of a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate.

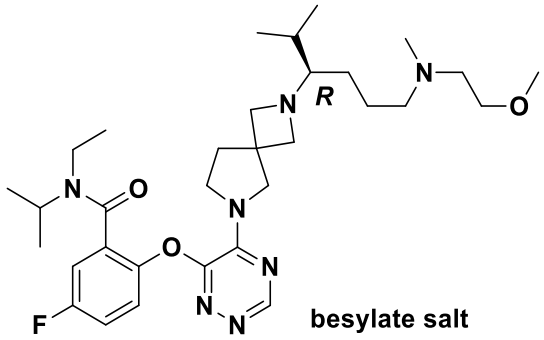
Figure 2: Efficacy study in Molm-14 subcutaneous (sc) model.

Figure 3: Efficacy study in disseminated OCI-AML3 model.

Figure 4 is an X-ray powder diffraction (XRPD) pattern of intermediate 234b.

CLAIMS

1. (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt



,

or a solvate thereof.

2. The compound according to claim 1 wherein the solvate is a hydrate.

3. The compound according to claim 1 wherein the compound is a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate,
wherein the crystalline form produces an X-ray powder diffraction pattern comprising peaks at 5.4, 7.2, 11.1, 11.9, and 21.7 degrees two theta ± 0.2 degrees two theta.

4. The crystalline form of claim 3, wherein the X-ray powder diffraction pattern may further comprise at least one peak selected from 13.7, 14.5, 14.7, 15.0, 16.5, 17.8, 19.0, 19.4, and 20.1 degrees two theta ± 0.2 degrees two theta.

5. The crystalline form of claim 3 or claim 4, further characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 1.

6. A pharmaceutical composition comprising a compound of any one of the preceding claims and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.

7. A process for preparing a pharmaceutical composition as defined in claim 6 comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound according to any one of claims 1 to 5.

8. A compound as claimed in any one of claims 1 to 5 or a pharmaceutical composition as claimed in claim 6 for use as a medicament.

9. Use of a compound as claimed in any one of claims 1 to 5 or a pharmaceutical composition as claimed in claim 6 in the manufacture of a medicament for the prevention or treatment of cancer.

10. Use of a compound as claimed in any one of claims 1 to 5 or a pharmaceutical composition as claimed in claim 6 in the manufacture of a medicament for the prevention or treatment of leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN).

11. The use according to claim 10 wherein the leukemia is (NPM1)-mutated leukemia.

12. The use according to claim 9, wherein cancer is selected from leukemias, lymphomas, myelomas or solid tumor cancers such as prostate cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer, liver cancer, melanoma and glioblastoma.

13. The use according to claim 10, wherein the leukemia is selected from acute leukemias, chronic leukemias, myeloid leukemias, myelogeneous leukemias, lymphoblastic leukemias, lymphocytic leukemias, Acute myelogeneous leukemias (AML), Chronic myelogenous leukemias (CML), Acute lymphoblastic leukemias (ALL), Chronic lymphocytic leukemias (CLL), T cell prolymphocytic leukemias (T-PLL), Large granular lymphocytic leukemia, Hairy cell leukemia (HCL), MLL-rearranged leukemias, MLL-PTD leukemias, MLL amplified leukemias, MLL-positive leukemias, and leukemias exhibiting *HOX*/*MEIS1* gene expression signatures.

14. A process for preparing the crystalline form of any one of claims 3 to 5, comprising the step of recrystallising Compound A, wherein the recrystallisation comprises the steps of:

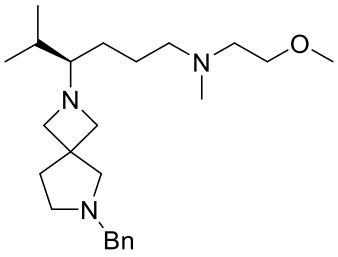
a) adding Compound A, or a hydrate or solvate thereof, to a mixture of suitable solvents, in the presence of benzenesulfonic acid, and adjusting to a temperature in the range of from about 20 °C to solvent reflux temperature;
b) seeding with crystalline form A;
c) yielding a precipitate of the crystalline form of any one of claims 3 to 5.

15. The process of claim 14, wherein the mixture of suitable solvents is a mixture of acetone, water and IPAc.

16. The process of claim 14, wherein the mixture of suitable solvents is a mixture of isopropanol, water and IPAc.

17. The process of claim 14, claim 15 or claim 16, wherein the temperature is about 25°C.

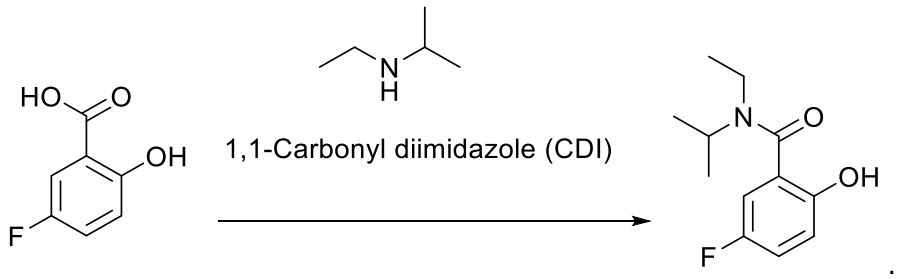
18. A crystalline form of



citric acid salt,

wherein the crystalline form produces an X-ray powder diffraction pattern comprising peaks at 5.82, 10.09 and 18.42 degrees two theta ± 0.2 degrees two theta.

19. A method to provide N-ethyl-5-fluoro-2-hydroxy-N-isopropylbenzamide via a one step reaction by reacting 5-fluoro-2-hydroxy-benzoic acid in the presence of the coupling agent CDI, in a suitable solvent:



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