

DESCRIPTION

POLYMORPH FORMS OF ICOTINIB MALEATE AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to new polymorphic forms of Icotinib maleate, processes for
5 preparing these new polymorphic forms, pharmaceutical compositions thereof, and use of new
polymorphic forms and pharmaceutical compositions for the treatment of cancer and cancer
occurrence-related diseases.

BACKGROUND OF THE INVENTION

Tyrosine kinase receptors are trans-membrane proteins that, in response to an extracellular
10 stimulus, propagate a signaling cascade to control cell proliferation, angiogenesis, apoptosis and
other important features of cell growth. One class of such receptors, epidermal growth factor
receptor (EGFR) tyrosine kinases, are overly expressed in many human cancers, including brain,
lung, liver, bladder, breast, head and neck, esophagus, gastrointestinal, breast, ovary, cervix or
thyroid cancer.

15 EGFR is expressed in many types of tumor cells. Binding of cognate ligands (including
EGF, TGF α (i.e., Transforming Growth Factor- α) and neuregulins) to the extracellular domain
causes homo- or heterodimerization between family members. The juxtaposition of
cytoplasmic tyrosine kinase domains results in transphosphorylation of specific tyrosine, serine
and threonine residues within each cytoplasmic domain. The formed phosphotyrosines act as
20 docking sites for various adaptor molecules and subsequent activation of signal transduction
cascades (Ras/mitogen-activated, PI3K/Akt and Jak/STAT) that trigger proliferative cellular
responses.

Various molecular and cellular biology and clinical studies have demonstrated that EGFR
tyrosine kinase inhibitors can block cancer cell proliferation, metastasis and other EGFR-related
25 signal transduction responses to achieve clinical anti-tumor therapeutic effects. Two oral EGFR
kinase inhibitors with similar chemical structures are Gefitinib (Iressa, AstraZeneca), approved

by the U.S. FDA for advanced non-small cell lung cancer in 2003 (and later withdrawn), and Erlotinib Hydrochloride (Tarceva, Roche and OSI), approved by the U.S. FDA for advanced non-small cell lung cancer and pancreatic cancer treatment in 2004.

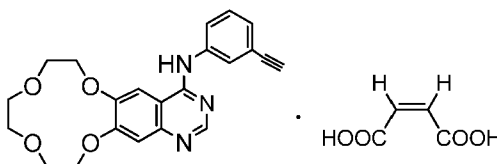
Many pharmaceutically active organic compounds can crystallize in more than one type of three-dimensional crystal structure. That is, the compounds may crystallize in different crystalline forms. This phenomenon (identical chemical structure but different crystalline structure) is referred to as polymorphism, and the species having different molecular structures are referred to as polymorphs.

Polymorphs of a particular organic pharmaceutical compound may have different physical properties, such as solubility and hygroscopicity, due to their distinct three-dimensional crystal structures. However, it is generally not possible to predict whether a particular organic compound will form different crystalline forms, let alone predict the structure and properties of the crystalline forms themselves. The discovery of a new crystalline or polymorph form of a pharmaceutically useful compound may provide a new opportunity for improving the overall characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing. It may be advantageous when this repertoire is enlarged by the discovery of new polymorphs of a useful compound.

Chinese Patent Publication No. CN1305860C discloses the structure of Icotinib (free base), on page 29, Example 15, Compound 23, and WO 2010/003313 disclosed Icotinib hydrochloride and its new crystalline polymorphs.

SUMMARY OF THE INVENTION

In general, the present invention relates to Icotinib maleate (i.e., the compound of Formula I), approximately pure polymorph forms thereof, and pharmaceutical acceptable salts thereof.



Formula I

In one aspect, the polymorph form is of Polymorph Form I and its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 6.1° , 8.1° ,

15.4°, 18.5°, 20.3° and 24.2°±0.2°.

In some embodiments of Polymorph Form I, its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 6.1°, 8.1°, 13.4°, 15.4°, 16.3°, 18.5°, 20.3° and 24.2°±0.2°.

5 In some other embodiments of Polymorph Form I, its X-ray powder diffraction pattern has characteristic peaks, expressed in terms of the interplanar distance, of 14.4Å, 10.9Å, 5.8Å, 4.8Å, 4.4Å, and 3.7Å.

In still some other embodiments of Polymorph Form I, its X-ray powder diffraction pattern has characteristic peaks, expressed in terms of the interplanar distance, of 14.4Å, 10.9Å,
10 6.6Å, 5.8Å, 5.4Å, 4.8Å, 4.4Å and 3.7Å.

In still some other embodiments of Polymorph Form I, its X-ray powder diffraction pattern is shown as in Figure 1.

In still some other embodiments of Polymorph Form I, it has a melting point of 173-176 °C.

15 In another aspect, the polymorph form is of Polymorph Form II and its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 7.5°, 19.0° and 31.2°±0.2°.

In some embodiments of Polymorph Form II, its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 7.5°, 15.0°, 19.0°, 23.8° and
20 31.2°±0.2°.

In some other embodiments of Polymorph Form II, its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 7.5°, 13.8°, 15.0°, 15.5°, 19.0°, 22.5°, 23.8° and 31.2°±0.2°.

In still some other embodiments of Polymorph Form II, its X-ray powder diffraction pattern has characteristic peaks, expressed in terms of the interplanar distance, of 11.8Å, 4.7Å
25 and 2.9Å.

In still some other embodiments of Polymorph Form II, its X-ray powder diffraction pattern has characteristic peaks, expressed in terms of the interplanar distance, of 11.8Å, 5.9Å, 4.7Å, 3.7Å and 2.9Å.

30 In still some other embodiments of Polymorph Form II, its X-ray powder diffraction

pattern has characteristic peaks, expressed in terms of the interplanar distance of 11.8Å, 6.4Å, 5.9Å, 5.7Å, 4.7Å, 4.0Å, 3.7Å and 2.9Å.

In still some other embodiments of Polymorph Form II, its X-ray powder diffraction pattern is shown as in Figure 2.

5 In still some other embodiments of Polymorph Form II, it has a melting point of 182-184 °C.

Polymorph Form I or II of this invention can have a purity of $\geq 85\%$, $\geq 95\%$, or even $\geq 99\%$.

10 In still another aspect, the invention provides processes for preparing a polymorph form of Icotinib maleate, each comprising the step of reacting Icotinib with maleic acid in a reaction media to produce Icotinib maleate in the polymorph form. The reaction between Icotinib and maleic acid, for example, can be carried out at the room temperature.

In some embodiments of the processes, the reaction media contains tetrahydrofuran (THF), isopropanol (IPA), dioxane, or 2-butanone, and the resultant polymorph is Polymorph Form I.

15 In some embodiments of the processes, the reaction media contains acetone, acetonitrile, ethanol, or a mixture of water and THF, and the resultant polymorph is Polymorph Form II.

In some other embodiments of the processes, the molar ratio of maleic acid and Icotinib ranges from 1:1 to 2:1 (e.g., 1:1, 1.5:1, or 2:1).

20 Some embodiments of the processes further include the step of reacting Icotinib hydrochloride with a base in a reaction media to produce Icotinib, before the step of reacting Icotinib with maleic acid. This reaction can be carried out, for example, at the temperature of 40-80°C.

Examples of a suitable base include sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate.

25 The reaction media can include, e.g., water and ethanol, water and IPA, water and methanol, or water and THF.

The polymorph forms of this invention, particularly Polymorph Form I and Polymorph Form II, unexpectedly exhibited significantly better bioavailability and chemical stability than Icotinib hydrochloride, the active ingredient of a drug currently in the marketplace.
30 Accordingly, the invention further provides pharmaceutical compositions comprising a

therapeutically effective amount of a polymorph form of this invention and a pharmaceutically acceptable excipient, adjuvant or carrier.

The pharmaceutical composition can further include a second therapeutically active ingredient, and can be in a form suitable for oral administration (e.g., a tablet or capsule).

5 Also within the scope of this invention is the use of a polymorph form or a pharmaceutical composition of this invention in the manufacturing of a medicament for the prevention or treatment in mammals of an excessive non-malignant disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular disease, or for mammalian embryo cell transplantation.

10 Also within the scope of this invention is the method for treating of an excessive non-malignant disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular disease, or for mammalian embryo cell transplantation by administering to a mammal patient in need thereof a polymorph form or a pharmaceutical composition of this invention.

The excessive non-malignant disease can be, for example, benign skin hyperplasia or benign prostatic hyperplasia. Or, the excessive non-malignant disease, pancreatitis, kidney
15 disease, cancer, angiogenesis or vascular occurrence-related illness is selected from: tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, and scleroderma, diabetes-induced skin diseases, diabetic retinopathy, premature retinopathy, age-related degeneration stains, hemangioma, glioma, Kaposi's internal tumor, ovarian cancer, breast cancer, lung cancer, pancreatic cancer, lymphoma, prostate, colon
20 and skin tumors and their complications.

All the polymorphs of the present invention are approximately pure.

The term "approximately pure" as herein used refers to at least 85 wt%, preferably at least 95 wt%, more preferably at least 99 wt% of the compound of Formula I exists in a polymorph form of the present invention, particularly in the polymorph forms of Form I or Form II.

25 The main peaks described in the polymorph forms above are reproducible and are within the error limit (the specified value ± 0.2).

In the present invention, "the X-ray powder diffraction pattern is shown as in Figure 1" refers to the X-ray powder diffraction pattern that show major peaks as in Figure 1, wherein major peaks refer to those with the relative intensity greater than 10%, preferably greater than
30 30%, relative to the highest peak (with its relative intensity designated to be 100%) in Figure 1.

Likewise, in the present invention, the X-ray powder diffraction pattern shown as in Figure 2 refers to the X-ray powder diffraction pattern that show major peaks as in Figure 2 wherein major peaks refer to those with the relative intensity greater than 10%, preferably greater than 30%, relative to the highest peak (with its relative intensity designated to be 100%) in Figure 2.

Crystallization in the present invention is related to dynamics and equilibrium among different polymorph forms under certain conditions. Therefore, those skilled in the art will realize that the resulting polymorph form depends on the kinetics and thermodynamics of the crystallization process. Under certain conditions (solvent system, temperature, pressure, and the concentration of the compound of the present invention), a polymorph form may be more stable than another one (or, actually be more stable than any other polymorph forms). However, the polymorphs that are less stable thermodynamically may be favorable in kinetics. The polymorph form may also be affected by factors other than kinetics, such as time, impurity distribution, agitation, presence or absence of polymorph seed. For purposes of this invention, various hydrate and solvate forms are included in the scope of "polymorph".

The present invention further provides a pharmaceutical composition, comprising a therapeutically effective amount of one or more polymorphs of Form I or Form II of the compound of Formula I, and a pharmaceutically acceptable excipient, adjuvant or carrier. Wherein, the pharmaceutical composition contains 1 wt%-99 wt%, preferably 1 wt%-70 wt%, more preferably 10 wt%-30 wt% of any one polymorph of Form I or Form II of the compound of Formula I.

The term "therapeutically effective amount" as herein used, refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The "therapeutically effective amount" can vary with the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In the case of combination therapy, the "therapeutically effective amount" refers to the total amount of the combination objects for the effective treatment of a disease, a disorder or a condition.

The pharmaceutical composition comprising the compound of the present invention can be administrated via oral, inhalation, rectal, parenteral or topical administration to a subject who needs treatment. For oral administration, the pharmaceutical composition may be a regular solid formulation such as tablets, powder, granule, capsules and the like, a liquid formulation
5 such as water or oil suspension or other liquid formulation such as syrup, solution, suspension or the like; for parenteral administration, the pharmaceutical composition may be solution, water solution, oil suspension concentrate, lyophilized powder or the like. Preferably, the formulation of the pharmaceutical composition is selected from tablet, coated tablet, capsule, suppository, nasal spray or injection, more preferably tablet or capsule. The pharmaceutical
10 composition can be a single unit administration with an accurate dosage. In addition, the pharmaceutical composition may further comprise additional active ingredients.

All formulations of the pharmaceutical composition of the present invention can be produced by the conventional methods in the pharmaceutical field. For example, the active ingredient can be mixed with one or more excipients, then to make the desired formulation.

15 The “pharmaceutically acceptable carrier” refers to conventional pharmaceutical carriers suitable for the desired pharmaceutical formulation, for example: a diluent, a vehicle such as water, various organic solvents, etc, a filler such as starch, sucrose, etc; a binder such as cellulose derivatives, alginates, gelatin and polyvinylpyrrolidone (PVP); a wetting agent such as glycerol; a disintegrating agent such as agar, calcium carbonate and sodium bicarbonate; an absorption
20 enhancer such as quaternary ammonium compound; a surfactant such as hexadecanol; an absorption carrier such as Kaolin and soap clay; a lubricant such as talc, calcium stearate, magnesium stearate, polyethylene glycol, etc. In addition, the pharmaceutical composition further comprises other pharmaceutically acceptable excipients such as a decentralizing agent, a stabilizer, a thickener, a complexing agent, a buffering agent, a permeation enhancer, a polymer,
25 aromatics, a sweetener, and a dye. Preferably, the excipient is suitable for desired formulation and administration type.

The term “disease” or “disorder” or “condition” refers to any disease, discomfort, illness, symptoms or indications.

In another aspect, the present invention provides use of the compounds (Icotinib maleate
30 and its polymorph forms) and/or the pharmaceutical compositions in manufacturing a

medicament for the treatment or prevention in mammals of excessive non-malignant hyperplasia disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular occurrence-related illness, or for the mammalian embryo cell transplantation. The excessive non-malignant hyperplasia disease can be a benign skin hyperplasia or a benign prostatic hyperplasia.

5 Preferably, the polymorph forms or pharmaceutical composition of the present invention can be used in manufacturing a medicament for the treatment or prevention in mammals of excessive non-malignant hyperplasia disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular occurrence-related illness selected from tumor angiogenesis, chronic inflammatory diseases such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, and
10 scleroderma, diabetes included skin diseases, diabetic retinopathy, premature retinopathy, age-related degeneration stains, hemangioma, glioma, Kaposi internal tumor, ovarian cancer, breast cancer, lung cancer, pancreatic cancer, lymphoma, prostate, colon and skin tumors and their complications.

Among the mammals mentioned herein, human beings are preferred.

15 This invention provides a method for treating malignant tissue hyperplasia in mammals. This treatment method includes application of an effective amount of Icotinib maleate and/or its polymorph forms and/or the pharmaceutical compositions to mammalian patients with hyperplasia disease. In some embodiments, the treatment method also includes use of MMP (matrix metalloproteinase) inhibitor, VEGFR (vascular endothelial growth factor receptor)
20 kinase inhibitors, HER2 inhibitor, VEGFR antibody drugs, and/or endostatin drugs. In some embodiments, the treatment method also includes using one or more anti-tumor agents such as mitotic inhibitors, alkylating agents, anti-metabolites, tumor antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, enzyme inhibitors, biological response modifiers, anti-hormone drugs and so on. The anti-tumor agents can be selected from carboplatin, paclitaxel,
25 gemcitabine, methotrexate, 5-FU, camptothecin, cyclophosphamide, BCNU and other medications.

Another purpose of this invention is to provide the use of the compounds (Icotinib maleate and its polymorphs) and/or the pharmaceutical compositions in manufacturing a medicament for treating a disease related to tyrosine kinase dysfunction.

30 Preferably, this invention provides a method for the treatment of disease caused by tyrosine

kinase dysfunction. This treatment method includes administering to a patient with the disease caused by tyrosine kinase dysfunction an effective amount of the compounds (Icotinib maleate and its polymorphs) and/or the pharmaceutical compositions. The tyrosine kinase dysfunction-related disease include, but are not limited to disease of brain, lung, liver, bladder, breast, head and neck, esophagus, gastrointestinal tract, ovary, cervix or thyroid tumors and their complications.

Target disease for the just described treatment method are preferably selected from brain cancer, lung cancer (such as non-small cell lung cancer (NSCLC)), kidney cancer, bone cancer, liver cancer, bladder cancer, breast cancer, lymphoma, or thyroid tumors and their complications.

The above-described methods can be applied in combination with any chemical therapy, biological therapy or radiation therapy.

The above-described treatment methods can further include application of anti-EGFR antibodies, anti-EGF antibodies, or both, in the same treatment.

The dosage of the active ingredient or compound when administered will be determined by the individual needs of the patient to treated, administration route, severity of disease or illness, dosing schedule, as well as evaluation and judgment of the designated doctor. However, based on the active compound, the preferred range of the effective dosage can be approximately 0.01-120mg daily per kilogram of body weight; or more preferably 1-50mg per day per kilogram of body weight in single or separate doses. In some cases, it is more suitable to apply the lower end of the above-described dosage range, while in other cases the higher dosage may be used without causing harmful side effects.

Another aspect of the present invention is to provide Icotinib maleate for clinical applications. In particular, the present invention related to clinical treatment with Icotinib maleate with the following treatment options for cancer patients: the dosage of Icotinib maleate and/or polymorph Form I or II can be 25-2100mg/day with the administration frequency being 1-3 times a day; a preferred dosage is 75-1200mg/day with the administration frequency being 2-3 times a day; an even more preferred dosage is 100-1200mg/day with the administration frequency being 2-3 times a day. Also within the scope of this invention is the use of a polymorph form or a pharmaceutical composition of this invention in the manufacturing of a medicament for the prevention or treatment in mammals of an excessive non-malignant disease,

pancreatitis, kidney disease, cancer, angiogenesis or vascular disease, or for mammalian embryo cell transplantation.

The excessive non-malignant disease can be, for example, benign skin hyperplasia or benign prostatic hyperplasia. Or, the excessive non-malignant disease, pancreatitis, kidney
5 disease, cancer, angiogenesis or vascular occurrence-related illness is selected from: tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis atherosclerosis, skin diseases such as psoriasis, and scleroderma, diabetes-induced skin diseases, diabetic retinopathy, premature retinopathy, agerelated degeneration stains, hemangionma, glioma, Kaposiinternal tumor, ovarian cancer, breast cancer, lung cancer, pancreatic cancer,
10 lymphoma, prostate, colon and skin tumors and their complications.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: The X-ray powder diffraction pattern of Polymorph Form I of the compound of Formula I .

Figure 2: The X-ray powder diffraction pattern of Polymorph Form II of the compound of
15 Formula I .

Figure3: The plasma concentration-time curves of Polymorph Form II of the compound of Formula I and Crystalline Form I of Icotinib hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

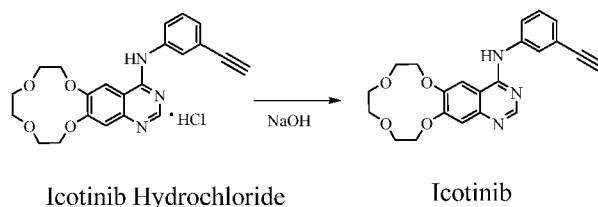
The present invention is further exemplified, but not limited, by the following examples that
20 illustrate the invention. The techniques or methods used in these examples, unless expressly stated otherwise, were conventional techniques or methods well known in the art.

The X-ray powder diffraction (XRPD) patterns for the polymorph forms of Icotinib maleate were generated on a PANalytical X-ray Diffraction System with Empyrean console. The diffraction peak positions were calibrated using silicon powder which had a 2θ value of 28.443
25 degree. An Empyrean Cu LEF X-ray tube K-Alpha radiation was used as the source.

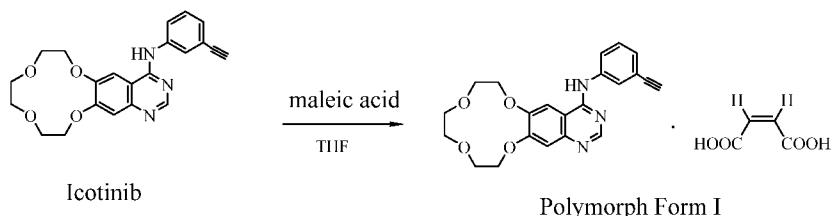
Example 1. Preparation of Polymorph Form I

100g Icotinib hydrochloride was dissolved in a mixture of 300ml ethanol and 200ml water.

A solution of 11.2g sodium hydroxide in 100ml water was added dropwisely at 60°C to the Icotibin hydrochloride solution until the pH value of the reaction solution reached 13. The reaction solution was stirred for 1hr and then cooled down to the room temperature. The precipitate was filtered and washed with purified water and dried for 8hrs under vacuum below 60°C to obtain 90g Icontinib.



Polymorph Form I of Icotinib maleate was obtained by reacting an Icontinib solution with a solution of maleic acid (1:1 molar ratio) in tetrahydrofuran (THF) at the room temperature. Detail procedures as following: 10mg Icontinib was dissolved in 1ml THF. 34.82mg maleic acid was also dissolved in 3ml THF to provide a 0.1mol/L maleic acid solution. 0.26ml of the maleic acid solution was added to the the Icontinib solution and the reaction mixture was stirred for 24 hrs, and then the Polymorph Form I was isolated. The melting point of the Polymorph Form is 173-176 °C.



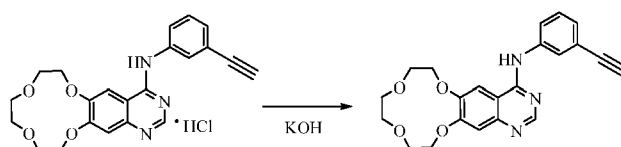
Example 2. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 1.

Example 3. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 1.

Example 4. Preparation of Polymorph Form I



10g Icotinib hydrochloride was dissolved in a mixture of 30ml isopropanol (IPA) and 20ml water, a solution of 1.6g potassium hydroxide in 10ml water was added to the Icotinib hydrochloride solution until the pH value of the reaction mixture reached 13. The reaction mixture was then stirred for 1-2hrs before cooling down to the room temperature. The precipitate was filtered and washed with purified water and dried under vacuum for 8-10hrs at a temperature below 50°C to give 7.9g Icotinib.

Polymorph Form I was obtained by reacting an Icotinib solution with a maleic acid solution at the 1:1 molar ratio in IPA at the room temperature. Detail procedures as following:

10mg Icotinib was dissolved in 1ml IPA. 34.82mg maleic acid was dissolved in 3ml IPA to obtain a 0.1mol/L maleic acid solution. 0.26ml of the 0.1mol/L maleic acid solution was then added to the Icotinib solution to give a solution which was stirred for 24 hrs, and then the Polymorph Form I was isolated.

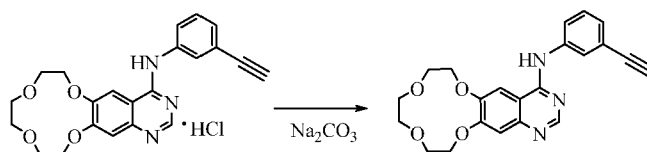
Example 5. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 4.

Example 6. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 4.

Example 7. Preparation of Polymorph Form I



5g Icotinib hydrochloride was dissolved in a mixture of 20ml methanol and 15ml water. To this Icotinib hydrochloride solution was added dropwisely a solution of 1.5g sodium

carbonate in 10ml water at 40°C until the pH value of the mixture reached 13. The reaction mixture was stirred for 1-2hrs before cooling down to the room temperature. The precipitate was filtered and washed with purified water and dried under vacuum for 8-10hrs below 60°C to give 4.0g Icontinib.

- 5 Polymorph Form I was obtained by reacting an Icontinib solution with a maleic acid solution (1:1 molar ratio) in dioxane at the room temperature. Detail procedures as following: 10mg Icontinib was dissolved in 1ml dioxane. 34.82mg maleic acid was dissolved in 3ml dioxane to obtain a 0.1mol/L maleic acid solution. 0.26ml the 0.1mol/L maleic acid solution was added to the Icontinib solution and the reaction mixture was stirred for 24hrs, and then the
- 10 Polymorph Form I was isolated.

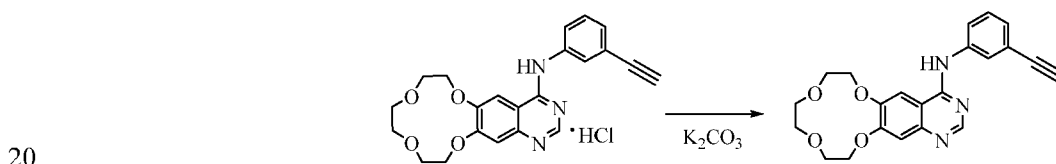
Example 8. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 7.

15 **Example 9. Preparation of Polymorph Form I**

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 7.

Example 10. Preparation of Polymorph Form I



- 25 5g Icotinib hydrochloride was dissolved in a mixture of 20ml THF and 15ml water, and to this Icotinib hydrochloride solution was added a solution of 1.9g potassium carbonate in 10ml water dropped at 50°C until the pH value of the reaction mixture reached 13. The reaction mixture was then stirred for 1-2hrs before cooling down to the room temperature. The precipitate was filtered and washed with purified water and then dried for 8-10hrs under vacuum at a temperature below 60°C to produce 4g Icontinib.

Polymorph Form I was obtained by reacting an Icontinib solution with a maleic acid solution (1:1 molar ratio) in 2-butanone at the room temperature. Detail procedures as following: 10mg Icontinib was dissolved in 1ml 2-butanone to provide an Icontinib solution. 34.82mg maleic acid was dissolved in 3ml 2-butanone to obtain a 0.1mol/L maleic acid solution. 5 0.26ml of the 0.1mol/L maleic acid solution was added to the Icontinib solution. The reaction mixture was stirred for 24hrs, and then the Polymorph Form I was isolated.

Example 11. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 10. 10

Example 12. Preparation of Polymorph Form I

Polymorph Form I was prepared by using the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 10.

Example 13. Preparation of the polymorph Form II

Polymorph Form II was prepared by reacting an Icontinib (from Example 1) solution with a solution of maleic acid (1:1 molar ratio) in acetone at the room temperature in accordance with the following steps.

10mg Icontinib was dissolved in 1ml acetone. 34.82mg maleic acid was dissolved in 3ml 20 acetone to obtain a 0.1mol/L maleic acid solution. 0.26ml of the 0.1mol/L maleic acid solution was added to the Icontinib solution and the reaction mixture was stirred for 24hrs to give Polymorph Form II, and then the Polymorph Form II was isolated. The melting point of the Polymorph Form is 182-184°C.

Example 14. Preparation of Polymorph Form II

Polymorph Form II was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 13. 25

Example 15. Preparation of Polymorph Form II

Polymorph Form II was prepared by using the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 13.

5 Example 16. Preparation of Polymorph Form II

Polymorph II was prepared in the same manner (molar ratio 1:1) and according to the same procedure as provided in Example 13, except that acetone was replaced by acetonitrile, and then the Polymorph Form II was isolated.

Example 17. Preparation of Polymorph Form II

10 Polymorph Form II was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 16.

Example 18. Preparation of Polymorph Form II

15 Polymorph Form II was prepared by changing the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 16.

Example 19. Preparation of Polymorph Form II

20 Polymorph II was prepared in the same manner (molar ratio 1 : 1) and according to the same procedure as provided in Example 13, except that acetone was replaced by ethanol, and then the Polymorph Form II was isolated.

Example 20. Preparation of Polymorph Form II

Polymorph Form II was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 19.

25 Example 21. Preparation of Polymorph Form II

Polymorph Form II was prepared by changing the molar ratio of maleic acid and Icotinib

1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 19.

Example 22. Preparation of Polymorph Form II

Polymorph II was prepared in the same manner (molar ratio 1:1) and according to the same procedure as provided in Example 13, except that acetone was replaced by a mixture of H₂O and THF (ratio 1 : 19, v/v), and then the Polymorph Form II was isolated.

Example 23. Preparation of Polymorph Form II

Polymorph Form II was prepared by using the molar ratio of maleic acid and Icotinib 2:1 instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 22.

Example 24. Preparation of Polymorph Form II

Polymorph Form II was prepared by using the molar ratio of maleic acid and Icotinib 1.5:1 (3:2) instead of 1:1 as Example 1 by following the same reaction conditions as described in Example 22.

Example 25. Pharmacokinetic Study of Icotinib Hydrochloride and Polymorph Form II of Icotinib Maleate

Drugs and reagents: the Icotinib hydrochloride used in this study was of Crystalline Form I disclosed by the WO2010/003313. Polymorph Form II of Icotinib maleate and Icotinib hydrochloride were ground to fine particles. The material content (purity) was not less than 99.0%. Sodium carboxymethyl cellulose was medical supply graded.

Experimental animals: SD rats were divided to an Icotinib hydrochloride group and a Polymorph Form II group, with both groups consisting of males.

Pharmaceutical preparation: the amount of each compound was weighed and then sodium carboxymethyl cellulose was added to result in the test compound's concentration of 0.5%. The solid mixture was then added to prepare a suspension thereof at a final concentration of 10mg/ml in water.

Administration and sample collection: each suspension was administered orally to fasted SD rats at a dose equivalent to 35mg/kg Icotinib in a dose volume of 5ml/kg. 0.4ml of blood

was collected in EDTA-K pre anticoagulant tubes at time intervals of 0.5, 1, 1.5, 2, 4, 6, 8 and 24hrs after the administration of the test compound, centrifuged at 3000rpm for 10 minutes, and 120µl plasma was collected and kept in cold storage.

Samples were analyzed by high performance liquid chromatography. The chromatographic conditions utilized C18-silane bonded silica as stationary phase, 0.02mol/L of sodium dihydrogen phosphate in acetonitrile (40:60, using sodium hydroxide solution to adjust pH to 5.0) as the mobile phase and a detection wavelength of 334nm. PK profile comparison of Polymorph Form II of Icotinib maleate and Crystalline Form I of Icotinib hydrochloride was summarized in Table 1 and Figure 3. Polymorph Form II of Icotinib maleate showed higher bioavailability than Crystalline Form I of Icotinib hydrochloride.

Table 1

	AUC ₍₀₋₂₄₎ (mg/L*h)	AUC _(0-∞) (mg/L*h)	T _{1/2} (h)	T _{max} (h)	C _{max} (mg/L)
Icotinib hydrochloride Crystalline form I	19.04±7.12	19.12±7.16	2.94±0.41	2.33±3.18	3.36±0.37
Form II	64.85±32.45	65.43±32.73	3.06±0.44	5.33±1.15	7.53±1.37

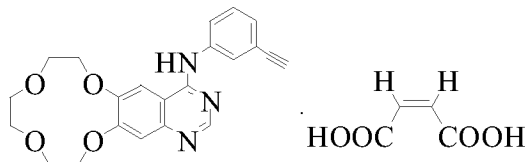
Example 26. Formulation of a Hard Gel Capsule

As a specific embodiment of an oral composition, about 100mg of the Polymorph Form of Example 1-24 is formulated with sufficient finely divided lactose to provide a total amount of about 580mg to about 590mg to fill a size 0 hard gel capsule.

Although the present invention has been fully described in connection with embodiments thereof with reference to the accompanying drawings, it is to be noted that various changes and modifications will become apparent to those skilled in the art. Such changes and modifications are to be understood as being included within the scope of the present invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A polymorph form of the compound of Formula I .



Formula I

2. The polymorph form of Claim 1, wherein the polymorph form is of Form I and its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 6.1° , 8.1° , 15.4° , 18.5° , 20.3° and $24.2^\circ \pm 0.2^\circ$.

3. The polymorph form of Claim 2, wherein its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 6.1° , 8.1° , 13.4° , 15.4° , 16.3° , 18.5° , 20.3° and $24.2^\circ \pm 0.2^\circ$.

4. The polymorph form of Claim 2 or 3, wherein the X-ray powder diffraction pattern is shown as in Figure 1.

5. The polymorph form of any one of Claims 2-4, wherein the melting point is 173-176 $^\circ\text{C}$.

6. The polymorph form of Claim 1, wherein the polymorph form is of Form II and its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 7.5° , 19.0° and $31.2^\circ \pm 0.2^\circ$.

7. The polymorph form of Claim 6, wherein its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 7.5° , 15.0° , 19.0° , 23.8° and $31.2^\circ \pm 0.2^\circ$.

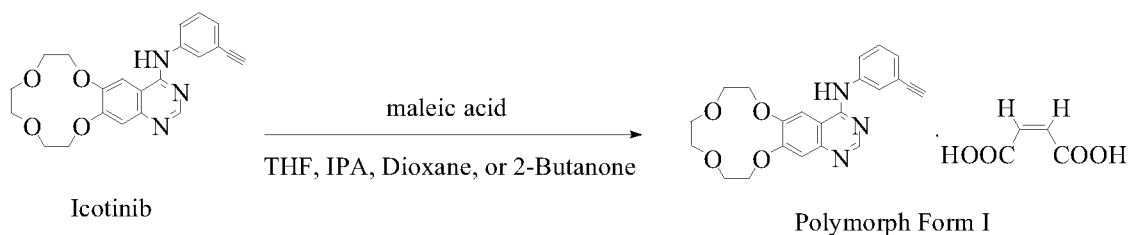
8. The polymorph form of Claim 6 or 7, wherein its X-ray powder diffraction pattern has characteristic peaks at diffraction angles 2θ of approximately 7.5° , 13.8° , 15.0° , 15.5° , 19.0° , 22.5° , 23.8° and $31.2^\circ \pm 0.2^\circ$.

9. The polymorph form of any one of Claims 6-8, wherein the X-ray powder diffraction pattern is shown as in Figure 2.

10. The polymorph form of any one of Claims 6-9, wherein the melting point is 182-184 $^\circ\text{C}$.

11. A process of preparing a polymorph form of Claim 1, comprising:

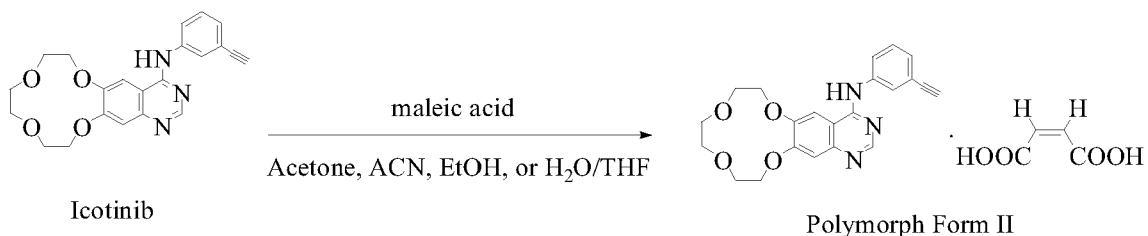
a).



reacting Icotinib with maleic acid in a reaction media of tetrahydrofuran (THF), isopropanol (IPA), dioxane, or 2-butanone at the room temperature, with a molar ratio between maleic acid and Icotinib ranging from 1:1 to 2:1, to produce the polymorph form of any one of Claims 2-5;

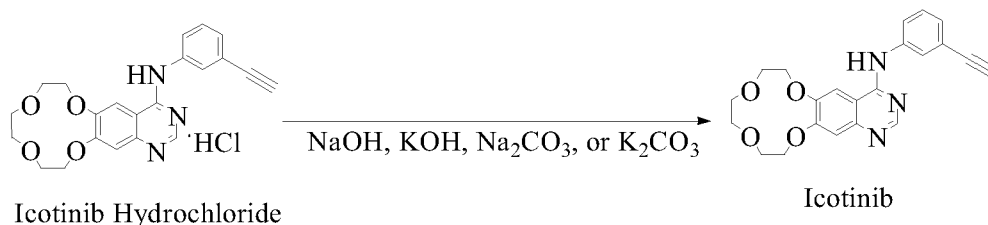
or

b).



reacting Icotinib with maleic acid in a reaction media of acetone, acetonitrile, ethanol, or water (H₂O) and THF (ratio 1:19, v/v) at the room temperature, with a molar ratio between maleic acid and Icotinib ranging from 1:1 to 2:1, to produce the polymorph form of any one of Claims 6-10.

12. The process of Claim 11, further comprising the step of reacting Icotinib hydrochloride with sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate in a reaction media of ethanol and H₂O, IPA and H₂O, methanol and H₂O or THF and H₂O at the temperature of 40-80°C to produce Icotinib, before the step of reacting Icotinib with maleic acid,



13. A pharmaceutical composition comprising a therapeutically effective amount of the polymorph form of any one of Claims 1-10 and a pharmaceutically acceptable excipient, adjuvant or carrier.

14. The pharmaceutical composition of Claim 13, wherein the polymorph form of any one of Claims 1-10 has a purity of $\geq 85\text{wt}\%$.

15. The pharmaceutical composition of Claim 13, wherein the polymorph form of any one of Claims 1-10 has a purity of $\geq 99\text{wt}\%$.

5 16. The pharmaceutical composition of any one of Claim 13-15, further comprising a second therapeutically active ingredient.

17. The pharmaceutical composition of any one of Claims 13-16, wherein the pharmaceutical composition is suitable for oral administration.

10 18. The pharmaceutical composition according to any one of Claims 13-17, wherein the pharmaceutical composition is in the form of tablet or capsule.

19. The pharmaceutical composition of any one of Claims 13-18, wherein the composition comprises 0.01wt%-99wt% of the polymorph form of any one of Claims 1-10.

20. The pharmaceutical composition of Claim 19, wherein the composition comprises 10wt%-50wt% of the polymorph form of any one of Claims 1-10.

15 21. Use of a polymorph form of any one of Claims 1-10 or a pharmaceutical composition of any one of Claims 13-20 in the manufacturing of a medicament for the prevention or treatment in mammals of an excessive non-malignant disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular disease, or for mammalian embryo cell transplantation.

20 22. The use of Claim 21, wherein the excessive non-malignant disease is benign skin hyperplasia or benign prostatic hyperplasia.

23. The use of claim 21 or 22, wherein the excessive non-malignant disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular occurrence-related illness is selected from: tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, and scleroderma, diabetes-induced skin diseases, diabetic
25 retinopathy, premature retinopathy, agerelated degeneration stains, hemangionma, glioma, Kaposiinternal tumor, ovarian cancer, breast cancer, lung cancer, pancreatic cancer, lymphoma, prostate, colon and skin tumors and their complications.

24. A method for treating in mammals of excessive non-malignant disease, pancreatitis, kidney disease, cancer, angiogenesis or vascular disease, or for mammalian embryo cell
30 transplantation, comprising administering to a mammal patient in need thereof a polymorph form

of any one of Claims **1-10** or a pharmaceutical composition of any one of Claims **13-20**.

25. The method of Claim **24**, wherein the excessive non-malignant disease is benign skin hyperplasia or benign prostatic hyperplasia.

26. The method of Claim **24** or **25**, wherein the excessive non-malignant disease,
5 pancreatitis, kidney disease, cancer, angiogenesis or vascular occurrence-related illness is selected from: tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis atherosclerosis, skin diseases such as psoriasis, and scleroderma, diabetes-induced skin diseases, diabetic retinopathy, premature retinopathy, agerelated degeneration stains, hemangionma, glioma, Kaposiinternal tumor, ovarian cancer, breast cancer,
10 lung cancer, pancreatic cancer, lymphoma, prostate, colon and skin tumors and their complications.