

The ability of a compound to exist in at least one crystal structure or solid state form is known as polymorphism. Many compounds may exist as polymorph crystals and those compounds may also exist in a solid amorphous state. Until polymorphism of a compound is discovered, it is highly unpredictable (1) whether a particular compound will exhibit polymorphism, (2) how to make any such unknown polymorphs, and (3) what the properties, such as stability, will be of any such unknown polymorphs. See, e.g., J. Bernstein "Polymorphism in Molecular Crystals", Oxford University Press, (2002).

Because the properties of any solid material depend on the structure as well as on the nature of the compound itself, different solid state forms of a compound can and often do exhibit different physical and chemical properties. Differences in chemical properties can be determined through a variety of analytical techniques to be used to characterize, analyze, and compare. And those differences in chemical properties may ultimately be used to differentiate among different solid state forms that may be discovered to exist. Furthermore, differences in physical properties, such as solubility and bioavailability, of solid state forms can be important when formulating a pharmaceutical compound. As such, novel crystalline and amorphous solid state forms of pharmaceutical compounds, such as the compound of Formula A, can be important in the development of such compounds.

The compound 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide was first described in patent WO 2009/137797 A2, and the methods of preparation thereof were also described therein.

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

Summary of the Invention

After a lot of exploration and research, we have found that the compound of Formula A (6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide) can exist in different crystalline forms, and can form solvates with certain solvents. The existence of various polymorphic forms of the compound of Formula A was explored in order to determine and prepare the most appropriate form of the compound for the pharmaceutical use. Based on these studies, the present invention provides the compound of Formula A in new crystalline forms, solvates and the

CLAIMS

What is claimed is:

1. Form I of 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide.
2. The Form I according to claim 1, wherein the X-ray powder diffractogram of the Form I has characteristic peaks expressed in degrees 2-theta at: 5.3, 10.7, 13.9, and 14.6, each of the diffraction angles having an error of about ± 0.2 degrees (2θ).
3. The Form I according to claim 1, wherein the X-ray powder diffractogram of the Form I has characteristic peaks expressed in degrees 2-theta at: 5.3, 7.3, 10.7, 13.9, 14.6, and 19.9, each of the diffraction angles having an error of about ± 0.2 degrees (2θ).
4. The Form I according to claim 1, wherein the X-ray powder diffractogram of the Form I has characteristic peaks expressed in degrees 2-theta at: 5.3, 7.3, 10.7, 13.9, 14.6, 16.3, and 19.9, each of the diffraction angles having an error of about ± 0.2 degrees (2θ).
5. The Form I according to claim 1, wherein the X-ray powder diffractogram of the Form I has characteristic peaks expressed in degrees 2-theta at: 5.3, 7.3, 10.7, 13.9, 14.6, 16.3, 19.9, 21.1, 21.3, and 25.8, each of the diffraction angles having an error of about ± 0.2 degrees (2θ).
6. The Form I according to claim 1, wherein the X-ray powder diffractogram of the Form I has characteristic peaks expressed in degrees 2-theta at: 5.3, 7.3, 10.7, 13.9, 14.6, 15.2, 16.3, 19.9, 21.1, 21.3, 23.1, 23.3, and 25.8, each of the diffraction angles having an error of about ± 0.2 degrees (2θ).
7. The Form I according to claim 1, wherein the Form I has an X-ray powder diffractogram as shown in Figure 1.

8. A pharmaceutical composition, comprising an effective amount of the Form I according to any one of claims 1 to 7, and at least one pharmaceutically acceptable carrier.
9. Use of the Form I according to any one of claims 1 to 7 in the manufacture of a medicament for treating an angiogenesis-related disorder associated with KDR inhibition.
10. The use of claim 9, wherein the disorder is selected from the group consisting of cancer, age-related macular degeneration, and chronic inflammatory disease.
11. The Form I according to any one of claims 1 to 7 for use in the treatment of diseases associated with KDR inhibition.
12. The Form I of claim 11, wherein the diseases are angiogenesis-related disorders.
13. The Form I of claim 11, wherein the diseases are selected from the group consisting of cancer, age-related macular degeneration and chronic inflammatory disease.
14. A method of preparing the Form I according to any one of claims 1 to 7, comprising:
 - (1) mixing compound 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide with at least one dissolution solvent or dissolution solvent mixture, and heating the mixture to reflux to obtain a solution;
wherein, said at least one dissolution solvent is selected from the group consisting of methanol, C₃₋₆ alkanol, acetic acid, and aprotic solvent; said dissolution solvent mixture is selected from a mixture of two or more aprotic solvents, or a mixture of water miscible organic solvent and water, in which the volume percentage of the water miscible organic solvent in said dissolution solvent mixture is less than about 50%;
 - (2) cooling the solution obtained in step (1) to ambient temperature slowly; then
 - (3) isolating to obtain the solid of Form I of 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-

- N*,2-dimethylbenzofuran-3-carboxamide;
- (4) drying the solid obtained in step (3).
15. A method of preparing the Form I according to any one of claims 1 to 7, comprising:
- (1) mixing compound 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide with at least one dissolution solvent, then heating the mixture to reflux to obtain the first solution; wherein said dissolution solvent is selected from the group consisting of ethanol, isopropanol, acetone, dichloromethane, dimethyl sulfoxide, and *N,N*-dimethylformamide;
 - (2) adding at least one anti-dissolution solvent to said first solution to obtain the second solution;
 - (3) leaving said second solution to cool spontaneously slowly to ambient temperature; then
 - (4) isolating to obtain the solid of Form I of 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide;
 - (5) drying the solid obtained in step (4).
16. A method of preparing the Form I according to any one of claims 1 to 7, comprising:
- (1) suspending the solid of compound 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide in an appropriate amount of a solvent system; wherein, said solvent system is selected from a dissolution solvent, or a solvent mixture of water miscible organic solvent and water, in which volume percentage of water miscible organic solvent in the solvent mixture is less than about 80%;
 - (2) stirring the suspension obtained in step (1) for a period of time;
 - (3) isolating to obtain the solid of the Form I of 6-((6,7-dimethoxyquinazolin-4-yl)oxy)-*N*,2-dimethylbenzofuran-3-carboxamide;
 - (4) drying the solid obtained in step (3).
17. The method according to claim 16, wherein the dissolution solvent is acetone.