

What is claimed:

1. Crystalline form of (S)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile, wherein said form is Form I, the X-ray powder diffractogram of Form I comprising the following diffraction angles (2 θ): 6.8, 10.0, 16.5, 20.1, and 22.6 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ);
or said form is Form IV, the X-ray powder diffractogram of Form IV comprising the following diffraction angles (2 θ): 4.6, 9.2, 15.5, 17.8, and 19.0 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ);
or said form is Form V, the X-ray powder diffractogram of Form V comprising the following diffraction angles (2 θ): 7.3, 11.6, 14.6, 19.3, and 23.4 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ).
2. The form of claim 1, wherein said form is Form I, the X-ray powder diffractogram of Form I comprising the following diffraction angles (2 θ): 6.8, 10.0, 13.7, 14.4, 15.3, 16.5, 20.1, 21.3, and 22.6 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ).
3. The form of claim 1, wherein said form is Form IV, the X-ray powder diffractogram of Form IV comprising the following diffraction angles (2 θ): 4.6, 9.2, 11.5, 12.0, 13.2, 15.5, 16.0, 17.8, 19.0, and 22.6 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ).
4. The form of claim 1, wherein said form is Form V, the X-ray powder diffractogram of Form V comprising the following diffraction angles (2 θ): 4.6, 7.3, 8.9, 11.6, 13.5, 14.6, 15.5, 18.0, 19.3, and 23.4 degrees, the measured 2 θ values each having an error of about ± 0.2 degrees (2 θ).
5. The form of any one of claims 1-4, wherein the content 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 is less than 40%, preferably less than 30%, preferably less than 20%, preferably less than 10%, preferably less than 5%, or preferably less than 1%, by weight.
6. A pharmaceutical composition, comprising an effective amount of one or more of the forms of any one of claims 1-5, and the pharmaceutically acceptable carriers.
7. Use of the forms of any one of claims 1-5 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.

5 8. A method of treating diseases associated with PI₃K activity, such as autoimmune diseases, inflammatory diseases, and cancer (preferably hematological malignancy), comprising administering to a subject in need thereof an effective amount of the forms of any one of claims 1-5, wherein, for example, said autoimmune diseases, inflammatory diseases, and cancer are selected from systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, allergic
10 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
15 myelogenous leukemia), multiple myeloma, and Waldenstrom's macroglobulinemia.

9. The forms of any one of claims 1-5 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,
20 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,
25 acute myeloid leukemia, and chronic myelogenous leukemia), multiple myeloma, and Waldenstrom's macroglobulinemia.

10. A method of preparing the form of claim 1 or 2, said form being Form I, 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 (such
30 as 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), and heating the mixture to reflux to obtain a solution;

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

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

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

or alternatively,

(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 (such as ethyl acetate, 1,4-dioxane, ethanol, or tetrahydrofuran) or with a mixed solvent consisting of tetrahydrofuran and water, and heating the mixture to reflux to obtain the first solution;

(2) adding at least one anti-dissolution solvent (such as water; isopropyl ether; or C₅₋₈ straight or branched alkane, e.g. n-heptane) 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 (such as water; isopropyl ether; or C₅₋₈ straight or branched alkane, e.g. n-heptane) until the solid precipitates; provided that, when said dissolution solvent in step (1) is ethanol, the 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);

or alternatively,

(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 (such as a single crystalline form, e.g. Form IV or Form V; or a mixture of two or more of crystalline forms) in a solvent (such as ethyl acetate, toluene, tetrahydrofuran, or 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;

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

11. A method of preparing the form of claim 1 or 3, said form being Form IV, 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 (such as C₁₋₆ alkanol, e.g. methanol, ethanol, i-propanol, and n-butanol; a mixture of i-propanol and acetic acid; or a mixture of methanol and acetic acid) or with a mixed solvent consisting of water-miscible organic solvent (such as C₁₋₆ alkanol, e.g. methanol, ethanol, i-propanol, and n-butanol) and water, and heating the mixture to reflux to obtain a solution;

(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);

or alternatively,

(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 (such as methanol, ethanol, i-propanol, or a mixture of 1,4-dioxane and ethanol) or with a mixed solvent consisting of water-miscible organic solvent (such as C₁₋₆ alkanol, e.g. methanol, ethanol, and
5 i-propanol; or a mixture of tetrahydrofuran and ethanol) and water, and heating the mixture to reflux to obtain the first solution;

(2) adding at least one anti-dissolution solvent (such as water) 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
10 solvent (such as water) 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);

or alternatively,

(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 (such as a single crystalline form, e.g.
15 Form I, Form IV, Form V, Form VI, or Form VIII; or a mixture of two or more of crystalline forms) in a solvent (such as methanol, ethanol, i-propanol, water, or a mixture of methanol and water);

(2) stirring the suspension obtained in step (1), provided that, when said solvent in step (1)
20 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).

12. A method of preparing the form of claim 1 or 4, said form being Form V, 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 (such as 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) or with a mixed solvent consisting of acetonitrile and water, and heating
30 the mixture to reflux to obtain a solution;

(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);

or alternatively,

(1) suspending the solid of compound (*S*)-4-amino-6-((1-(3-chloro-6-phenylimidazo[1,2-*b*]
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pyridazin-7-yl)ethyl)amino)pyrimidine-5-carbonitrile (such as a single crystalline form, e.g. Form I, Form IV, or Form V; or a mixture of two or more of crystalline forms) in acetonitrile;

- (2) stirring the suspension obtained in step (1);
- (3) isolating to obtain the solid Form V of compound of Formula A;
- 5 (4) optionally drying the solid obtained in step (3).