

The crystalline forms of a compound

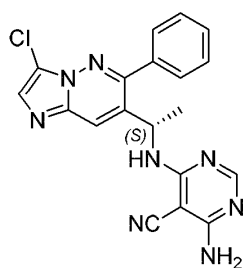
Field of the Invention

The present invention belongs to the pharmaceutical field, and provides novel crystalline forms, solvates and the crystalline forms thereof of the compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-b]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, and the pharmaceutical compositions comprising the same as well as the methods of preparing the same and the use thereof.

Background of the Invention

PI₃K (phosphatidylinositol-3-kinase) is a family of lipid kinases, and abnormality in PI₃K-mediated signaling pathway is believed to play critical roles in the occurrence and development of a variety of malignant tumors. Dysregulation and overactivation of the PI₃K/AKT pathway has been found in cancer cells. PI₃K δ is also involved in mammalian immune system functions, including signal transduction of B-cell, T-cell, mast cell, dendritic cell, neutrophil, NK cell, and monocyte / phagocyte. Studies have shown that, inhibition of PI₃K, including selective inhibition of PI₃K δ activity is useful for the treatment of autoimmune diseases or inflammatory diseases, such as: systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease, psoriasis, and asthma. In addition, inhibition of PI₃K, including selective inhibition of PI₃K δ activity is also useful in treating cancer, especially hematological malignancy such as: lymphoma, leukemia, and multiple myeloma.

The relevant compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-b]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the present invention, with the chemical structure of Formula A, has the effect of effectively inhibiting PI₃K, especially inhibiting PI₃K δ activity. Thus, it is useful in treating diseases responsive to inhibition of PI₃K activity, such as the treatment of autoimmune diseases, inflammatory diseases, and cancer.



Formula A

The phenomenon that a compound could exist in two or more crystal structures is known as

polymorphism. Many compounds may exist as various polymorph crystals and also in a solid amorphous form. However, until polymorphism of a compound is discovered, it is highly unpredictable (1) whether a particular compound will exhibit polymorphism, (2) how to prepare any such unknown polymorphs, and (3) how are the properties, such as stability, of any such unknown polymorphs. See, e.g., J. Bernstein "Polymorphism in Molecular Crystals", Oxford University Press, (2002).

Since the properties of a solid material depend on the structure as well as on the nature of the compound itself, different solid forms of a compound can and often do exhibit different physical and chemical properties as well as different biopharmaceutical properties. Differences in chemical properties can be determined, analyzed and compared through a variety of analytical techniques. Those differences may ultimately be used to differentiate among different solid forms. Furthermore, differences in physical properties, such as solubility, and biopharmaceutical properties, such as bioavailability, are also of importance when describing the solid state of a pharmaceutical compound. Similarly, in the development of a pharmaceutical compound, such as compound of Formula A, new crystalline and amorphous forms of the pharmaceutical compound are also of importance.

The compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile as well as the preparation thereof was described in patent application WO2016045591A1.

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Contents of the Invention

Summary

Upon extensive explorations and researchs, we have found that compound of Formula A (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile can exist in different crystalline forms (i.e. polymorphs), and can form solvates with certain solvents. We have made extensive studies on the polymorphs of compound of Formula A and have finally prepared and determined the crystalline forms which meet the requirement of pharmaceutical use. Based on these studies, the present invention provides the various crystalline forms of compound of Formula A and the solvates and the crystalline forms thereof, which are designated as Form I, Form IV, Form V, Form VI, and Form VIII respectively.

In one aspect, the polymorphs of compound of Formula A or the solvates thereof provided by the present invention have good crystallinity and good stability and are non-hygroscopic.

Firstly, the present invention provides crystalline Form I of (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, i.e. Form I of compound of Formula A.

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Secondly, the present invention provides crystalline Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, i.e. Form IV of compound of Formula A.

Further, the present invention provides crystalline Form V of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, i.e. Form V of compound of Formula A.

Even further, the present invention provides the solvates of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, which are acetone solvate, and water and i-propanol solvate of compound of Formula A.

Even further, the present invention provides the solvates of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, which are monoacetone solvate, and water and i-propanol solvate (containing 3 molecules of water and 0.5 molecule of i-propanol) of compound of Formula A.

Even further, the present invention provides monoacetone solvate of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, which is Form VI of compound of Formula A.

Even further, the present invention provides water and i-propanol solvate (containing 3 molecules of water and 0.5 molecule of i-propanol) of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, which is Form VIII of compound of Formula A.

In another aspect, the present invention provides the methods of preparation for the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII), which are reproducible and easy in operation.

In still another aspect, the present invention provides the pharmaceutical compositions comprising an effective amount of one or more of the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII), and remaining amount of at least one pharmaceutically acceptable carrier.

The present invention further provides a method of treating diseases responsive to inhibition of PI₃K activity, comprising administering to a subject in need thereof an effective amount of one or more of the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, or Form VIII) of the present invention.

The present invention further provides a use of the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, or Form VIII) in the manufacture of a medicament for treating diseases responsive to inhibition of PI₃K activity. In some embodiments, said diseases responsive to inhibition of PI₃K activity are selected from autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy). In some embodiments, said autoimmune diseases or inflammatory diseases are selected from systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease, psoriasis, and asthma. In some embodiments, said cancer is selected from lymphoma (such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, mantle cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Burkitt lymphoma, B cell lymphoma, T cell lymphoma, NK cell lymphoma, and diffuse large B-cell lymphoma), leukemia (such as chronic lymphocytic leukemia, acute lymphocytic leukemia, acute myeloid leukemia, and chronic myelogenous leukemia), multiple myeloma, and Waldenstrom's macroglobulinemia.

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Brief Description of the Figures

Figure 1 shows an X-ray powder diffractogram of Form I of compound of Formula A, wherein the horizontal axis (X-axis) plots the diffraction angle 2 theta, and the vertical axis (Y-axis) plots the diffraction intensity (%).

Figure 2 shows a differential scanning calorimetry (DSC) profile of Form I of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature (°C), and the vertical axis (Y-axis) plots the heat flow (mW).

Figure 3 shows a Thermogravimetric (TG) profile of Form I of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature (°C), and the vertical axis (Y-axis) plots the weight percentage (%).

Figure 4 shows an X-ray powder diffractogram of Form IV of compound of Formula A, wherein the horizontal axis (X-axis) plots the diffraction angle 2 theta, and the vertical axis (Y-axis) plots the diffraction intensity (%).

Figure 5 shows a differential scanning calorimetry (DSC) profile of Form IV of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature (°C), and the vertical axis (Y-axis) plots the heat flow (mW).

Figure 6 shows a Thermogravimetric (TG) profile of Form IV of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature (°C), and the vertical axis (Y-axis) plots the weight percentage (%).

Figure 7 shows an X-ray powder diffractogram of Form V of compound of Formula A,

wherein the horizontal axis (X-axis) plots the diffraction angle 2θ , and the vertical axis (Y-axis) plots the diffraction intensity (%).

Figure 8 shows a differential scanning calorimetry (DSC) profile of Form V of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature ($^{\circ}\text{C}$), and the vertical axis (Y-axis) plots the heat flow (mW).

Figure 9 shows a Thermogravimetric (TG) profile of Form V of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature ($^{\circ}\text{C}$), and the vertical axis (Y-axis) plots the weight percentage (%).

Figure 10 shows an X-ray powder diffractogram of Form VI of monoacetone solvate of compound of Formula A, wherein the horizontal axis (X-axis) plots the diffraction angle 2θ , and the vertical axis (Y-axis) plots the diffraction intensity (%).

Figure 11 shows a differential scanning calorimetry (DSC) profile of Form VI of monoacetone solvate of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature ($^{\circ}\text{C}$), and the vertical axis (Y-axis) plots the heat flow (mW).

Figure 12 shows a Thermogravimetric (TG) profile of Form VI of monoacetone solvate of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature ($^{\circ}\text{C}$), and the vertical axis (Y-axis) plots the weight percentage (%).

Figure 13 shows an X-ray powder diffractogram of Form VIII of water and i-propanol solvate of compound of Formula A, wherein the horizontal axis (X-axis) plots the diffraction angle 2θ , and the vertical axis (Y-axis) plots the diffraction intensity (%).

Figure 14 shows a differential scanning calorimetry (DSC) profile of Form VIII of water and i-propanol solvate of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature ($^{\circ}\text{C}$), and the vertical axis (Y-axis) plots the heat flow (mW).

Figure 15 shows a Thermogravimetric (TG) profile of Form VIII of water and i-propanol solvate of compound of Formula A, wherein the horizontal axis (X-axis) plots the temperature ($^{\circ}\text{C}$), and the vertical axis (Y-axis) plots the weight percentage (%).

Figure 16 shows a dynamic vapor sorption (DVS) isotherm Plot of Form I of compound of Formula A, wherein the horizontal axis (X-axis) plots the relative humidity (%), and the vertical axis (Y-axis) plots the weight change percentage (%).

Figure 17 shows a dynamic vapor sorption (DVS) isotherm Plot of Form IV of compound of Formula A, wherein the horizontal axis (X-axis) plots the relative humidity (%), and the vertical axis (Y-axis) plots the weight change percentage (%).

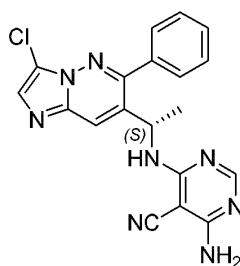
Figure 18 shows a dynamic vapor sorption (DVS) isotherm Plot of Form V of compound of Formula A, wherein the horizontal axis (X-axis) plots the relative humidity (%), and the vertical axis (Y-axis) plots the weight change percentage (%).

Definitions

Unless indicated otherwise, the following abbreviations or terms as used in the present application (including the specification and the claims) have the meanings as set forth below. It is to be noted that the singular forms and the articles “a”, “an” and “the” in the specification and the claims include plural references, unless clearly indicated otherwise.

The term “crystalline forms of the present invention” as used herein refers to the crystalline forms Form I, Form IV, Form V, Form VI, or Form VIII of compound of Formula A or the solvates thereof, or any mixture thereof. “Form”, “crystalline form” and “polymorph” may be used interchangeably herein.

The term “compound of Formula A” or “(S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-b]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile” as used herein refers to a compound having the following chemical structure of Formula A (also referenced as “Compound A”):



Formula A.

The term “C₁₋₆ alcohol” as used herein refers to a fully saturated straight or branched alkyl alcohol having 1, 2, 3, 4, 5, or 6 carbon atoms. Examples include but not limited to methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol, t-butanol, n-pentanol, i-pentanol, n-hexanol, and the like.

The term “C₅₋₈ straight or branched alkane” as used herein refers to a fully saturated straight or branched hydrocarbon having 5, 6, 7, or 8 carbon atoms. Examples include but not limited to n-pentane, n-hexane, n-heptane, n-octane, and the like.

The term “about” as used herein refers to the deviation from a given numerical value of no more than $\pm 10\%$.

The term “substantially free of other forms” as used herein means that the content of said other forms is less than 50%, preferably less than 40%, preferably less than 30%, preferably less than 20%, preferably less than 10%, preferably less than 5%, preferably less than 1% by weight, based on the total weight of the forms.

The term “solution” as used herein means a mixture of one or more solutes in one or more

solvents, for certain use. Solution is intended to encompass homogeneous mixtures as well as heterogeneous mixtures, such as slurries or other suspension mixtures having insoluble (not dissolved) material.

The term “organic solvent” as used herein is broadly intended to mean any appropriate
5 organic solvent for certain use disclosed herein.

The term “dissolution solvent” as used herein refers to any appropriate organic solvent which is capable of dissolving, in whole or in part, the solutes under appropriate conditions, such as an appropriate amount and an appropriate temperature, e.g., room temperature or an elevated temperature.

10 The term “anti-dissolution solvent” as used herein refers to any appropriate organic solvent in which the substance has less solubility than in the dissolution solvent.

The term “effective amount” of compound of Formula A and the crystalline forms thereof, solvates and the crystalline forms thereof means an amount which is effective in alleviating or improving the diseases responsive to inhibition of PI₃K activity, such as autoimmune diseases,
15 inflammatory diseases, and cancer (preferably hematological malignancy) when administered to an individual, which may be a human, animal or the like, wherein the diseases responsive to inhibition of PI₃K activity, such as autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy) include but not limited to systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease,
20 psoriasis, asthma, lymphoma (such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, mantle cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Burkitt lymphoma, B cell lymphoma, T cell lymphoma, NK cell lymphoma, and diffuse large B-cell lymphoma), leukemia (such as chronic lymphocytic leukemia, acute lymphocytic leukemia, acute myeloid leukemia, and chronic myelogenous leukemia), multiple myeloma, and
25 Waldenstrom's macroglobulinemia. “Effective amount” may vary with various factors, such as compound, state of disease to be treated, severity of disease to be treated, age and health status of the individual, administration route and form, judgement of the attending physician or a veterinary practitioner, and so on.

The term “individual” or “subject” as used herein means mammals and non-mammals.
30 Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but not limited to, birds, and the like. The term “individual” or
35 “subject” does not denote a particular age or sex.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel crystalline forms, solvates and the crystalline forms thereof of compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile.

The crystalline forms of the present invention have good crystallinity and good stability and are non-hygrosopic. The crystalline forms of the present invention have good reproducibility and can realize repeatable amplified production; moreover, they are stable in ordinary formulations, so it is convenient for them to be used in the manufacture of formulations and treatment of diseases. In addition, the crystalline forms of the present invention have high purity and less solvent residue, which meet the quality requirements of bulk drug, such as ICH Q3A.

The person of ordinary skill in the art can verify the above advantages of the crystalline forms of the present invention according to the test methods disclosed in the pharmacopoeias and the modification thereof, or the conventional methods in the art.

As described herein, the crystalline forms of the present invention may be identified by one or more solid state analytical methods. For example, the crystalline forms of the present invention may be identified by one or more methods, e.g., X-ray powder diffraction, lattice parameters of a single crystal, Fourier Infrared Spectroscopy, differential scanning calorimetry analytical data, and/or a thermogravimetric curve. Moreover, if the identified or analytical result by one of those methods is consistent with that of the forms of the present invention, it does not mean that the result by any other methods is consistent with that of the forms of the present invention.

As described herein, the new crystalline forms may be identified according to X-ray powder diffraction. However, it is known in the art that the peak intensity and/or measured peaks in the X-ray powder diffractogram may vary with the different experiment condition, e.g., different diffraction test conditions and/or preferred orientations or like. Furthermore, the measured 2θ value may be subjected to an error of about $\pm 0.2^\circ$ due to different instrument precision. However, it is known that, compared with the positions of peaks, the relative intensity values of the peaks more depend on certain properties of the tested samples, e.g., crystal size in the sample, orientation effect of crystalline and purity of the analysed materials. Therefore, the deviation of the peak intensity at about $\pm 20\%$ or greater may occur. However, despite of experimental errors, instrument errors, preferred orientation and the like, one skilled in the art can obtain sufficient information from the XRPD data provided herein to identify Form I and any other crystalline forms of the present invention.

Form I

The present invention provides Form I of compound of Formula A.

In some embodiments, Form I of compound of Formula A may be identified according to X-ray powder diffraction. In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form I of compound of Formula A include 6.8, 10.0, 16.5, 20.1, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form I of compound of Formula A include 6.8, 10.0, 13.7, 14.4, 15.3, 16.5, 20.1, 21.3, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

10 In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form I of compound of Formula A include 6.8, 8.0, 10.0, 12.1, 13.7, 14.4, 15.0, 15.3, 16.5, 18.7, 20.1, 21.3, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

15 In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form I of compound of Formula A include 6.8, 7.6, 8.0, 10.0, 12.1, 12.6, 13.7, 14.4, 15.0, 15.3, 16.2, 16.5, 17.0, 18.7, 20.1, 21.3, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

20 In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form I of compound of Formula A include 6.8, 7.6, 8.0, 10.0, 12.1, 12.6, 13.7, 14.4, 15.0, 15.3, 16.2, 16.5, 17.0, 17.9, 18.7, 20.1, 21.3, 22.6, 23.1, 25.4, 26.1, and 29.0 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, Form I of compound of Formula A has a diffractogram as shown in Figure 1.

25 In some embodiments, Form I of compound of Formula A may be characterized by differential scanning calorimetry (DSC). In some embodiments, Form I of compound of Formula A has a DSC curve as shown in Figure 2. In the DSC profile, the endothermic peak of Form I of compound of Formula A is at about 261.2-262.1°C.

30 In some embodiments, Form I of compound of Formula A may be characterized by thermogravimetric analysis (TGA). In some embodiments, Form I of compound of Formula A has a TGA curve as shown in Figure 3, indicating that Form I is an anhydrous material or a neat crystal.

In some embodiments, Form I of compound of Formula A is substantially free of other crystalline forms as described herein. For example, the content by weight of Form I of compound of Formula A is at least 99%, at least 95%, at least 90%, or even lower to 80%. Further, the content by weight of Form I of compound of Formula A is at least 70%, or at least 60%. Even

further, the content by weight of Form I of compound of Formula A is at least 50%.

Methods of Preparing Form I

Method A

5 The present invention relates to a method of preparing Form I of compound of Formula A, comprising:

(1) mixing the compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with at least one dissolution solvent, and heating the mixture to reflux to obtain a solution; for example, said at least one dissolution solvent is
10 selected from ethyl acetate, tetrahydrofuran, 1,4-dioxane, butanone, toluene, dichloromethane, a mixture of ethanol and acetic acid, a mixture of ethyl acetate and acetone, a mixture of ethyl acetate and i-propanol, or a mixture of butanone and ethanol;

(2) cooling the solution obtained in step (1) until the solid precipitates;

(3) isolating to obtain the solid Form I of compound of Formula A;

15 (4) optionally drying the solid obtained in step (3).

In some embodiments, said at least one dissolution solvent is selected from ethyl acetate, tetrahydrofuran, 1,4-dioxane, butanone, toluene, and dichloromethane.

In some embodiments, said at least one dissolution solvent is selected from ethanol/acetic acid (about 25/4 in V/V), ethyl acetate/acetone (from about 7/3 to about 3/7 in V/V), ethyl
20 acetate/i-propanol (from about 7/3 to about 3/7 in V/V), butanone/ethanol (from about 1/1 to about 1/4 in V/V), and the like.

In some embodiments, said cooling the solution may be carried out by cooling slowly while stirring, for example, stirring at a moderate rate, e.g., at a rate ranging from 50 to 200 rpm.

In some embodiments, said cooling the solution may be carried out by cooling naturally or
25 at a controlled temperature to room temperature or lower temperature, such as 25-30°C, 20-25°C, 5-10°C, and the like.

In some embodiments, the drying temperature and drying time can be determined conventionally by one skilled in the art, being appropriate so that the solid is dried sufficiently and the desired crystalline properties are maintained. In some embodiments, the drying
30 temperature is 55-60°C, such as 55°C, 58°C, or 60°C. In some embodiments, the drying time is 1-24 hours, such as 1 hour, 1.5 hours, 2 hours, or 16 hours.

Method B

The present invention provides a further method of preparing Form I of compound of
35 Formula A, comprising:

(1) mixing the compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with at least one dissolution solvent or with a mixed solvent consisting of tetrahydrofuran and water, and heating the mixture to reflux to obtain the first solution; for example, said at least one dissolution solvent is selected from one or more of
5 ethyl acetate, 1,4-dioxane, ethanol, and tetrahydrofuran;

(2) adding at least one anti-dissolution solvent into said first solution to obtain the second solution, and then cooling the second solution until the solid precipitates; or alternatively, firstly cooling said first solution, and then adding at least one anti-dissolution solvent until the solid precipitates; provided that, when said dissolution solvent in step (1) is ethanol, the
10 anti-dissolution solvent is not water;

(3) isolating to obtain the solid Form I of compound of Formula A;

(4) optionally drying the solid obtained in step (3).

In some embodiments, said tetrahydrofuran and water are mixed in an appropriate ratio. In some embodiments, the volume ratio of tetrahydrofuran to water is about 4/1.

15 In some embodiments, said anti-dissolution solvent is selected from water, C₅₋₈ straight or branched alkane (such as *n*-heptane), and isopropyl ether.

In some embodiments, the volume ratio of said at least one dissolution solvent or the mixed solvent consisting of tetrahydrofuran and water to said at least one anti-dissolution solvent ranges from about 1/3 to about 6/1, such as 1/2.7, 1/1.33, 1/1, 1.2/1, 5.4/1.

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Method C

The present invention provides a further method of preparing Form I of compound of Formula A, comprising:

(1) suspending the solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile in a solvent; for example, said solvent is
25 selected from one or more of ethyl acetate, toluene, tetrahydrofuran, and ethanol;

(2) stirring the suspension obtained in step (1), provided that, when said solvent in step (1) is ethanol, the stirring time should not be less than 24 hours;

(3) isolating to obtain the solid Form I of compound of Formula A;

30 (4) optionally drying the solid obtained in step (3).

In some embodiments, said solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile used in step (1) may be in any forms, such as a single crystalline form or amorphous form, e.g., Form IV or Form V, or a mixture of two or more of crystalline forms or amorphous form.

35 In some embodiments, in said step (1), the compound (*S*)-4-amino-6-((1-(3-chloro-6-

phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile is not dissolved completely in the suspension system, i.e., part of the compound remains as solid.

In some embodiments, said solvent is selected from one or more of ethyl acetate and toluene.

5 In some embodiments, heating may be applied in said step (2) when stirring the suspension, and the heating temperature is not higher than the boiling point of the solvent system, such as by heating to reflux.

It is to be understood that, Form I of compound of Formula A may be prepared through one or more of above methods.

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Form IV

The present invention provides Form IV of compound of Formula A.

In some embodiments, Form IV of compound of Formula A may be identified according to X-ray powder diffraction. In some embodiments, the X-ray powder diffraction characteristic
15 diffraction angles (2θ) of Form IV of compound of Formula A include 4.6, 9.2, 15.5, 17.8, and 19.0 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form IV of compound of Formula A include 4.6, 9.2, 11.5, 12.0, 13.2, 15.5, 16.0, 17.8, 19.0, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

20 In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form IV of compound of Formula A include 4.6, 9.2, 9.7, 11.3, 11.5, 12.0, 13.2, 13.8, 14.7, 15.5, 16.0, 17.8, 19.0, 22.3, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of
25 Form IV of compound of Formula A include 4.6, 7.2, 8.2, 9.2, 9.7, 11.3, 11.5, 12.0, 13.2, 13.8, 14.4, 14.7, 15.5, 16.0, 16.5, 17.8, 19.0, 22.3, and 22.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form IV of compound of Formula A include 4.6, 7.2, 8.2, 9.2, 9.7, 11.3, 11.5, 12.0, 13.2, 13.8,
30 14.4, 14.7, 15.5, 16.0, 16.5, 17.8, 18.2, 19.0, 19.5, 21.1, 21.6, 22.3, 22.6, and 23.6 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, Form IV of compound of Formula A has a diffractogram as shown in Figure 4.

In some embodiments, Form IV of compound of Formula A may be characterized by
35 differential scanning calorimetry (DSC). In some embodiments, Form IV of compound of

Formula A has a DSC curve as shown in Figure 5. In the DSC profile, the endothermic peak of Form IV of compound of Formula A is at about 261.8-263.8°C.

In some embodiments, Form IV of compound of Formula A may be characterized by thermogravimetric analysis (TGA). In some embodiments, Form IV of compound of Formula A has a TGA curve as shown in Figure 6, indicating that Form IV is an anhydrous material or a neat crystal.

In some embodiments, Form IV of compound of Formula A is substantially free of other crystalline forms as described herein. For example, the content by weight of Form IV of compound of Formula A is at least 99%, at least 95%, at least 90%, or even lower to 80%. Further, the content by weight of Form IV of compound of Formula A is at least 70%, or at least 60%. Even further, the content by weight of Form IV of compound of Formula A is at least 50%.

Methods of Preparing Form IV

Method A

The present invention relates to a method of preparing Form IV of compound of Formula A, comprising:

(1) mixing the compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with at least one dissolution solvent or with a mixed solvent consisting of water-miscible organic solvent and water, and heating the mixture to reflux to obtain a solution; for example, said at least one dissolution solvent is selected from C₁₋₆ alkanol, a mixture of *i*-propanol and acetic acid, or a mixture of methanol and acetic acid; said water-miscible organic solvent is selected from C₁₋₆ alkanol, provided that, said water-miscible organic solvent is not *t*-butanol;

(2) cooling the solution obtained in step (1) until the solid precipitates;

(3) isolating to obtain the solid Form IV of compound of Formula A;

(4) optionally drying the solid obtained in step (3).

In some embodiments, said C₁₋₆ alkanol is selected from methanol, ethanol, *i*-propanol, and *n*-butanol. In some embodiments, said C₁₋₆ alkanol is selected from methanol, ethanol, and *i*-propanol. In some embodiments, said C₁₋₆ alkanol is selected from ethanol.

In some embodiments, said water-miscible organic solvent is selected from ethanol, *i*-propanol, and *n*-butanol.

In some embodiments, the volume percentage of said water-miscible organic solvent in said mixed solvent is not more than about 95%, such as 95%, 90%, 80%, 70%, and the like.

In some embodiments, said at least one dissolution solvent is selected from *i*-propanol/acetic acid (about 22/1 in V/V), methanol/acetic acid (about 25/3 in V/V), and the

like.

In some embodiments, said cooling the solution may be carried out by cooling slowly while stirring, for example, stirring at a moderate rate, e.g., at a rate ranging from 50 to 200 rpm. In some embodiments, stirring is applied after cooling, and the stirring time is preferably not more than 24 hours.

In some embodiments, said cooling the solution may be carried out by cooling naturally or at a controlled temperature (e.g., at a cooling rate of 0.2°C/min, 0.5°C/min, 2°C/min, and the like) to room temperature or lower temperature, such as 20-25°C, 0-5°C, and the like.

In some embodiments, the drying temperature and drying time can be determined conventionally by one skilled in the art, being appropriate so that the solid is dried sufficiently and the desired crystalline properties are maintained. In some embodiments, the drying temperature is 50-60°C, such as 55°C. In some embodiments, the drying time is 1-24 hours, such as 1.5 hours, 2 hours, 5 hours, or 17 hours.

Method B

The present invention provides a further method of preparing Form IV of compound of Formula A, comprising:

(1) mixing the compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with at least one dissolution solvent or with a mixed solvent consisting of water-miscible organic solvent and water, and heating the mixture to reflux to obtain the first solution; for example, said at least one dissolution solvent is selected from methanol, ethanol, i-propanol, or a mixture of 1,4-dioxane and ethanol; said water-miscible organic solvent is selected from C₁₋₆ alkanol, or a mixture of tetrahydrofuran and ethanol;

(2) adding at least one anti-dissolution solvent into said first solution to obtain the second solution, and then cooling the second solution until the solid precipitates; or alternatively, firstly cooling said first solution, and then adding at least one anti-dissolution solvent until the solid precipitates;

(3) isolating to obtain the solid Form IV of compound of Formula A;

(4) optionally drying the solid obtained in step (3).

In some embodiments, said at least one dissolution solvent is selected from 1,4-dioxane/ethanol (about 1/5 in V/V), and the like.

In some embodiments, said water-miscible organic solvent is selected from C₁₋₆ alkanol, such as methanol, ethanol, and i-propanol. In some embodiments, the volume percentage of said water-miscible organic solvent in said mixed solvent consisting of water-miscible organic solvent and water is not more than about 95%, such as 95%, 80%, 70%, and the like.

In some embodiments, said water-miscible organic solvent and water are mixed in an appropriate ratio. In some embodiments, the volume ratio of the water-miscible organic solvent to water ranges from about 6/1 to 4/1, such as methanol/water (about 16/3 in V/V), tetrahydrofuran/ethanol /water (about 1/99/25, about 5/95/25, or about 10/90/25 in V/V).

5 In some embodiments, said anti-dissolution solvent is selected from water.

In some embodiments, the volume ratio of said at least one dissolution solvent or the mixed solvent consisting of water-miscible organic solvent and water to said at least one anti-dissolution solvent ranges from about 1/3 to about 2/1, such as 1/2.1, 1/1.4, 1/1, 1.36/1.

10 In some embodiments, said anti-dissolution solvent can be added all in one portion or added in batches.

Method C

The present invention provides a further method of preparing Form IV of compound of Formula A, comprising:

15 (1) suspending the solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile in a solvent; wherein, said solvent is selected from C₁₋₆ alkanol, water, or a mixed solvent consisting of water-miscible organic solvent (such as those selected from methanol, ethanol, and i-propanol) and water;

(2) stirring the suspension obtained in step (1), provided that, when said solvent in step (1) is ethanol, the stirring time should be less than 24 hours;

(3) isolating to obtain the solid Form IV of compound of Formula A;

(4) optionally drying the solid obtained in step (3).

25 In some embodiments, said solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile used in step (1) may be in any forms, for example a single crystalline form or amorphous form, such as Form I, Form IV, Form V, Form VI, or Form VIII, or a mixture of two or more of crystalline forms or amorphous form.

30 In some embodiments, in said step (1), the compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile is not dissolved completely in the suspension system, i.e., part of the compound remains as solid.

In some embodiments, said C₁₋₆ alkanol is selected from methanol, ethanol, and i-propanol.

35 In some embodiments, said water-miscible organic solvent is selected from methanol. In some embodiments, the volume percentage of said water-miscible organic solvent in said mixed

solvent is less than about 25%, such as 10%.

In some embodiments, heating may be applied in said step (2) when stirring the suspension, and the heating temperature is not higher than the boiling point of the solvent system, such as 60-70°C, 70-80°C, 75-85°C, and the like. Said heating can facilitate the conversion of the solid in the suspension system to Form IV of compound of Formula A.

It is to be understood that, Form IV of compound of Formula A may be prepared through one or more of above methods.

Form V

The present invention provides Form V of compound of Formula A.

In some embodiments, Form V of compound of Formula A may be identified according to X-ray powder diffraction. In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form V of compound of Formula A include 7.3, 11.6, 14.6, 19.3, and 23.4 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form V of compound of Formula A include 4.6, 7.3, 8.9, 11.6, 13.5, 14.6, 15.5, 18.0, 19.3, and 23.4 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form V of compound of Formula A include 4.6, 7.3, 8.9, 10.0, 11.2, 11.6, 13.5, 14.6, 15.5, 16.0, 18.0, 19.3, 20.0, and 23.4 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form V of compound of Formula A include 4.6, 7.3, 8.9, 10.0, 11.2, 11.6, 13.5, 14.6, 15.5, 16.0, 18.0, 19.3, 20.0, 22.7, 23.4, 25.1, 26.0, and 27.2 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form V of compound of Formula A include 4.6, 7.3, 8.9, 10.0, 11.2, 11.6, 13.5, 14.6, 15.5, 16.0, 17.7, 18.0, 19.3, 20.0, 22.7, 23.4, 24.0, 25.1, 26.0, 27.2, 28.4, and 29.7 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, Form V of compound of Formula A has a diffractogram as shown in Figure 7.

In some embodiments, Form V of compound of Formula A may be characterized by differential scanning calorimetry (DSC). In some embodiments, Form V of compound of Formula A has a DSC curve as shown in Figure 8. In the DSC profile, the endothermic peak of Form V of compound of Formula A is at about 261.4-262.4°C.

In some embodiments, Form V of compound of Formula A may be characterized by thermogravimetric analysis (TGA). In some embodiments, Form V of compound of Formula A has a TGA curve as shown in Figure 9, indicating that Form V is an anhydrous material or a neat crystal.

In some embodiments, Form V of compound of Formula A is substantially free of other crystalline forms as described herein. For example, the content by weight of Form V of compound of Formula A is at least 99%, at least 95%, at least 90%, or even lower to 80%. Further, the content by weight of Form V of compound of Formula A is at least 70%, or at least 60%. Even further, the content by weight of Form V of compound of Formula A is at least 50%.

Methods of Preparing Form V

Method A

The present invention relates to a method of preparing Form V of compound of Formula A, comprising:

- (1) mixing the compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with at least one dissolution solvent or with a mixed solvent consisting of acetonitrile and water, and heating the mixture to reflux to obtain a solution; for example, said at least one dissolution solvent is selected from acetonitrile, a mixture of acetonitrile and acetic acid, a mixture of acetonitrile and ethyl acetate, a mixture of acetonitrile and butanone, a mixture of acetonitrile and tetrahydrofuran, or a mixture of acetone and ethanol;
- (2) cooling the solution obtained in step (1) until the solid precipitates;
- (3) isolating to obtain the solid Form V of compound of Formula A;
- (4) optionally drying the solid obtained in step (3).

In some embodiments, said at least one dissolution solvent is selected from acetonitrile.

In some embodiments, in said mixed solvent consisting of acetonitrile and water, the volume percentage of said acetonitrile in said mixed solvent is 90%.

In some embodiments, said at least one dissolution solvent is selected from acetonitrile/acetic acid (about 14/1 in V/V), acetonitrile/ethyl acetate (about 7/3 in V/V), acetonitrile/butanone (about 1/1 in V/V), acetonitrile/tetrahydrofuran (about 7/3 in V/V), acetone/ethanol (about 1/4 in V/V), and the like.

In some embodiments, said cooling the solution may be carried out by cooling slowly while stirring, for example, stirring at a moderate rate, e.g., at a rate ranging from 50 to 200 rpm.

In some embodiments, said cooling the solution may be carried out by cooling naturally or at a controlled temperature to room temperature or lower temperature, such as 20-25°C, -10 - -5°C, and the like.

In some embodiments, the drying temperature and drying time can be determined conventionally by one skilled in the art, being appropriate so that the solid is dried sufficiently and the desired crystalline properties are maintained. In some embodiments, the drying temperature is 50-60°C, such as 50°C or 60°C. In some embodiments, the drying time is 1-24
5 hours, such as 1 hour or 16 hours.

Method B

The present invention provides a further method of preparing Form V of compound of Formula A, comprising:

- 10 (1) suspending the solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile in acetonitrile;
- (2) stirring the suspension obtained in step (1);
- (3) isolating to obtain the solid Form V of compound of Formula A;
- (4) optionally drying the solid obtained in step (3).

15 In some embodiments, said solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile used in step (1) may be in any forms, for example a single crystalline form or amorphous form, such as Form I, Form IV, or Form V, or a mixture of two or more of crystalline forms or amorphous form.

In some embodiments, in said step (1), the compound
20 (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile is not dissolved completely in the suspension system, i.e., part of the compound remains as solid.

In some embodiments, heating may be applied in said step (2) when stirring the suspension, and the heating temperature is not higher than the boiling point of the solvent system, such as
25 70-80°C.

It is to be understood that, Form V of compound of Formula A may be prepared through one or more of above methods.

Acetone solvate

30 The present invention further provides acetone solvate of compound of Formula A.

In some embodiments, acetone solvate of compound of Formula A is monoacetone solvate.

In some embodiments, monoacetone solvate of compound of Formula A is Form VI.

In some embodiments, Form VI of monoacetone solvate of compound of Formula A may be characterized by X-ray powder diffraction. The X-ray powder diffraction characteristic
35 diffraction angles (2θ) of Form VI include 8.6, 10.4, 12.0, 15.0, and 19.7 degrees, the measured

2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form VI of monoacetone solvate of compound of Formula A include 6.9, 8.6, 9.8, 10.4, 12.0, 13.4, 15.0, 19.7, 20.6, 23.8, and 29.8 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form VI of monoacetone solvate of compound of Formula A include 6.9, 8.6, 9.8, 10.4, 12.0, 13.4, 15.0, 15.8, 16.8, 18.0, 19.7, 20.6, 23.3, 23.8, 26.2, and 29.8 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form VI of monoacetone solvate of compound of Formula A include 6.9, 8.6, 9.8, 10.4, 12.0, 13.4, 15.0, 15.8, 16.8, 18.0, 19.4, 19.7, 20.6, 21.0, 22.5, 23.0, 23.3, 23.8, 25.0, 26.2, and 29.8 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form VI of monoacetone solvate of compound of Formula A include 6.9, 8.6, 9.0, 9.8, 10.4, 12.0, 13.4, 15.0, 15.8, 16.2, 16.8, 17.3, 18.0, 18.2, 18.9, 19.4, 19.7, 20.6, 21.0, 21.6, 22.5, 23.0, 23.3, 23.8, 24.5, 25.0, 26.2, and 29.8 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, Form VI of monoacetone solvate of compound of Formula A has a diffractogram as shown in Figure 10.

In some embodiments, Form VI of monoacetone solvate of compound of Formula A may be characterized by differential scanning calorimetry (DSC). In some embodiments, Form VI of monoacetone solvate of compound of Formula A has a DSC curve as shown in Figure 11. In the DSC profile, the endothermic peaks of Form VI of monoacetone solvate of compound of Formula A are at about 97.3-106.0°C and about 262.3-265.0°C.

In some embodiments, Form VI of monoacetone solvate of compound of Formula A may be characterized by thermogravimetric analysis (TGA). In some embodiments, Form VI of monoacetone solvate of compound of Formula A has a TGA curve as shown in Figure 12, indicating that Form VI is a solvate. The result of further gas chromatography (GC) test shows that the Form contains 1 molecule of acetone. Form VI is a monoacetone solvate.

In some embodiments, Form VI of monoacetone solvate of compound of Formula A is substantially free of other crystalline forms as described herein. For example, the content by weight of Form VI of monoacetone solvate of compound of Formula A is at least 99%, at least 95%, at least 90%, or even lower to 80%. Further, the content by weight of Form VI of monoacetone solvate of compound of Formula A is at least 70%, or at least 60%. Even further,

the content by weight of Form VI of monoacetone solvate of compound of Formula A is at least 50%.

Methods of Preparing Form VI

5 Method A

The present invention relates to a method of preparing Form VI of compound of Formula A, comprising:

- (1) mixing the compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with at least one dissolution solvent or with a mixed solvent consisting of acetone and water, and heating the mixture to reflux to obtain a solution; 10 wherein, said at least one dissolution solvent is selected from acetone, or a mixed solvent consisting of acetone and i-propanol;
- (2) cooling the solution obtained in step (1) until the solid precipitates;
- (3) isolating to obtain the solid Form VI of compound of Formula A;
- 15 (4) optionally drying the solid obtained in step (3).

In some embodiments, in said mixed solvent consisting of acetone and water, the volume percentage of said acetone in said mixed solvent is 95% or 75%.

In some embodiments, said acetone and i-propanol are mixed in an appropriate ratio. In some embodiments, the volume ratio of acetone to i-propanol is about 7/3.

- 20 In some embodiments, said cooling the solution may be carried out by cooling naturally or at a controlled temperature to room temperature or lower temperature, such as 25-30°C, 20-25°C, 0-5°C, and the like.

- In some embodiments, the drying temperature and drying time can be determined conventionally by one skilled in the art, being appropriate so that the solid is dried sufficiently and the desired crystalline properties are maintained. In some embodiments, the drying condition 25 is drying in the air for 30 minutes.

Method B

- The present invention provides a further method of preparing Form VI of compound of 30 Formula A, comprising:

- (1) suspending the solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile in acetone or a mixed solvent consisting of acetone and water;
- (2) stirring the suspension obtained in step (1);
- 35 (3) isolating to obtain the solid Form VI of compound of Formula A;

(4) optionally drying the solid obtained in step (3).

In some embodiments, said solid of compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile used in step (1) may be in any forms, for example a single crystalline form or amorphous form, such as Form I or Form V,
5 or a mixture of two or more of crystalline forms or amorphous form.

In some embodiments, in said step (1), the compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile is not dissolved completely in the suspension system, i.e., part of the compound remains as solid.

10 In some embodiments, said acetone and water are mixed in an appropriate ratio. In some embodiments, the volume ratio of acetone to water is about 3/1.

In some embodiments, in said step (2), the time for stirring the suspension is not less than 48 hours, such as 6 days.

It is to be understood that, Form VI of compound of Formula A may be prepared through
15 one or more of above methods.

Water and i-propanol solvate

The present invention further provides water and i-propanol solvate of compound of Formula A.

20 In some embodiments, water and i-propanol solvate of compound of Formula A contains 3 molecules of water and 0.5 molecule of i-propanol.

In some embodiments, water and i-propanol solvate (containing 3 molecules of water and 0.5 molecule of i-propanol) of compound of Formula A is Form VIII.

In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula
25 A may be characterized by X-ray powder diffraction. The X-ray powder diffraction characteristic diffraction angles (2θ) of Form VIII include 7.0, 8.3, 11.4, 15.3, and 23.1 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of
30 Form VIII of water and i-propanol solvate of compound of Formula A include 7.0, 8.3, 9.8, 10.7, 11.4, 15.3, 15.7, 22.4, and 23.1 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of
35 Form VIII of water and i-propanol solvate of compound of Formula A include 7.0, 8.3, 9.8, 10.7, 11.4, 13.3, 14.2, 15.3, 15.7, 17.7, 22.4, 23.1, 25.4, and 26.9 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form VIII of water and i-propanol solvate of compound of Formula A include 7.0, 8.3, 9.8, 10.7, 11.4, 13.3, 13.8, 14.2, 15.3, 15.7, 17.7, 19.0, 19.4, 20.3, 22.4, 23.1, 23.5, 25.4, and 26.9 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

5 In some embodiments, the X-ray powder diffraction characteristic diffraction angles (2θ) of Form VIII of water and i-propanol solvate of compound of Formula A include 7.0, 8.3, 9.8, 10.7, 11.4, 13.3, 13.8, 14.2, 15.3, 15.7, 17.7, 19.0, 19.4, 19.6, 20.3, 21.4, 22.4, 23.1, 23.5, 24.0, 25.0, 25.4, 26.9, and 27.2 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ).

10 In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula A has a diffractogram as shown in Figure 13.

In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula A may be characterized by differential scanning calorimetry (DSC). In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula A has a DSC curve as shown in
15 Figure 14. In the DSC profile, the endothermic peaks of Form VIII of water and i-propanol solvate of compound of Formula A are at about 64.1-81.7°C and about 261.5-262.2°C.

In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula A may be characterized by thermogravimetric analysis (TGA). In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula A has a TGA curve as shown in Figure
20 15, indicating that Form VIII is a solvate. The results of further Karl-Fischer moisture determination (KF) and gas chromatography (GC) test show that the Form contains 3 molecules of water and 0.5 molecule of i-propanol. Form VIII is a water and i-propanol solvate containing 3 molecules of water and 0.5 molecule of i-propanol.

In some embodiments, Form VIII of water and i-propanol solvate of compound of Formula
25 A is substantially free of other crystalline forms as described herein. For example, the content by weight of Form VIII of water and i-propanol solvate of compound of Formula A is at least 99%, at least 95%, at least 90%, or even lower to 80%. Further, the content by weight of Form VIII of water and i-propanol solvate of compound of Formula A is at least 70%, or at least 60%. Even further, the content by weight of Form VIII of water and i-propanol solvate of compound of
30 Formula A is at least 50%.

Methods of Preparing Form VIII

The present invention relates to a method of preparing Form VIII of compound of Formula A, comprising:

35 (1) mixing the compound (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin

-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with a mixed solvent consisting of i-propanol and water, and heating the mixture to reflux to obtain a solution;

(2) cooling the solution obtained in step (1) until the solid precipitates, and then stirring the mixture (preferably for no less than 72 hours);

5 (3) isolating to obtain the solid Form VIII of compound of Formula A;

(4) optionally drying the solid obtained in step (3).

In some embodiments, in said mixed solvent consisting of i-propanol and water, the volume percentage of said i-propanol in said mixed solvent is 70%.

10 In some embodiments, the drying temperature and drying time can be determined conventionally by one skilled in the art, being appropriate so that the solid is dried sufficiently and the desired crystalline properties are maintained. In some embodiments, the drying condition is drying in the air for 50-100 minutes.

The features of each embodiment for above methods of preparing the crystalline forms of compound of Formula A or its solvates can be arbitrary combined. Each embodiment obtained from such arbitrary combinations is included within the scope of the present invention, as if these embodiments obtained from such arbitrary combinations are specifically and individually listed herein.

20 **Pharmaceutical Compositions and Methods of Treatment**

The crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) are useful in the treatment of diseases, such as autoimmune diseases, inflammatory diseases, and cancer. The cancer is preferably hematological malignancy. The autoimmune diseases, inflammatory diseases, and cancer include but not limited to systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease, psoriasis, asthma, lymphoma (such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, mantle cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Burkitt lymphoma, B cell lymphoma, T cell lymphoma, NK cell lymphoma, and diffuse large
30 B-cell lymphoma), leukemia (such as chronic lymphocytic leukemia, acute lymphocytic leukemia, acute myeloid leukemia, and chronic myelogenous leukemia), multiple myeloma, and Waldenstrom's macroglobulinemia.

The present invention provides the method of treating diseases responsive to inhibition of PI₃K activity, comprises administering the active pharmaceutical ingredients comprising
35 compound of Formula A, or one or more of the crystalline forms of compound of Formula A, the

solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, or Form VIII).

In some embodiments, the treatment method is directed to at least one disease responsive to inhibition of PI₃K activity, such as autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy). An effective amount of a pharmaceutical composition of the present invention is administered to a subject in need thereof, wherein the pharmaceutical composition comprises at least one pharmaceutically acceptable carrier and one or more of the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, or Form VIII).

The dosing amount of the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, or Form VIII) to achieve the desired biological effect may depend on a number of factors, e.g., the intended use, the mode of administration, and the clinical condition of the patient. The daily dose may, for example, range from 0.01 mg to 3 g/day (such as from 0.05 mg to 2 g/day, even from 100 mg to 1g /day). Unit dose formulations which can be administered orally include, for example, tablets or capsules.

For the therapy of the above-mentioned conditions, the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof may be administered as such, but typically in the form of a pharmaceutical composition formulated with one or more pharmaceutically acceptable carriers or excipients.

Representative carriers or excipients should be compatible with the other ingredients of the composition and do not have harmful effect on the patient's health. The carrier or excipient may be a solid or a liquid or both, and may be formulated with the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and/or Form VIII) into a pharmaceutical composition or a unit dosage form (for example, a tablet, a capsule), which may contain from 0.05% to 95% by weight of the crystalline forms of compound of Formula A, the solvates of compound of Formula A or the crystalline forms thereof. The pharmaceutical compositions described herein can be produced by known pharmaceutical formulating methods, such as those involving mixing with pharmaceutically acceptable carriers and/or excipients and diluents.

In some embodiments, the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) may be

combined with at least one component, such as carrier and/or excipient and/or diluent, which may be selected from sweeteners, flavoring agents, coloring agents, dyes, and emulsifiers.

In some embodiments, the conversion of the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) will not occur when formulating with the one or more pharmaceutically acceptable carriers and/or excipients and/or diluents. In other embodiments, the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, or Form VIII) may be converted, in whole or in part, to one or more other crystalline forms or amorphous form, or to a non-solid form, when formulating with the one or more pharmaceutically acceptable carriers and/or excipients and/or diluents. In some embodiments, Form I or other crystalline forms described herein can be dissolved when formulated into a pharmaceutical composition. Accordingly, in such “dissolved” cases, Form I or other crystalline forms no longer exists in their respective forms in the pharmaceutical composition.

In some embodiments, the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) is formulated into a suitable dosage form.

Pharmaceutical compositions described herein may be dosage forms suitable for oral and peroral (for example sublingual) administration. The suitable mode of administration may depend on not only the condition in each individual case and severity of the condition to be treated, but also the nature of the specific forms of the active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) used in preparing the pharmaceutical composition.

Suitable pharmaceutical compositions for oral administration prepared from the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) may be in the form of unit dosage forms such as capsules, cachets, and tablets, including suckable tablets, each of which is prepared with a defined amount of the at least one active pharmaceutical ingredient described herein; as well as in the forms selected from powders, granules, solutions, suspensions in an aqueous or nonaqueous liquid, and oil-in-water and water-in-oil emulsions. Those compositions may, as already mentioned, be prepared by any suitable pharmaceutical formulation methods, such as those including a step wherein the at least one active pharmaceutical ingredient selected from the crystalline forms of

compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) and a carrier and/or excipient and/or diluent (which may consist of one or more added ingredients) are combined. The compositions can generally be produced by uniformly and homogeneously mixing the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) with liquid or finely divided solid carriers, after which the product can be shaped.

The at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) can also be administered in combination with one or more other active ingredients (such as in the synergetic therapy). When administered as a combination, the active ingredients can be formulated as separate compositions that are administered at the same time or sequentially at different times (such as administered sequentially in any orders) through the same or different administration routes, or the active ingredients can be administered in the same pharmaceutical composition.

In some embodiments, the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) can be administered in combination with one or more other active ingredients with known therapeutical effect, for example for the treatment of diseases responsive to inhibition of PI₃K activity, such as autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy).

The phrase “combination”, as described herein, defines the combined use of the at least one active pharmaceutical ingredient selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII) with one or more other active ingredients, such as, the combined use in the treatment of autoimmune diseases or inflammatory diseases (for example, in combination with immunosuppressants, steroids), the combined use in the treatment of cancer, especially hematological malignancy (for example, in combination with BTK inhibitors, SYK inhibitors, JAK inhibitors, Bcl-2 inhibitors, anti-CD20 monoclonal antibodies, Lenalidomide). Examples of BTK inhibitors include but not limited to Ibrutinib, ACP-196 (Acalabrutinib), CC-292 (Spebrutinib), ONO-4059 (Tirabrutinib), BGB-3111, and GDC-0853. Examples of SYK inhibitors include but not limited to GS-9973 (Entospletinib) and HMPL-523. Examples of JAK inhibitors include but not limited to Ruxolitinib. Examples of Bcl-2 inhibitors include but not limited to Venetoclax (ABT-199), ABT-263 (Navitoclax), and BCL201 (S55746). Examples of

anti-CD20 monoclonal antibodies include but not limited to Rituximab, Ofatumumab, and Obinutuzumab.

Examples of immunosuppressants include but not limited to corticoids (e.g., fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide, or budesonide), disease-modifying agents (e.g., antimalarials, methotrexate, sulfasalazine, mesalamine, azathioprine, 6-mercaptopurine, metronidazole, or D-penicillamine), non-steroidal anti-inflammatory drugs (e.g., acetaminophen, aspirin, sodium salicylate, sodium cromoglycate, magnesium salicylate, choline magnesium salicylate, salicylsalicylic acid, ibuprofen, naproxen, diclofenac, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, piroxicam, indomethacin, ketoprofen, ketorolac tromethamine, meclofenamate, meclofenamate sodium, mefenamic acid, nabumetone, oxaprozin, phenyl butyl nitron (PBN), sulindac, or tolmetin), COX-2 inhibitors, inhibitors of cytokine synthesis/release (e.g., anti-cytokine antibodies, anti-cytokine receptor antibodies, and the like).

Examples of steroids include but not limited to glucocorticoids, such as budesonide, beclomethasone dipropionate, fluticasone propionate, ciclesonide, mometasone furoate, and the like.

In addition, the at least one active pharmaceutical ingredient selected from the crystalline forms, the solvates and the crystalline forms thereof of the present invention can also be used in combination with other anti-neoplastic agents. As used herein, the term "anti-neoplastic agent" refers to any agent that is useful for treating the cancer. Examples of anti-neoplastic agent include but not limited to: radiotherapy agent, immunotherapy agent, DNA damaging chemotherapeutic agents, and chemotherapeutic agents that disrupt cell replication.

DNA damaging chemotherapeutic agents include but not limited to, for example, topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and adriacin); topoisomerase II inhibitors (e.g., etoposide, teniposide, mitoxantrone, idarubicin, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, dacarbazine, methotrexate, mitomycin, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitabine, gemcitabine, fludarabine, cytarabine, azacitidine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea).

Chemotherapeutic agents those disrupt cell replication include but not limited to: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors (e.g., bortezomib); NF-kappa B inhibitors,

including inhibitors of I kappa B kinase; antibodies which bind to proteins overexpressed in cancers and thereby down-regulate cell replication (e.g., trastuzumab, rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed, or activated in cancers, the inhibition of which can down-regulates cell replication.

Furthermore, methods described herein are not limited by the sequence of administration; the one or more other active ingredients may be administered simultaneously to, prior to or after the administration of the at least one active pharmaceutical ingredient. The at least one active pharmaceutical ingredient in the combination described above is selected from the crystalline forms of compound of Formula A, the solvates of compound of Formula A and the crystalline forms thereof (such as Form I, Form IV, Form V, Form VI, and Form VIII).

The following non-limiting examples are provided.

Experiments

The compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile raw material used in the examples were prepared according to WO2016045591A1.

All reagents, except intermediates, used in this disclosure are commercially available. The names of all compounds, except the reagents, were generated by ChemDraw Professional 16.0.

Unless otherwise indicated, X-ray powder diffractograms were obtained using Germany Bruker D8 ADVANCE X-ray diffractometer (target: Cu; voltage: 40kV; electric current: 40mA; scanning speed: 4 degrees/min; step size: 0.02 degree; scanning range: 3-45 degrees).

Unless otherwise indicated, differential scanning calorimetry (DSC) was performed on Germany NETZSCH DSC 204F1 (purge gas: nitrogen; flow rate: 20-60 mL min⁻¹; heating rate: 5-10°C/min; temperature range: 30°C to 300°C). The samples were measured in the pricked aluminum pans. Indium was used for temperature calibration. Alternatively, DSC was performed on DSC Q2000 of American TA company.

Unless otherwise indicated, thermogravimetric (TG) analyses were obtained using Germany NETZSCH TGA 209F1 (purge gas: nitrogen; heating rate: 10°C/min); or were obtained using TG Q500 of American TA company.

Example 1 Preparation of Form I of compound of Formula A

0.86g of compound of Formula A was dissolved in 28mL of ethyl acetate under heating and stirring. Then the solution was cooled to room temperature and stirred for 17 hours at a

moderate rate. Then the precipitate was filtered and dried at 60°C under vacuum for 1.5 hours to give 0.53g of solid.

The obtained powder sample is Form I of compound of Formula A, the X-ray powder diffractogram of which is shown in Figure 1. Peaks (2θ) chosen from the figure have the following values: 6.8, 7.6, 8.0, 10.0, 12.1, 12.6, 13.7, 14.4, 15.0, 15.3, 16.2, 16.5, 17.0, 17.9, 18.7, 20.1, 21.3, 22.6, 23.1, 25.4, 26.1, and 29.0 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ), wherein characteristic peaks (2θ) are at 6.8, 10.0, 16.5, 20.1, and 22.6 degrees. DSC result is given in Figure 2, showing that the endothermic peak of Form I is at about 261.2-262.1°C.

Example 2 Preparation of Form I of compound of Formula A

An appropriate amount of compound of Formula A were suspended in an appropriate amount of the solvents listed in Table 1 respectively. The suspensions were heated to the temperatures listed in Table 1 to dissolve. Then the solutions were cooled to 20-25°C. Then the precipitates were filtered respectively to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form I of compound of Formula A obtained in Example 1.

Table 1

Amount of compound of Formula A/solvent	Solvent	Heating temperature
150mg/1.2mL	1,4-dioxane	80-85°C
150mg/1.5mL	tetrahydrofuran	60-70°C
80mg/1.16L	ethanol/acetic acid (volume ratio 25/4)	75-80°C

Example 3 Preparation of Form I of compound of Formula A

An appropriate amount of compound of Formula A were suspended in an appropriate amount of the solvents listed in Table 2 respectively. The suspensions were heated to the temperatures listed in Table 2 to dissolve. Then the solutions were cooled to 20-25°C and stirred for a period of time at a moderate rate. Then the precipitates were filtered respectively to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form I of compound of Formula A obtained in Example 1.

Table 2

Amount of compound of Formula A/solvent	Solvent	Heating temperature	Stirring time
100mg/3.2mL	ethyl acetate/acetone (volume ratio 7/3)	50-60°C	17 hours
100mg/3.7mL	ethyl acetate/acetone (volume ratio 1/1)	50-60°C	17 hours

100mg/4mL	ethyl acetate/acetone (volume ratio 3/7)	50-60°C	17 hours
100mg/3.4mL	ethyl acetate/i-propanol (volume ratio 3/7)	70-80°C	17 hours
100mg/2.3mL	ethyl acetate/i-propanol (volume ratio 1/1)	70-80°C	17 hours
100mg/2.4mL	ethyl acetate/i-propanol (volume ratio 7/3)	70-80°C	17 hours
110mg/2mL	butanone	70-80°C	17 hours
90mg/2mL	butanone/ethanol (volume ratio 1/1)	70-80°C	17 hours
80mg/2.2mL	butanone/ethanol (volume ratio 1/4)	75-85°C	18 hours

Example 4 Preparation of Form I of compound of Formula A

0.55g of compound of Formula A was suspended in 15.5mL of ethyl acetate, and heated to 70-80°C to dissolve. Then the solution was cooled to 5-10°C and stirred for 1 hour at a moderate rate. Then the precipitate was filtered and dried at 55°C under vacuum for 16 hours to give 0.36g of sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form I of compound of Formula A obtained in Example 1.

Example 5 Preparation of Form I of compound of Formula A

2.4g of compound of Formula A was suspended in 265mL of toluene, and heated to 100-110°C to dissolve. Then the solution was cooled to 20-25°C. Then the precipitate was filtered and dried at 55°C under vacuum for 16 hours to give 2.19g of sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form I of compound of Formula A obtained in Example 1.

Example 6 Preparation of Form I of compound of Formula A

130mg of compound of Formula A was suspended in 20mL of dichloromethane, and heated to gentle reflux to dissolve. The solution was stirred under refluxing for 1 hour, and then cooled to 20-25°C. A small amount of solid precipitated. 5mL of dichloromethane was added, and stirring continued for 4 hours. The solid sample was obtained by filtration. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form I of compound of Formula A obtained in Example 1.

Example 7 Preparation of Form I of compound of Formula A

100mg of compound of Formula A was suspended in 2mL of a mixed solvent (tetrahydrofuran/water, volume ratio 4/1), and heated to 60-70°C to dissolve. The solution was cooled to 25-30°C, and no solid precipitated after 1 hour. Then 2mL of water was added, and stirred for 18 hours. Then the precipitate was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form I of

compound of Formula A obtained in Example 1.

Example 8 Preparation of Form I of compound of Formula A

1.08g of compound of Formula A was suspended in 37mL of ethyl acetate, and heated to
5 70-80°C to dissolve. Then the solution was cooled to 25-30°C and stirred for 2 hours. Then the
precipitate was filtered and dried at 58°C under vacuum for 2 hours to give the first batch of
sample. Then 100mL of isopropyl ether was added to the filtrate, and stirred for 17 hours. Then
the precipitate was filtered again, and dried at 58°C under vacuum for 2 hours to give the second
batch of sample. Upon measurement, the X-ray powder diffractograms of the obtained two
10 batches of samples are both consistent with that of Form I of compound of Formula A obtained
in Example 1.

Example 9 Preparation of Form I of compound of Formula A

120mg of compound of Formula A was suspended in 4.5mL of ethanol, heated to 75-85°C
15 to dissolve, and filtered while hot. Then 6mL of n-heptane was added to the filtrate. The solution
was cooled to 25-30°C and stirred for 16 hours. Then the precipitate was filtered to give the
sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent
with that of Form I of compound of Formula A obtained in Example 1.

20 **Example 10 Preparation of Form I of compound of Formula A**

110mg of compound of Formula A was suspended in 1.2mL of 1,4-dioxane and heated to
80-85°C to dissolve. 1mL of n-heptane was added. Then the solution was cooled to 20-25°C and
stirred for 18 hours. Then the precipitate was filtered and dried at 55°C under vacuum for 4 hours
to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample
25 is consistent with that of Form I of compound of Formula A obtained in Example 1.

Example 11 Preparation of Form I of compound of Formula A

0.52g of compound of Formula A was suspended in 27mL of ethyl acetate, heated to
75-85°C to dissolve, and filtered while hot to remove the small amount of insoluble materials.
30 Then the filtrate was reheated to 75-85°C to dissolve all the solids, and 5mL of n-heptane was
added. Then the mixture was cooled to 20-25°C and stirred for 17 hours. Then the precipitate
was filtered and dried at 55°C under vacuum for 2 hours to give the sample. Upon measurement,
the X-ray powder diffractogram of the obtained sample is consistent with that of Form I of
compound of Formula A obtained in Example 1.

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Example 12 Preparation of Form I of compound of Formula A

The solids of compound of Formula A (a mixture of Form IV and Form V) were suspended in ethyl acetate and toluene respectively, and heated to reflux. Then the solids of compound of Formula A (a mixture of Form IV and Form V) were added till excess solids were present in each system. The obtained suspensions were stirred under reflux for 2 hours, cooled to 20-25°C, and allowed to stand for 18 hours. Then the solids were filtered respectively to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form I of compound of Formula A obtained in Example 1.

Example 13 Preparation of Form I of compound of Formula A

The solid of compound of Formula A (a mixture of Form IV and Form V) was suspended in 0.7 mL of tetrahydrofuran, and heated to reflux. Then the solids of compound of Formula A (a mixture of Form IV and Form V) were added till excess solids were present in the system. The obtained suspension was stirred under reflux for 2 hours, and allowed to stand for 10 minutes. Then 0.5 mL of the supernatant was removed to another vial, and tetrahydrofuran in the vial was removed by purging nitrogen, followed by drying at 60°C under vacuum for 1 hour to give the solid sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form I of compound of Formula A obtained in Example 1.

Example 14 Preparation of Form I of compound of Formula A

An appropriate amount of the solids of compound of Formula A (the forms were as listed in Table 3) were suspended in an appropriate amount of the solvents listed in Table 3 respectively. The suspensions were stirred at 25-30°C for a period of time, and filtered respectively to give each solid sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form I of compound of Formula A obtained in Example 1.

Table 3

Amount of the solid of compound of Formula A / solvent	Form of compound of Formula A	Solvent	Stirring time
40mg/1mL	Form IV	ethanol	8 days
160mg/2.5mL	Form V	ethyl acetate	20 days
160mg/2.5mL	Form V	toluene	20 days

Example 15 Preparation of Form IV of compound of Formula A

3.59g of compound of Formula A was dissolved with 100mL of 90% ethanol by heating to 70-80°C. Then the solution was cooled to room temperature slowly and stirred at a moderate rate.

Then the precipitate was collected by filtration and dried to give 1.64g of solid.

The obtained solid sample is Form IV of compound of Formula A, the X-ray powder diffractogram of which is shown in Figure 4. Peaks (2 θ) chosen from the figure have the following values: 4.6, 7.2, 8.2, 9.2, 9.7, 11.3, 11.5, 12.0, 13.2, 13.8, 14.4, 14.7, 15.5, 16.0, 16.5, 17.8, 18.2, 19.0, 19.5, 21.1, 21.6, 22.3, 22.6, and 23.6 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ), wherein characteristic peaks (2 θ) are at 4.6, 9.2, 15.5, 17.8, and 19.0 degrees. DSC result is given in Figure 5, showing that the endothermic peak of Form IV is at about 261.8-263.8°C.

10 **Example 16 Preparation of Form IV of compound of Formula A**

81.2mg of compound of Formula A was dissolved in 3mL of ethanol under heating to reflux, and stirred for 20 minutes. After heating was stopped, the solution was cooled naturally to 20-25°C and stirred for 1 hour at a moderate rate. Then the precipitate was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 17 Preparation of Form IV of compound of Formula A

81.4mg of compound of Formula A was dissolved in 2.2mL of 95% ethanol under heating to reflux, and stirred for 30 minutes. After heating was stopped, the solution was cooled naturally to 20-25°C and stirred for 1 hour at a moderate rate. Then the precipitate was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 18 Preparation of Form IV of compound of Formula A

An appropriate amount of compound of Formula A were dissolved in various solvents under heating conditions respectively. Then each obtained solution was cooled to a certain temperature and stirred for a period of time at a moderate rate respectively. Then the precipitates were filtered respectively to give each sample (the specific conditions were as listed in Table 4). Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Table 4

Amount of compound of Formula A/solvent	Solvent	Heating condition	Cooling condition, temperature and stirring time
80mg/3.5mL	ethanol	reflux	Cooled naturally to 20-25°C, stirred for 17 hours

71.6mg/6mL	i-propanol	reflux	Cooled to 20-25°C within 2-3 hours, stirred for 1 hour
80mg/3.66mL	i-propanol/acetic acid (volume ratio 175/8)	75-85°C	Cooled naturally to 20-25°C, stirred for 18 hours
80mg/1.12mL	methanol/acetic acid (volume ratio 25/3)	60-70°C	Cooled naturally to 20-25°C, stirred for 18 hours

Example 19 Preparation of Form IV of compound of Formula A

An appropriate amount of compound of Formula A were dissolved in various solvents under heating conditions respectively. Then each obtained solution was cooled to a certain temperature and stirred for a period of time at a moderate rate respectively. Then the precipitates were filtered and dried respectively to give each sample (the specific conditions were as listed in Table 5). Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Table 5

Amount of compound of Formula A / solvent	Solvent	Heating condition	Cooling temperature and stirring condition, time	Drying condition
10.26g/120mL	80% ethanol	reflux	Cooled to 0-5°C at 0.2°C min ⁻¹ , stirred for 12 hours	Dried at 55°C under vacuum for 5 hours
100mg/4.5mL	methanol	reflux	Cooled naturally to 20-25°C, stirred for 4 hours	Dried at 55°C under vacuum for 2 hours
1.01g/21mL	95% i-propanol	80-85°C	Cooled to 20-25°C, stirred for 18 hours; further cooled to 0-5°C, stirred for 6 hours	Dried at 55°C under vacuum for 17 hours
0.4g/6.2mL	90% i-propanol	75-85°C	Cooled to 0-5°C, stirred for 2 hours	Dried at 55°C under vacuum for 17 hours
0.5g/6.2mL	80% i-propanol	75-85°C	Cooled to 0-5°C, stirred for 2 hours	Dried at 55°C under vacuum for 17 hours
1.02g/11.5mL	70% i-propanol	80-85°C	Cooled to 20-25°C, stirred for 18 hours; further cooled to 0-5°C, stirred for 6 hours	Dried at 55°C under vacuum for 17 hours
0.71g/6mL	90% n-butanol	90-100°C	Cooled to 0-5°C, stirred for 2 hours	Dried at 55°C under vacuum for 17 hours

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Example 20 Preparation of Form IV of compound of Formula A

100mg of compound of Formula A was dissolved in a mixed solvent of methanol/water

(8.0mL/1.5mL) at 60-65°C, and kept at 60-65°C for 30 minutes. Then the solution was cooled to 20-25°C, and only a small amount of solid precipitated. Then 7mL of water was added to the mixture and stirring continued for 17 hours. Then the precipitate was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 21 Preparation of Form IV of compound of Formula A

0.99g of compound of Formula A was dissolved in 24mL of 95% ethanol at 75-85°C, 40mL of water was added, and the mixture was kept at 75-85°C for 30 minutes. Then the mixture was cooled to 20-25°C, and another 10mL of water was added and stirred for 1 hour. Then the mixture was further cooled to 0-5°C and stirred for 2 hours. Then the precipitate was filtered and dried at 55°C under vacuum for 1.5 hours to give 0.80g of sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 22 Preparation of Form IV of compound of Formula A

6.05g of compound of Formula A was dissolved in 90mL of 80% ethanol under heating to reflux. The solution was cooled to 70°C at a cooling rate of 0.5°C/min, and no solid precipitated; 90mL of water was added to the solution slowly within 80 minutes, and a large amount of solid precipitated. The mixture was stirred at 70°C for 100 minutes; cooled to 60°C at a cooling rate of 0.5°C/min and stirred for 2 hours; then the mixture was cooled to 50°C at a cooling rate of 0.5°C/min and stirred for 2 hours; and then the mixture was cooled to 0°C at a cooling rate of 0.2°C/min and stirred for 5.5 hours. Then the mixture was stirred at 0-5°C for further 5 hours. Then the precipitate was filtered, dried at room temperature for 3 days, and further dried at 55°C under vacuum for 2 hours to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 23 Preparation of Form IV of compound of Formula A

5.04g of compound of Formula A was dissolved in 65mL of 70% i-propanol under heating to reflux. 90mL of water was added to the solution quickly. Then the solution was cooled to 20-25°C at a rate of 2°C/min, and stirred for 5 hours. Then the precipitate was filtered and dried at 55°C under vacuum for 16 hours to give 4.96g of sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 24 Preparation of Form IV of compound of Formula A

190mg of compound of Formula A was dissolved in 3.3mL of a mixed solvent (1,4-dioxane/ethanol, volume ratio 1/5) at 80-85°C. 6mL of water was added to the solution, cooled to 20-25°C, and stirred for 18 hours. Then the precipitate was filtered and dried at 55°C under vacuum for 4 hours to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 25 Preparation of Form IV of compound of Formula A

4g of compound of Formula A were dissolved in 60mL of mixed solvents (tetrahydrofuran/ethanol/water, volume ratios were 1/99/25, 5/95/25, and 10/90/25 respectively) at 80-85°C respectively, and stirred at 80-85°C for 30 minutes. Then the solutions were cooled to 60°C at a rate of 0.5°C/min respectively, and stirred at 60°C for 1.5 hours. 60mL of water were added dropwise (adding time was 1 hour) to the solutions respectively. The mixture was stirred at 60°C for 1 hour after the addition of water; cooled to 25°C at a rate of 0.5°C/min respectively, and stirred for 17.5 hours; cooled to 0°C at a rate of 0.5°C/min respectively, and stirred for 2 hours. Then the solids were filtered respectively, washed with 5mL of 40% ethanol, and dried at 55°C under vacuum for 18 hours to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 26 Preparation of Form IV of compound of Formula A

120mg of solid of compound of Formula A (Form I) was slurried with 4mL of water at 75-85°C for 1 hour. Then the suspension was cooled to 20-25°C and stirred for 3 hours. 0.8 mL of ethanol was added to the mixture and stirring continued for 16 hours. Then the solid was filtered to give the product. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 27 Preparation of Form IV of compound of Formula A

An appropriate amount of the solvents listed in Table 6 were placed in flasks at 20-25°C respectively, and the solids of compound of Formula A (a mixture of Form IV and Form V) were added till excess solids were present in the solutions. Then the mixtures were heated to the temperatures listed in Table 6 respectively, and the solids of compound of Formula A (a mixture of Form IV and Form V) were added till excess solids were present in each system. Then the

mixtures were stirred under the temperatures listed in Table 6 for 2 hours, cooled to 20-25°C, and allowed to stand for 18 hours respectively. Then the solids were filtered respectively to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form IV of compound of Formula A obtained in Example 15.

5 Table 6

Solvent	Temperature
methanol	60-70°C
10% methanol	60-70°C
ethanol	70-80°C
i-propanol	75-85°C

Example 28 Preparation of Form IV of compound of Formula A

An appropriate amount of the solids of compound of Formula A (the forms were as listed in Table 7) were suspended in an appropriate amount of water respectively. Then the suspensions were stirred under certain temperatures for a period of time, and filtered respectively to give each solid sample (the specific conditions were as listed in Table 7). Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Table 7

Amount of the solid of compound of Formula A / water	Form of compound of Formula A	Temperature	Stirring time
40mg/2mL	Form VI	20-25°C	4 days
30mg/1mL	Form I	25-30°C	8 days
30mg/1mL	Form IV	25-30°C	8 days
30mg/1mL	Form V	25-30°C	8 days
200mg/5mL	Form VIII	20-25°C	1 day

Example 29 Preparation of Form IV of compound of Formula A

An appropriate amount of the solid of compound of Formula A (Form VI) was heated at 120°C under vacuum for 3 hours to give the sample. Alternatively, an appropriate amount of the solid of compound of Formula A (Form VI) was dried under vacuum firstly at 50°C for 0.5 hour, then at 55°C for 4 hours, and finally at 120°C for 0.5 hour to give the sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form IV of compound of Formula A obtained in Example 15.

Example 30 Preparation of Form V of compound of Formula A

0.83g of compound of Formula A was suspended in 85mL of acetonitrile, and heated to

70-80°C to dissolve. Then the solution was cooled to 20-25°C and stirred for 17 hours at a moderate rate. Then the precipitate was filtered and dried at 60°C under vacuum for 1 hour to give 0.62g of solid.

The obtained powder sample is Form V of compound of Formula A, the X-ray powder
5 diffractogram of which is shown in Figure 7. Peaks (2θ) chosen from the figure have the following values: 4.6, 7.3, 8.9, 10.0, 11.2, 11.6, 13.5, 14.6, 15.5, 16.0, 17.7, 18.0, 19.3, 20.0, 22.7, 23.4, 24.0, 25.1, 26.0, 27.2, 28.4, and 29.7 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ), wherein characteristic peaks (2θ) are at 7.3, 11.6, 14.6, 19.3, and 23.4 degrees. DSC result is given in Figure 8, showing that the endothermic peak of Form V is at
10 about 261.4-262.4°C.

Example 31 Preparation of Form V of compound of Formula A

700mg of compound of Formula A was suspended in a mixed solvent of acetonitrile/acetic acid (20mL/1.4mL), and heated to 75-80°C to dissolve. Then the solution was cooled to 20-25°C
15 and stirred for 1 hour at a moderate rate. Then the precipitate was filtered and dried at 55°C under vacuum for 1 hour to give 300mg of solid. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form V of compound of Formula A obtained in Example 30.

Example 32 Preparation of Form V of compound of Formula A

1g of compound of Formula A was suspended in 50mL of 90% acetonitrile, and heated to 70-80°C to dissolve. Then the solution was cooled to 20-25°C and stirred for 15 hours at a moderate rate; then further cooled to -10 - -5°C and stirred for 3 hours at a moderate rate. Then the precipitate was filtered and dried at 60°C under vacuum for 16 hours to give 0.72g of solid.
25 Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form V of compound of Formula A obtained in Example 30.

Example 33 Preparation of Form V of compound of Formula A

An appropriate amount of compound of Formula A were suspended in an appropriate
30 amount of the solvents listed in Table 8 respectively. The suspensions were heated to the temperatures listed in Table 8 to dissolve. Then the solutions were cooled to 20-25°C and stirred for a period of time at a moderate rate. Then the precipitates were filtered respectively to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form V of compound of Formula A obtained in Example 30.

Table 8

Amount of compound of Formula A / solvent	Solvent	Heating temperature	Stirring time
80mg/2.36mL	acetonitrile/acetic acid (volume ratio 55/4)	75-80°C	18 hours
80mg/3.2mL	acetone/ethanol (volume ratio 1/4)	55-60°C	17 hours
90mg/6mL	ethyl acetate/acetonitrile (volume ratio 3/7)	70-80°C	17 hours
110mg/6mL	butanone/acetonitrile (volume ratio 1/1)	70-80°C	17 hours
90mg/3.8mL	tetrahydrofuran/acetonitrile (volume ratio 3/7)	60-70°C	17 hours

Example 34 Preparation of Form V of compound of Formula A

The solid of compound of Formula A (a mixture of Form IV and Form V) was suspended in an appropriate amount of acetonitrile, and heated to reflux. Then the solids of compound of Formula A (a mixture of Form IV and Form V) were added till excess solids were present in the system. The obtained suspension was stirred under reflux for 2 hours, cooled to 20-25°C, and allowed to stand for 18 hours. Then the solid was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form V of compound of Formula A obtained in Example 30.

Example 35 Preparation of Form V of compound of Formula A

160mg of sample of Form I of compound of Formula A and 180mg of sample of Form IV of compound of Formula A were mixed with 8mL of acetonitrile respectively, stirred at 70-80°C for 4 hours, and then cooled to 22-28°C and stirred for 7 days. Another 3mL of acetonitrile was added to each mixture respectively. The mixtures were reheated to 70-80°C and stirred for 4 hours; then cooled to 22-28°C and stirred for 16 hours. Then the solids were filtered respectively and dried at 50°C under vacuum for 30 minutes to give each sample. Upon measurement, the X-ray powder diffractogram of each of the obtained samples is consistent with that of Form V of compound of Formula A obtained in Example 30.

Example 36 Preparation of Form VI of compound of Formula A

3g of compound of Formula A was suspended in 130mL of acetone, and heated to 55-60°C to dissolve. Then the solution was cooled to 25-30°C and stirring continued for about 18 hours. Then the precipitate was filtered and dried in the air for 30 minutes to give 2.15g of product. The content of acetone (gas chromatography, GC): 10.86%.

The obtained powder sample is Form VI of compound of Formula A, the X-ray powder diffractogram of which is shown in Figure 10. Peaks (2 θ) chosen from the figure have the

following values: 6.9, 8.6, 9.0, 9.8, 10.4, 12.0, 13.4, 15.0, 15.8, 16.2, 16.8, 17.3, 18.0, 18.2, 18.9, 19.4, 19.7, 20.6, 21.0, 21.6, 22.5, 23.0, 23.3, 23.8, 24.5, 25.0, 26.2, and 29.8 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ), wherein characteristic peaks (2θ) are at 8.6, 10.4, 12.0, 15.0, and 19.7 degrees. DSC result is given in Figure 11, showing that the endothermic peaks of Form VI are at about 97.3-106.0°C and about 262.3-265.0°C.

Example 37 Preparation of Form VI of compound of Formula A

Compound of Formula A was dissolved in 2.5mL of 95% acetone to saturation at 40-45°C, and filtered while hot to remove the insoluble materials. Then the filtrate was cooled to 20-25°C and stirring continued for 2 hours. Then the precipitate was filtered to give the product. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form VI of compound of Formula A obtained in Example 36.

Example 38 Preparation of Form VI of compound of Formula A

80mg of compound of Formula A was suspended in 3.7mL of acetone, heated to 50-60°C to dissolve, and stirred for 30 minutes. Then the mixture was filtered. Then the solution was cooled to 0-5°C quickly with ice-bath and was stirred for further 1 hour. Then the precipitate was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form VI of compound of Formula A obtained in Example 36.

Example 39 Preparation of Form VI of compound of Formula A

80mg of compound of Formula A was suspended in 8mL of a mixed solvent of acetone/i-propanol (volume ratio 7/3), and heated to 50-60°C to dissolve. Then heating was stopped, and the solution was cooled naturally to 20-25°C. Then the precipitate was filtered to give the sample. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form VI of compound of Formula A obtained in Example 36.

Example 40 Preparation of Form VI of compound of Formula A

700mg of compound of Formula A was suspended in 20mL of a mixed solvent of acetone/water (volume ratio 3/1), heated to 50-60°C to dissolve, and filtered while hot. Then the filtrate was cooled to 20-25°C and was stirred for further 1 hour; further cooled to 0-5°C and stirred for 30 minutes. Then a small amount of sample was filtered to give the first batch of sample. Then 30mL of water was added to the rest mixture and stirring continued at 20-25°C for 17 hours. Then the precipitate was filtered to give the second batch of sample. Upon

measurement, the X-ray powder diffractograms of the obtained two batches of samples are consistent with that of Form VI of compound of Formula A obtained in Example 36.

Example 41 Preparation of Form VI of compound of Formula A

70mg of the solid of compound of Formula A (a mixture of Form I and Form V) was suspended in 0.9mL of a mixed solvent of acetone/water (volume ratio 3/1), stirred at 25-30°C for 6 days, and filtered to give the solid. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form VI of compound of Formula A obtained in Example 36.

Example 42 Preparation of Form VIII of compound of Formula A

10.2g of compound of Formula A was mixed with 130mL of 70% i-propanol, heated to reflux to dissolve, and stirred at 75-80°C for 30 minutes. Then the solution was cooled to 45-55°C and stirred for further 2 hours; further cooled to 23-30°C and stirred for about 6 days. Then the precipitate was filtered and dried in the air for 100 minutes to give the product. The content of water (KF): 10.8%; the content of i-propanol (gas chromatography, GC): 6.8%.

The obtained powder sample is Form VIII of compound of Formula A, the X-ray powder diffractogram of which is shown in Figure 13. Peaks (2θ) chosen from the figure have the following values: 7.0, 8.3, 9.8, 10.7, 11.4, 13.3, 13.8, 14.2, 15.3, 15.7, 17.7, 19.0, 19.4, 19.6, 20.3, 21.4, 22.4, 23.1, 23.5, 24.0, 25.0, 25.4, 26.9, and 27.2 degrees, the measured 2θ values each having an error of about ± 0.2 degrees (2θ), wherein characteristic peaks (2θ) are at 7.0, 8.3, 11.4, 15.3, and 23.1 degrees. DSC result is given in Figure 14, showing that the endothermic peaks of Form VIII are at about 64.1-81.7°C and about 261.5-262.2°C.

Example 43 Preparation of Form VIII of compound of Formula A

3.9g of the sample of Form IV of compound of Formula A was suspended in 50mL of 70% i-propanol, and stirred at room temperature for 3 days to give the first batch of sample for testing. The suspension was stirred for further 3 days. 10mL of 70% i-propanol was added to the suspension and stirring continued for 2 days. Then the solid was collected by filtration, and dried at room temperature in the air for 50 minutes to give the second batch of sample. Upon measurement, the X-ray powder diffractograms of the obtained two batches of samples are consistent with that of Form VIII of compound of Formula A obtained in Example 42.

Example 44 Preparation of Form VIII of compound of Formula A

200mg of the sample of Form IV of compound of Formula A was suspended in 4mL of

90% i-propanol. The mixture was stirred at 20-25°C for 4 days, and filtered to give the solid. Upon measurement, the X-ray powder diffractogram of the obtained sample is consistent with that of Form VIII of compound of Formula A obtained in Example 42.

5 **Example 45 Stability of Form I, Form IV, and Form V under high temperature, high humidity and illumination conditions**

Determination method: the test samples of Form I, Form IV, and Form V of compound of Formula A were placed on the culture dishes respectively, which were uncovered and placed in sealed clean containers. The containers were placed under the conditions of a temperature of 60°C, a temperature of 25°C and a relative humidity of 92.5%±5%, and an illumination of 4500lx±500lx respectively for 10 days. Then sampled, investigated for the purity and crystalline form of the samples, and compared the investigation results. The results were shown in Table 9.

Table 9

Test condition		High temperature (60°C)		High humidity (92.5%RH)		Illumination (4500Lx)	
Sampling time	0 day	5 days	10 days	5 days	10 days	5 days	10 days
Form	I	I	I	I	I	I	I
Chemical purity (%)	99.76	99.63	99.63	99.65	99.60	99.61	99.45
Form	IV	IV	IV	IV	IV	IV	IV
Chemical purity (%)	99.27	99.57	99.68	99.68	99.68	99.59	99.55
Form	V	V	V	V	V	V	V
Chemical purity (%)	99.70	99.88	99.87	99.88	99.87	99.85	99.81

15 Conclusion: the data in Table 9 illustrate that, the chemical purity and crystalline form of Form I, Form IV, and Form V of compound of Formula A are not changed after placed under high temperature, high humidity, and illumination conditions for 10 days, showing that Form I, Form IV, and Form V are stable.

20 **Example 46 Stability of Form IV mixed with excipients**

Determination method: 50mg of samples of Form IV of compound of Formula A were mixed with 200mg of excipients starch and microcrystalline cellulose respectively. The mixtures were used as test samples and placed on the culture dishes respectively, which were uncovered and placed in sealed clean containers. Then the containers were placed under the conditions of a temperature of 60°C, a temperature of 25°C and a relative humidity of 92.5%±5%, and an

illumination of 4500lx±500lx respectively for 30 days. Then sampled, investigated for the change of crystalline form of the samples, and compared the investigation results. The results were shown in Table 10.

Table 10

Test material	Test time	Test condition	Test result
Form			Form IV
Mixture of starch	0 day		Form IV
	30 days	High temperature (60°C)	Form IV
		High humidity (92.5%RH)	Form IV
		illumination (4500Lx)	Form IV
Mixture of microcrystalline cellulose	0 day		Form IV
	30 days	High temperature (60°C)	Form IV
		High humidity (92.5%RH)	Form IV
		illumination (4500Lx)	Form IV

5

Conclusion: the data in Table 10 illustrate that, the mixtures of Form IV of compound of Formula A with starch or microcrystalline cellulose are stable under high temperature, high humidity, and illumination conditions, indicating that Form IV is stable under the test conditions.

10 Example 47 Solubility of Form I, Form IV, and Form V in different buffers

Determination method: excess amount of samples of Form I, Form IV, and Form V of compound of Formula A were suspended in the buffers of different pH respectively. The system was saturated by shaking for a period of time at 37°C in a water bath of constant temperature. Then the system was filtered, and the filtrate was used for determining solubility of the samples.

15 The solubility of each Form was shown in Table 11. The buffers of different pH were prepared according to the US pharmacopeia (USP40-NF35).

Table 11

pH value of buffer	Solubility (mg/mL)		
	Form I*	Form IV**	Form V**
pH 1.2	10.78	8.56	9.64
pH 2.1	0.8	0.5	0.58
pH 4.5	0.04	0.02	0.02
pH 6.8	0.03	0.02	0.02

*: shaken at 37°C water bath for 0.5 hour, **: shaken at 37°C water bath for 2 hours.

20 Conclusion: the data in Table 11 illustrate that, in the test buffers, Form I, Form IV, and Form V of compound of Formula A all have good solubility.

Example 48 Hygroscopicity of Form I, Form IV, and Form V

Determination method: the test samples of Form I, Form IV, and Form V of compound of Formula A were placed in the sample dishes of the dynamic vapor sorption instrument (DVS-INTRINSIC) respectively. Then the weight gains by moisture absorption of the samples
5 were measured at a relative humidity of 0-95% at 25°C. The results were shown in Figure 16, Figure 17, and Figure 18.

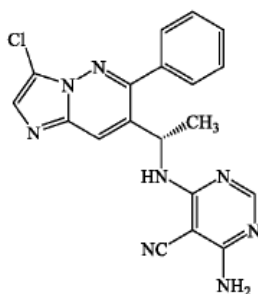
Conclusion: the curves in Figure 16, Figure 17, and Figure 18 illustrate that, Form I, Form IV, and Form V of compound of Formula A all are non-hygroscopic.

10 It is to be understood that, the examples and embodiments described herein are only for interpretation purposes, and various improvements or modifications in view of these would be suggested to those skilled in the art and are within the spirit and scope of present application and the scope of the appended claims. All the publications, patents and patent applications cited herein are incorporated herein by reference for all purposes.

15

What is claimed:

1. A crystalline form of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A:



Formula A

wherein the crystalline form is Form IV; and
wherein crystalline Form IV is characterized by an X-ray powder diffractogram comprising characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $4.6^{\circ} \pm 0.2^{\circ}2\theta$, $9.2^{\circ} \pm 0.2^{\circ}2\theta$, $15.5^{\circ} \pm 0.2^{\circ}2\theta$, $17.8^{\circ} \pm 0.2^{\circ}2\theta$, and $19.0^{\circ} \pm 0.2^{\circ}2\theta$.

2. The crystalline form of claim 1, wherein the crystalline form is further characterized by an X-ray powder diffractogram comprising additional characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $11.5^{\circ} \pm 0.2^{\circ}2\theta$, $12.0^{\circ} \pm 0.2^{\circ}2\theta$, $13.2^{\circ} \pm 0.2^{\circ}2\theta$, $16.0^{\circ} \pm 0.2^{\circ}2\theta$, and $22.6^{\circ} \pm 0.2^{\circ}2\theta$.

3. The crystalline form of claim 1, wherein the crystalline form has less than 40% by weight of other crystalline forms of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile.

4. The crystalline form of claim 3, wherein the crystalline form has less than 30% by weight of other crystalline forms of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile.

5. The crystalline form of claim 3, wherein the crystalline form has less than 20% by weight of other crystalline forms of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile.

6. The crystalline form of claim 3, wherein the crystalline form has less than 10% by weight of other crystalline forms of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile.

7. The crystalline form of claim 3, wherein the crystalline form has less than 5% by weight of other crystalline forms of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-

yl)ethyl)amino)pyrimidine-5-carbonitrile.

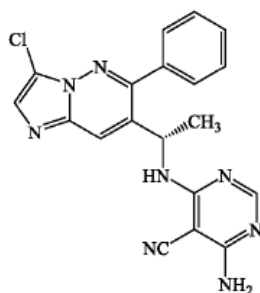
8. The crystalline form of claim 3, wherein the crystalline form has less than 1% by weight of other crystalline forms of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile.

9. A pharmaceutical composition, comprising an effective amount of the crystalline form of any one of claims 1-8, and one or more pharmaceutically acceptable carriers.

10. Use of the crystalline form of any one of claims 1-8 in the manufacture of a medicament for treating diseases associated with PI₃K activity, such as autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy), wherein, for example, said autoimmune diseases, inflammatory diseases, and cancer are selected from systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease, psoriasis, asthma, lymphoma (such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, mantle cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Burkitt lymphoma, B cell lymphoma, T cell lymphoma, NK cell lymphoma, and diffuse large B-cell lymphoma), leukemia (such as chronic lymphocytic leukemia, acute lymphocytic leukemia, acute myeloid leukemia, and chronic myelogenous leukemia), multiple myeloma, and Waldenstrom's macroglobulinemia.

11. The crystalline form of any one of claims 1-8 for use in the treatment of diseases associated with PI₃K activity, such as autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy), wherein, for example, said autoimmune diseases, inflammatory diseases, and cancer are selected from systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic rhinitis, chronic obstructive pulmonary disease, psoriasis, asthma, lymphoma (such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, mantle cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, Burkitt lymphoma, B cell lymphoma, T cell lymphoma, NK cell lymphoma, and diffuse large B-cell lymphoma), leukemia (such as chronic lymphocytic leukemia, acute lymphocytic leukemia, acute myeloid leukemia, and chronic myelogenous leukemia), multiple myeloma, and Waldenstrom's macroglobulinemia.

12. A process for preparing the crystalline form of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A of claim 1:



Formula A

wherein the crystalline form is Form IV; and

wherein crystalline Form IV is characterized by an X-ray powder diffractogram comprising characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $4.6^{\circ} \pm 0.2^{\circ}2\theta$, $9.2^{\circ} \pm 0.2^{\circ}2\theta$, $15.5^{\circ} \pm 0.2^{\circ}2\theta$, $17.8^{\circ} \pm 0.2^{\circ}2\theta$, and $19.0^{\circ} \pm 0.2^{\circ}2\theta$;

wherein the process comprises the following steps:

(1) mixing (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with:

- (a) at least one dissolution solvent selected from the group consisting of (i) methanol, ethanol, isopropanol, or *n*-butanol, (ii) a mixture of acetic acid and isopropanol, and (iii) a mixture of acetic acid and methanol; or
- (b) a mixed solvent consisting of water and a water-miscible organic solvent selected from the group consisting of methanol, ethanol, isopropanol, and *n*-butanol;

and heating the mixture to reflux to obtain a solution;

(2) cooling the solution obtained in step (1) above until (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile precipitates;

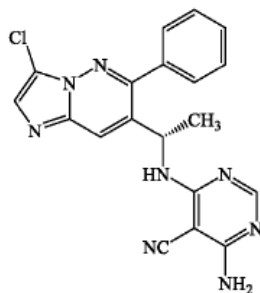
(3) isolating Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A; and

(4) optionally drying Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A obtained in step (3) above.

13. The process of claim 12, wherein the crystalline form is further characterized by an X-ray powder diffractogram comprising additional characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $11.5^{\circ} \pm 0.2^{\circ}2\theta$, $12.0^{\circ} \pm 0.2^{\circ}2\theta$, $13.2^{\circ} \pm 0.2^{\circ}2\theta$, $16.0^{\circ} \pm 0.2^{\circ}2\theta$, and $22.6^{\circ} \pm 0.2^{\circ}2\theta$.

14. A process for preparing the crystalline form of (S)-4-amino-6-((1-(3-chloro-6-

phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A of claim 1:



Formula A

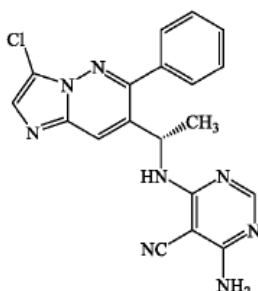
wherein the crystalline form is Form IV; and

wherein crystalline Form IV is characterized by an X-ray powder diffractogram comprising characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $4.6^{\circ} \pm 0.2^{\circ}2\theta$, $9.2^{\circ} \pm 0.2^{\circ}2\theta$, $15.5^{\circ} \pm 0.2^{\circ}2\theta$, $17.8^{\circ} \pm 0.2^{\circ}2\theta$, and $19.0^{\circ} \pm 0.2^{\circ}2\theta$;

wherein the process comprises the following steps:

- (1) mixing (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with:
 - (a) at least one dissolution solvent selected from the group consisting of (i) methanol, (ii) ethanol, (iii) isopropanol, and (iv) a mixture of ethanol and 1,4-dioxane; or
 - (b) a mixed solvent consisting of water and a water-miscible organic solvent selected from the group consisting of (i) methanol, ethanol, or isopropanol, and (ii) a mixture of ethanol and tetrahydrofuran;
 and heating the mixture to reflux to obtain a first solution;
- (2) adding water to the first solution obtained in step (1) above, to obtain a second solution;
- (3) cooling the second solution obtained in step (2) above until (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A precipitates;
- (4) isolating Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A; and
- (5) optionally drying Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A obtained in step (4) above.

15. A process for preparing the crystalline form of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A of claim 1:



Formula A

wherein the crystalline form is Form IV; and

wherein crystalline Form IV is characterized by an X-ray powder diffractogram comprising characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $4.6^{\circ} \pm 0.2^{\circ}2\theta$, $9.2^{\circ} \pm 0.2^{\circ}2\theta$, $15.5^{\circ} \pm 0.2^{\circ}2\theta$, $17.8^{\circ} \pm 0.2^{\circ}2\theta$, and $19.0^{\circ} \pm 0.2^{\circ}2\theta$;

wherein the process comprises the following steps:

(1) mixing (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile with:

(a) at least one dissolution solvent selected from the group consisting of (i) methanol, (ii) ethanol, (iii) isopropanol, and (iv) a mixture of ethanol and 1,4-dioxane; or

(b) a mixed solvent consisting of water and a water-miscible organic solvent selected from the group consisting of (i) methanol, ethanol, or isopropanol, and (ii) a mixture of ethanol and tetrahydrofuran;

and heating the mixture to reflux to obtain a first solution;

(2) cooling the first solution obtained in step (1) above, to obtain a second solution;

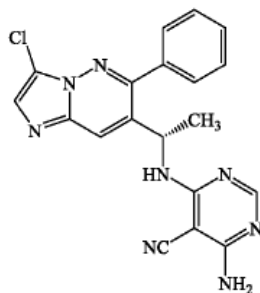
(3) adding water to the second solution obtained in step (2) above until (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A precipitates;

(4) isolating Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A; and

(5) optionally drying Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A obtained in step (4) above.

16. A process for preparing the crystalline form of (S)-4-amino-6-((1-(3-chloro-6-

phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A of claim 1:



Formula A

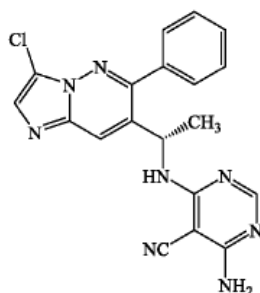
wherein the crystalline form is Form IV; and

wherein crystalline Form IV is characterized by an X-ray powder diffractogram comprising characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $4.6^{\circ} \pm 0.2^{\circ}2\theta$, $9.2^{\circ} \pm 0.2^{\circ}2\theta$, $15.5^{\circ} \pm 0.2^{\circ}2\theta$, $17.8^{\circ} \pm 0.2^{\circ}2\theta$, and $19.0^{\circ} \pm 0.2^{\circ}2\theta$;

wherein the process comprises the following steps:

- (1) suspending (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile in a solvent selected from the group consisting of (i) methanol, (ii) isopropanol, (iii) water, and (iv) a mixture of methanol and water;
- (2) stirring the suspension obtained in step (1) above;
- (3) isolating Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A; and
- (4) optionally drying Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A obtained in step (3) above.

17. A process for preparing the crystalline form of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A of claim 1:



Formula A

wherein the crystalline form is Form IV; and

wherein crystalline Form IV is characterized by an X-ray powder diffractogram comprising characteristic peaks at diffraction angles ($^{\circ}2\theta$) of $4.6^{\circ} \pm 0.2^{\circ}2\theta$, $9.2^{\circ} \pm 0.2^{\circ}2\theta$, $15.5^{\circ} \pm 0.2^{\circ}2\theta$, $17.8^{\circ} \pm 0.2^{\circ}2\theta$, and $19.0^{\circ} \pm 0.2^{\circ}2\theta$;

wherein the process comprises the following steps:

- (1) suspending (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile in ethanol;
- (2) stirring the suspension obtained in step (1) above for less than 24 hours;
- (3) isolating Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A; and
- (4) optionally drying Form IV of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile of the Formula A obtained in step (3) above.