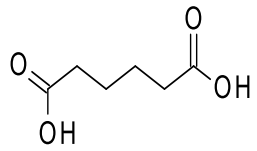
cocrystalline forms of the above FGFR3 inhibitors and pharmaceutical compositions thereof.

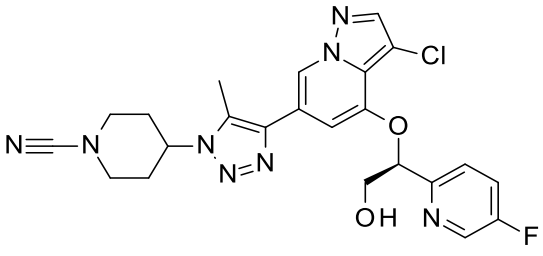
Isomer 2 Forms

Disclosed herein is a cocrystalline form that comprises Isomer 2 and gallic acid coformer. Gallic acid, also known as 3,4,5-trihydroxybenzoic acid, has the structure illustrated below:



.

In a first aspect of the present disclosure, there is provided a cocrystalline form of



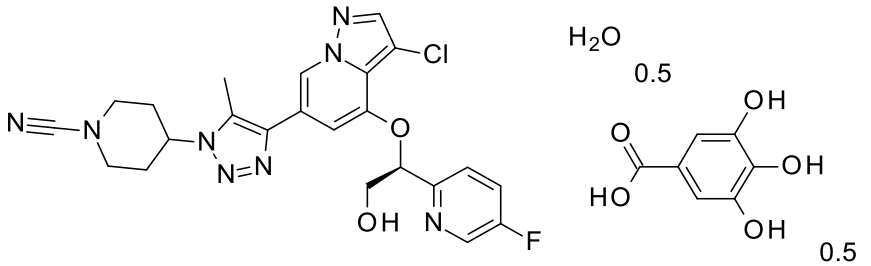
("Isomer 2") and a gallic acid coformer.

In one example, gallic acid may have a variable water content between anhydrous and gallic acid mono-hydrate. In one example, gallic acid is anhydrous gallic acid. In one example, gallic acid is gallic acid mono-hydrate.

In one example, THF may have a variable water content. In one example, THF is anhydrous THF. In one example, THF is wet THF. In one example, THF may contain some water. In one example, water is added to THF.

In an example, the cocrystalline form has a ratio of Isomer 2 to gallic acid of about 2:1.

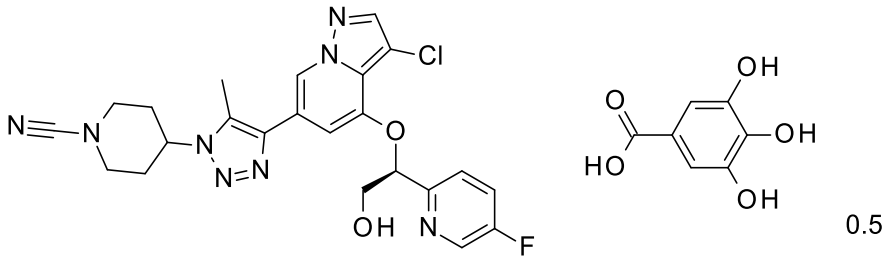
In an example, the cocrystalline form further comprises a solvent. In an example, the solvent is water and the cocrystalline form is a hydrate. In an example, the cocrystalline form has a hemihydrate (herein referred to as "the cocrystalline form of Formula I"). In one example, the cocrystalline form of Formula I is



(Formula I).

In one example, the cocrystalline form of Formula I has variable water content. In one example, the cocrystalline form of Formula I has water content ranging from about 0% to about 3.2% by thermogravimetric analysis (TGA).

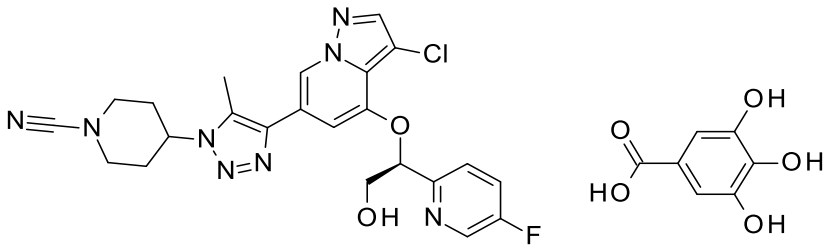
In an example, the cocrystalline form is a form after water loss of the cocrystalline form of Formula I, a "dehydrated hydrate". In one example, the cocrystalline form of Formula I is dehydrated (herein referred to as "the cocrystalline form of Formula II"). In one example, the cocrystalline form of Formula II is



(Formula II).

Disclosed herein is a cocrystalline form comprising Isomer 2 and Mono-Gallate coformer. In an example, the cocrystalline form has a ratio of Isomer 2 to gallic acid about 1:1 (herein referred to as "the cocrystalline form of Formula III").

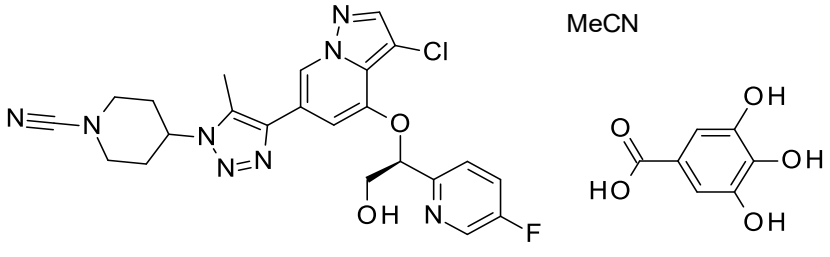
In one example, the cocrystalline form of Formula III is



(Formula III).

In an example, the cocrystalline form of Formula III has a solvent. In an example, the solvent is acetonitrile. In an example, the cocrystalline form of Formula III has a mono-acetonitrile solvent (herein referred to as "the cocrystalline form of Formula IV").

In one example, the cocrystalline form of Formula IV is

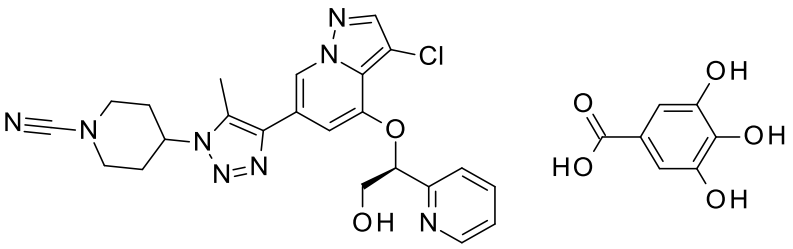


(Formula IV).

Isomer A Forms

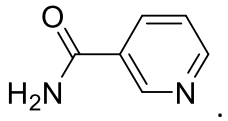
Disclosed herein is a cocrystalline form of Isomer A and gallic acid coformer. In one example, a cocrystalline form comprises Isomer A and Mono-Gallate coformer.

In one example, the cocrystalline form of Formula V ratio of Isomer A to gallic acid is about 1:1 (herein referred to as “the cocrystalline form of Formula V”). In one example, the the cocrystalline form of Formula V is



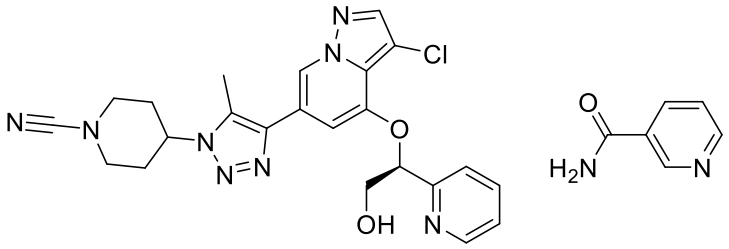
(Formula V).

Disclosed herein is a cocrystalline form of Isomer A and nicotinamide coformer. Nicotinamide, also known as pyridine-3-carboxamide, has the structure illustrated below:



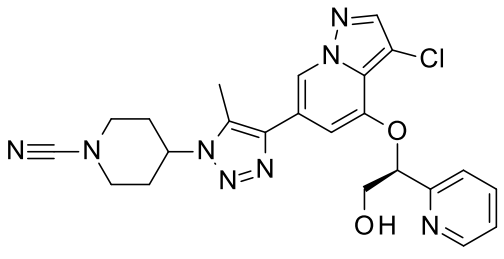
.

In one example, a cocrystalline form comprises Isomer A and mono-nicotinamide coformer. In one example, the ratio of Isomer A to nicotinamide is about 1:1 (herein referred to as “the cocrystalline form of Formula VI”). In one example, the cocrystalline form of Formula VI is



(Formula VI).

In another aspect of the present disclosure, there is provided a cocrystalline form of Isomer A:



, and a gallic acid coformer or a nicotinamide coformer.

Also disclosed are pharmaceutical compositions comprising the above identified cocrystalline forms, methods of using the cocrystalline forms to treat conditions treatable by the inhibition of FGFR3, and methods of synthesizing the cocrystalline forms.

Accordingly, described herein are cocrystalline forms of FGFR3 and pharmaceutical compositions thereof. Preferably, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, diluent or excipient. In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a cocrystalline form as disclosed herein and further comprising a pharmaceutically acceptable carrier, diluent or excipient. Further described is the pharmaceutical composition wherein the composition contains at least about 80% by wt. of any of the cocrystalline forms. Further described is the pharmaceutical composition

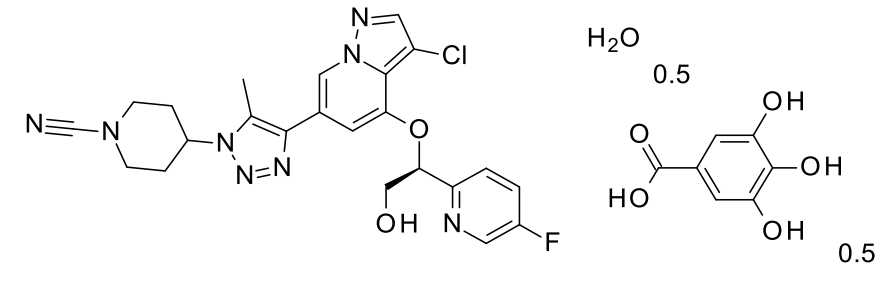
wherein the composition contains at least about 90% by wt. of any of the cocrystalline forms. Further described is the pharmaceutical composition wherein the composition contains at least about 95% by wt. of any of the cocrystalline forms.

In a further aspect of the present disclosure, there is provided the cocrystalline form as disclosed herein for use in therapy.

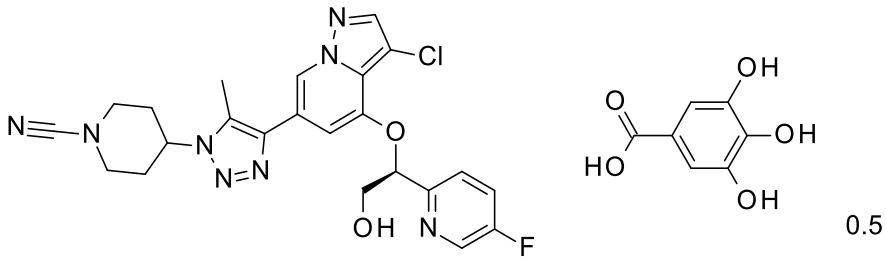
In one example, the pharmaceutical composition is for use in therapy.

In another example, disclosed herein is the use of the cocrystalline form of Formulae I, II, V, or VI, in therapy to treat a disease that is selected from the group consisting of systemic sclerosis, fibrosis, pulmonary fibrosis, achondroplasia, thanatophoric dysplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), muenke syndrome, and cancer.

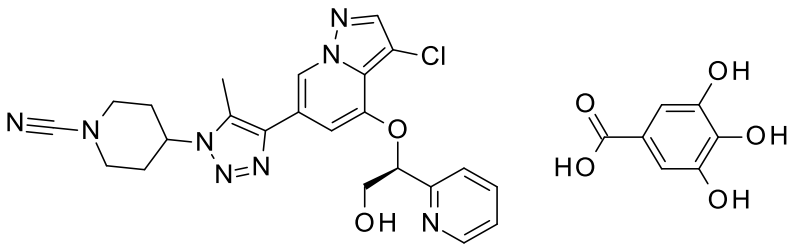
Disclosed herein is a method of treating a FGFR3-associated cancer comprising administering to a patient in need thereof an effective amount of the cocrystalline form of Formulae I, II, V, or VI:



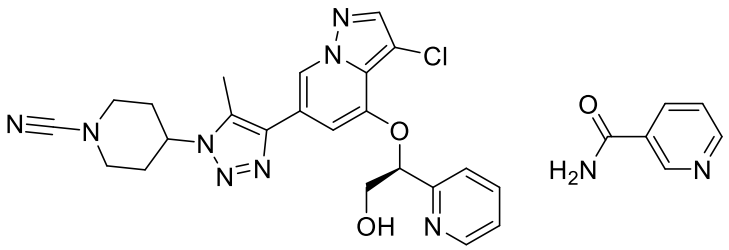
(Formula I),



(Formula II),



(Formula V), or

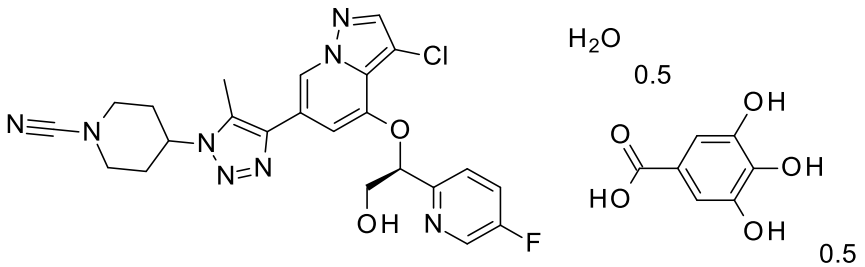


(Formula VI)

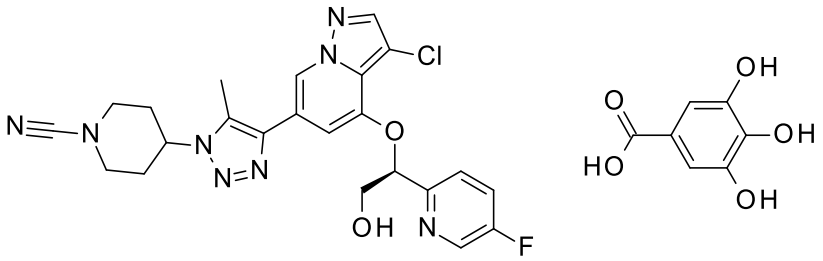
, or pharmaceutical compositions thereof.

In one example, a method of treating a FGFR3-associated cancer comprises administering to a patient in need thereof an effective amount of the cocrystalline form of Formulae I, II, V, or VI, or pharmaceutical compositions thereof.

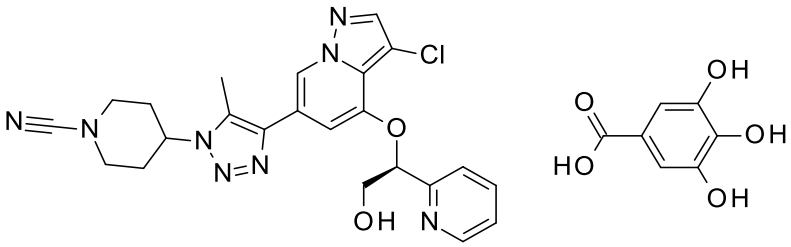
In an example, disclosed herein is a cocrystalline form of Formulae I, II, V, or VI:



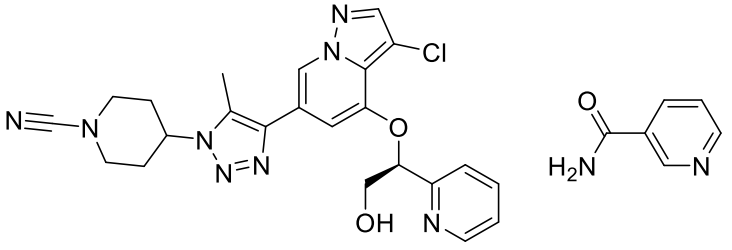
(Formula I),



(Formula II),



(Formula V), or



(Formula VI),

for use in treatment of a FGFR3-associated cancer.

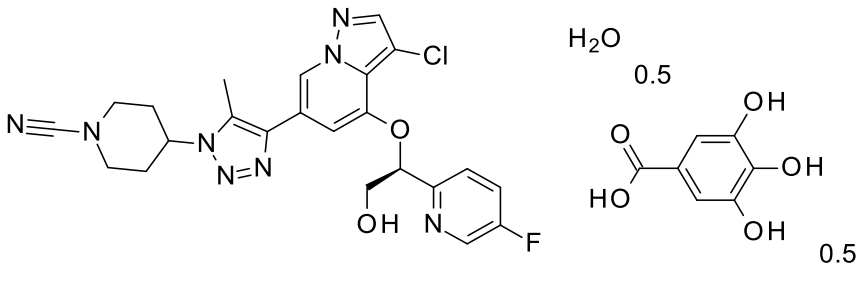
In one example, the cocrystalline form of Formulae I, II, V, or VI, for use in treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is non-muscle invasive bladder cancer.

In one example, the cocrystalline form of Formulae I, II, V, or VI, for use in treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is intermediate risk non-muscle invasive bladder cancer.

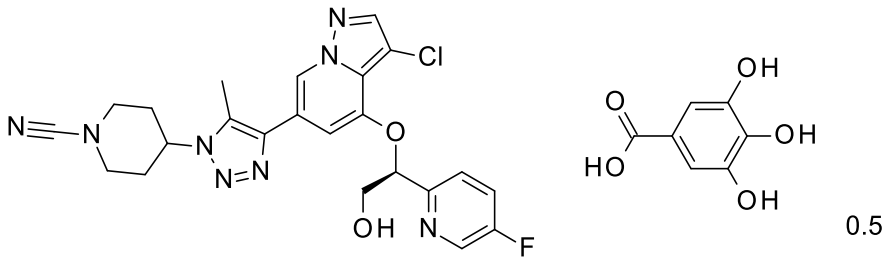
In one example, the cocrystalline form of Formulae I, II, V, or VI, for use in treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer or Bacillus Calmette-Guerin (BCG) recurrent non-muscle invasive bladder cancer.

In one example, the cocrystalline form of Formulae I, II, V, or VI, for use in treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is high risk non-muscle invasive bladder cancer.

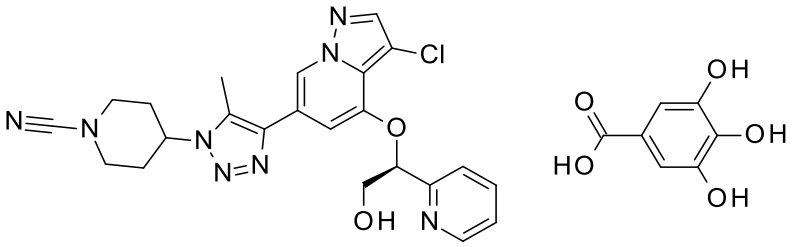
In an example, disclosed herein is the use of an effective amount of a cocrystalline form of Formulae I, II, V, or VI:



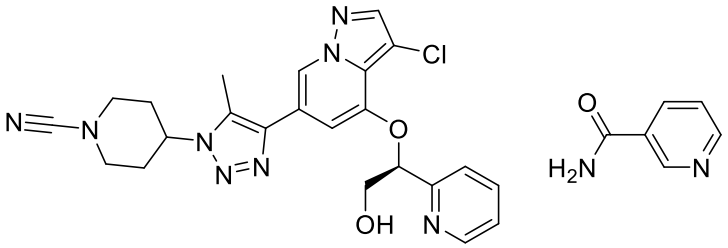
(Formula I),



(Formula II),



(Formula V), or



(Formula VI),

or pharmaceutical compositions thereof, in the manufacture of a medicament for treatment of a FGFR3-associated cancer.

In another aspect of the present disclosure, there is provided a use of the cocrystalline form as disclosed herein in the manufacture of a medicament for treatment of a FGFR3-associated cancer.

In one example, disclosed herein is the use of an effective amount of the cocrystalline form of Formulae I, II, V, or VI, or pharmaceutical compositions thereof in the manufacture of a medicament for treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is non-muscle invasive bladder cancer.

In one example, disclosed herein is the use of an effective amount of the cocrystalline form of Formulae I, II, V, or VI, or pharmaceutical compositions thereof in the manufacture of a medicament for treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is intermediate risk non-muscle invasive bladder cancer.

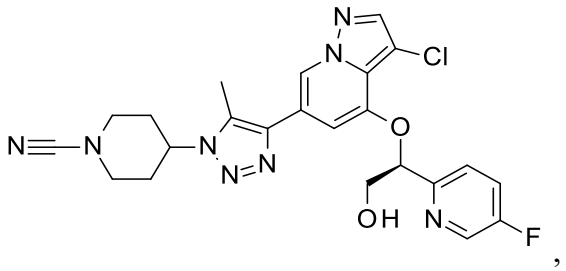
In one example, disclosed herein is the use of an effective amount of the cocrystalline form of Formulae I, II, V, or VI, or pharmaceutical compositions thereof in the manufacture of a medicament for treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer or Bacillus Calmette-Guerin (BCG) recurrent non-muscle invasive bladder cancer.

In one example, disclosed herein is the use of an effective amount of the cocrystalline form of Formulae I, II, V, or VI, or pharmaceutical compositions thereof in the manufacture of a medicament for treatment of a FGFR3-associated cancer, wherein the FGFR3-associated cancer is high risk non-muscle invasive bladder cancer.

In another example, disclosed herein is a process for the preparation of the cocrystalline form of Formula I comprising adding 4-[4-[3-Chloro-4-[1-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carbonitrile, Isomer 2 and gallic acid to a solvent to give a slurry, adding cyclopentyl methyl ether to the slurry to form a white precipitate. In an example, the process for the preparation of the cocrystalline form of Formula I further comprises seeding the slurry with the cocrystalline form of Formula I.

In yet another aspect of the present disclosure, there is provided a method for the preparation of the cocrystalline form as disclosed herein, comprising the steps of:

adding 4-[4-[3-Chloro-4-[1-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carbonitrile, Isomer 2:



,

and gallic acid to a solvent to give a slurry, and

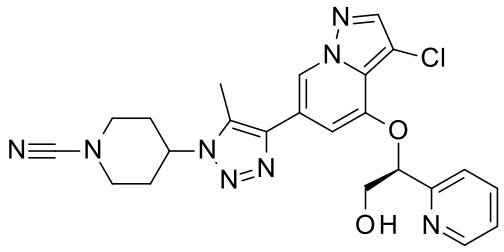
adding cyclopentyl methyl ether to the slurry to form a white precipitate.

Disclosed herein is a process for preparing the cocrystalline form of Formula II comprising the step of heating the cocrystalline form of Formula I.

Disclosed herein is a process for the preparation of the cocrystalline form of Formula IV comprising the step of combining the cocrystalline form of Formula I with acetonitrile.

Disclosed herein is a process for the preparation of the the cocrystalline form of Formula V comprising the step of adding gallic acid to Isomer A dissolved in ethyl acetate.

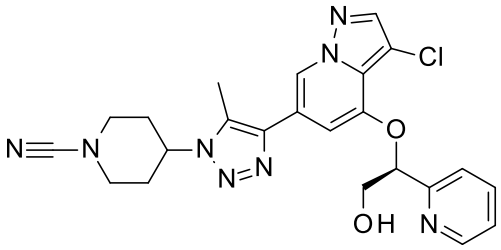
In a further aspect of the present disclosure, there is provided a method for the preparation of the cocrystalline form as disclosed herein, comprising the step of adding



gallic acid to dissolved in ethyl acetate.

Disclosed herein is a process for the preparation of the cocrystalline form of Formula VI comprising the step of dissolving Isomer A in ethyl acetate saturated with nicotinamide.

In another aspect of the present disclosure, there is provided method for the preparation of the cocrystalline form as disclosed herein, comprising the step of dissolving



in ethyl acetate saturated with nicotinamide.

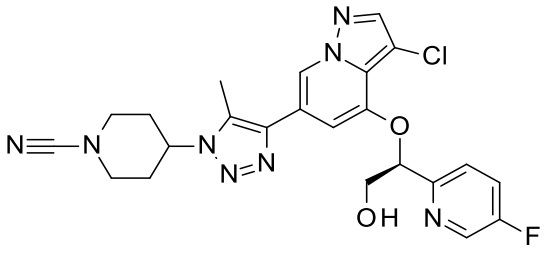
Detailed Description

In one embodiment, the cocrystalline form of Formula I has variable water content. In one embodiment, the cocrystalline form of Formula I has water content ranging from about 0% to about 3.2%.

In one embodiment, the cocrystalline form of Formula I and the cocrystalline form of Formula II are each characterized by having an x-ray powder diffraction (XRPD) pattern using CuKα radiation comprising a peak at 8.4° and one or more peaks at 6.7°, 9.2°, 10.0°, 13.4°, 14.1°, 15.6°, 16.9°, 18.4°, 19.6°, 21.3°, 23.4°, or 24.2° with a tolerance for the diffraction angles of ± 0.2 degrees. In one embodiment, the cocrystalline form of Formula I and the cocrystalline form of Formula II are each characterized by having an x-ray powder diffraction (XRPD) pattern using CuKα radiation comprising a peak at 8.4° and four or more peaks at 6.7°, 9.2°, 10.0°, 13.4°, 14.1°, 15.6°, 16.9°, 18.4°, 19.6°, 21.3°, 23.4°, or 24.2° with a tolerance for the diffraction angles of ± 0.2 degrees. In one embodiment, the cocrystalline form of Formula I and the cocrystalline form of Formula II

What is claimed is:

1. A cocrystalline form of

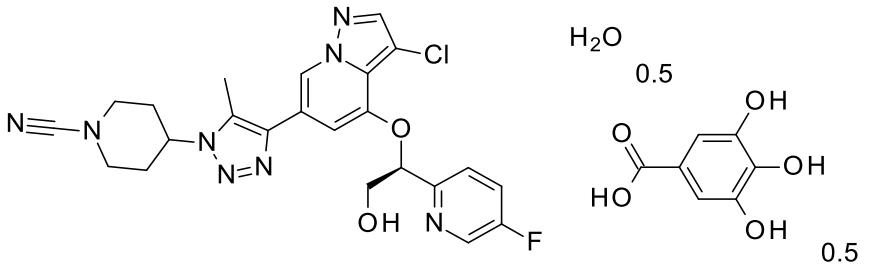


("Isomer 2") and a gallic acid coformer.

2. The cocrystalline form of claim 1 wherein the ratio of Isomer 2 to gallic acid is about 2:1.

3. The cocrystalline form of claim 1 or 2 wherein water content ranges from about 0% to about 3.2%.

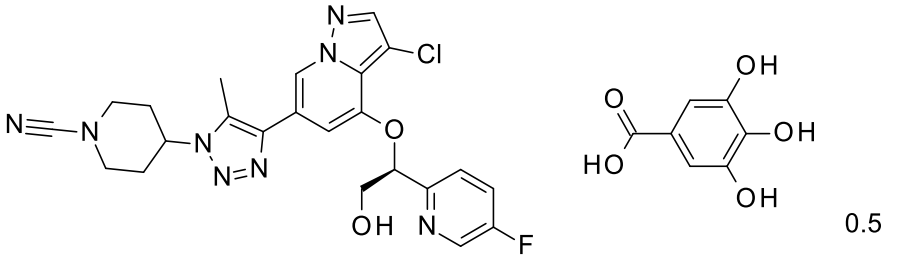
4. The cocrystalline form of any one of claims 1 to 3 wherein the cocrystalline form is



.

5. The cocrystalline form of claim 4 that is dehydrated or partially dehydrated.

6. The cocrystalline form of any one of claims 1 to 3, or 5 wherein the cocrystalline form is



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7. The cocrystalline form of any one of claims 1 to 6 characterized by having an XRPD pattern using CuKα radiation comprising a peak at 8.4° and one or more peaks

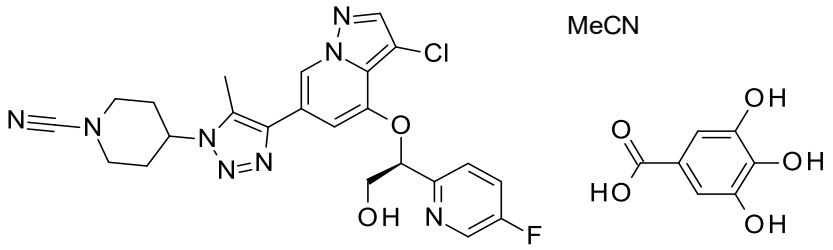
at 6.7°, 9.2°, 10.0°, 13.4°, 14.1°, 15.6°, 16.9°, 18.4°, 19.6°, 21.3°, 23.4°, or 24.2° with a tolerance for the diffraction angles of ± 0.2 degrees.

8. The cocrystalline form of any one of claims 1 to 7 characterized by an XRPD pattern using CuKα radiation having a diffraction peak at diffraction angle 2-theta of 8.4° in combination with one or more of the peaks selected from the group consisting of 15.6°, 21.3°, 6.7°, and 23.4°; with a tolerance for the diffraction angles of ± 0.2 degrees.

9. The cocrystalline form of any one of claims 1 to 8 characterized by a ^{13}C solid state NMR spectrum which comprises peaks referenced to the carbonyl resonance of glycine selected from the group consisting of 8.1, 11.1, 26.6, 28.2, 32.3, 35.0, 80.7, 81.7, 99.6, 102.3, 110.9, 158.0, 160.0, 168.2, and 175.0, with a tolerance of ± 0.2 ppm.

10. The cocrystalline form of claim 1 wherein the ratio of Isomer 2 to gallic acid is about 1:1.

11. The cocrystalline form of claim 1 or 10 wherein the cocrystalline form is

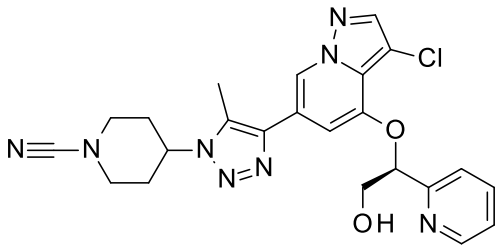


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12. The cocrystalline form of any one of claims 1, 10, or 11 characterized by having an XRPD pattern using CuKα radiation comprising a peak at 14.6° and one or more peaks at 5.7°, 6.5°, 9.8°, 13.0°, 13.5°, 16.5°, 17.1°, 18.9°, 19.7°, 23.8°, or 24.5° with a tolerance for the diffraction angles of ± 0.2 degrees.

13. The cocrystalline form of any one of claims 1, or 10-12 characterized by an XRPD pattern using CuKα radiation having a diffraction peak at diffraction angle 2-theta of 14.6° in combination with one or more of the peaks selected from the group consisting of 9.8°, 23.8°, 6.5°, and 19.7°; with a tolerance for the diffraction angles of ± 0.2 degrees.

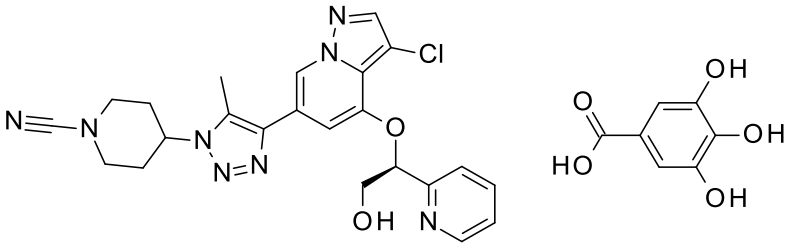
14. A cocrystalline form of Isomer A:



, and a gallic acid coformer or a nicotinamide coformer.

15. The cocrystalline form of claim 14 wherein the ratio of Isomer A to gallic acid is about 1:1.

16. The cocrystalline form of claim 14 or 15 wherein the cocrystalline form is



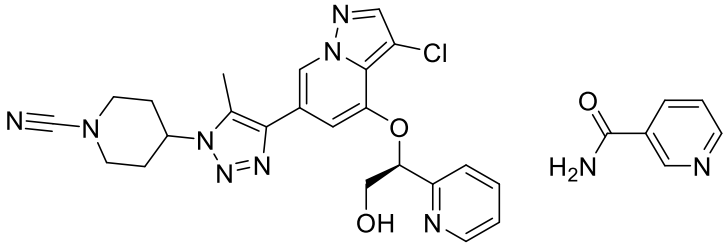
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17. The cocrystalline form of any one of claims 14 to 16 characterized by having an XRPD pattern using CuKα radiation comprising a peak at 6.9° and one or more peaks at 9.1°, 10.5°, 12.7°, 15.7°, 16.3°, 16.8°, 17.1°, 17.9°, 18.4°, 21.0°, or 23.4° with a tolerance for the diffraction angles of ± 0.2 degrees.

18. The cocrystalline form of any one of claims 14 to 17 characterized by having an XRPD pattern using CuKα radiation comprising a peak at 6.9° in combination with one or more of the peaks selected from the group consisting of 12.7°, 18.4°, 9.1°, and 23.4° with a tolerance for the diffraction angles of ± 0.2 degrees.

19. The cocrystalline form of claim 14 wherein the ratio of Isomer A to nicotinamide is about 1:1.

20. The cocrystalline form of claim 14 or 19 wherein the cocrystalline form is



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21. The cocrystalline form of any one of claims 14, 19 or 20 characterized by having an XRPD pattern using CuKα radiation comprising a peak at 13.7° and one or more peaks at 6.8°, 8.2°, 9.6°, 12.3°, 15.8°, 17.5°, 17.9°, 18.7°, 19.0°, 22.2°, 22.9°, 24.7°, or 26.1° with a tolerance for the diffraction angles of ± 0.2 degrees.

22. The cocrystalline form of any one of claims 14, 19 to 21 characterized by having an XRPD pattern using CuKα radiation comprising a peak at 13.7° in combination with one or more of the peaks selected from the group consisting of 9.6°, 17.9°, and 24.7° with a tolerance for the diffraction angles of ± 0.2 degrees.

23. A pharmaceutical composition comprising the cocrystalline form according to any one of claims 1 to 22 and further comprising a pharmaceutically acceptable carrier, diluent or excipient.

24. The cocrystalline form according to any one of claims 1 to 22 for use in therapy.

25. Use of the cocrystalline form according to any one of claims 1 to 22 in the manufacture of a medicament for treatment of a FGFR3-associated cancer.

26. The use of claim 25, wherein the FGFR3-associated cancer is selected from the group consisting of breast cancer, invasive ductal breast cancer, invasive lobular breast cancer, lung cancer, non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer, small-cell lung cancer, urothelial cancer, bladder cancer, urothelial bladder cancer, advanced urothelial cancer, advanced urothelial bladder cancer, metastatic urothelial cancer, metastatic urothelial bladder cancer, non-muscle invasive urothelial cancer, non-muscle invasive bladder cancer, muscle invasive urothelial cancer, muscle invasive bladder cancer, upper tract cancer, urothelial upper tract cancer, urethral cancer, gastric cancer, pancreatic cancer, prostate cancer, colorectal cancer, multiple myeloma, liver cancer, melanoma, cutaneous melanoma, head and neck cancer, oral cancer, thyroid cancer, renal cancer, renal pelvis cancer, glioblastoma, endometrial cancer, cervical cancer, ovarian cancer, and testicular cancer.

27. The use of claim 25 or 26, wherein the FGFR3-associated cancer is selected from the group consisting of urothelial cancer, bladder cancer, urothelial bladder cancer, advanced urothelial bladder cancer, metastatic urothelial bladder cancer, non-muscle invasive bladder cancer, and muscle invasive bladder cancer.

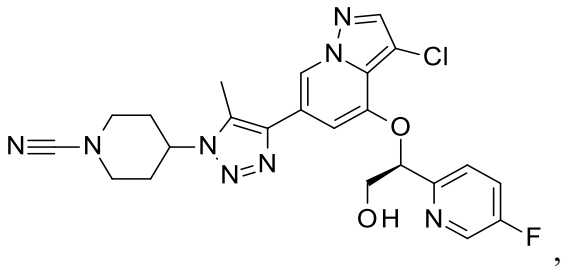
28. The use of any one of claims 25 to 27, wherein the FGFR3-associated cancer is intermediate risk non-muscle invasive bladder cancer.

29. The use of any one of claims 25 to 27, wherein the FGFR3-associated cancer is Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer or Bacillus Calmette-Guerin (BCG) recurrent non-muscle invasive bladder cancer.

30. The use of any one of claims 25 to 27, wherein the FGFR3-associated cancer is high risk non-muscle invasive bladder cancer.

31. A method for the preparation of the cocrystalline form according to any one of claims 1 to 9, comprising the steps of:

adding 4-[4-[3-Chloro-4-[1-(5-fluoro-2-pyridyl)-2-hydroxy-ethoxy]pyrazolo[1,5-a]pyridin-6-yl]-5-methyl-triazol-1-yl]piperidine-1-carbonitrile, Isomer 2:

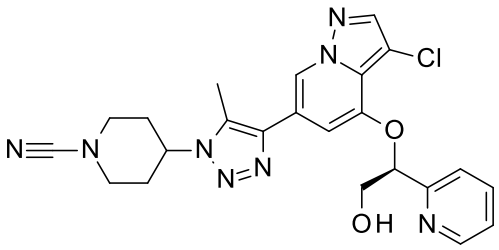


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and gallic acid to a solvent to give a slurry, and

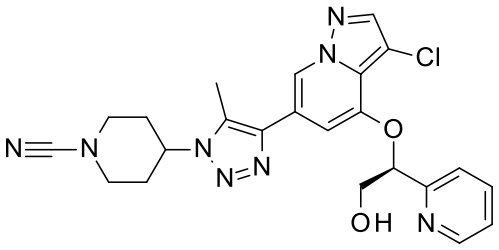
adding cyclopentyl methyl ether to the slurry to form a white precipitate.

32. A method for the preparation of the cocrystalline form according to any one of claims 14 to 18, comprising the step of adding gallic acid to



dissolved in ethyl acetate.

33. A method for the preparation of the cocrystalline form according to any one of claims 14, 19 to 22, comprising the step of dissolving



in ethyl acetate saturated with nicotinamide.