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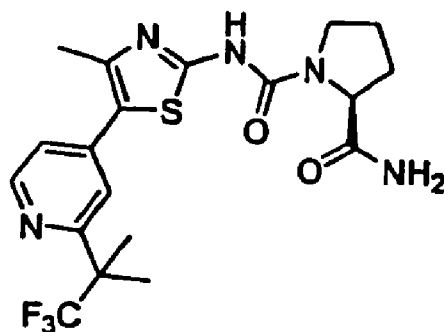
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(54) Title: A CRYSTALLINE FORM OF (S)-PYRROLIDINE-1,2-DICARBOXYLIC ACID 2-AMIDE 1-(4-METHYL-5-[2-(2,2,2-TRIFLUORO-1,1-DIMETHYL-ETHYL)-PYRIDIN-4-YL]-THIAZOL-2-YL)-AMIDE AND ITS USE AS PI3K INHIBITOR



(I)

(57) Abstract: The present invention relates to specific solid forms of (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-(4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl)-amide, (I), and its hydrates and solvates. The present invention further relates to processes for preparing said solid forms, pharmaceutical compositions comprising said solid forms, and methods of using said solid forms and pharmaceutical compositions to treat disease.

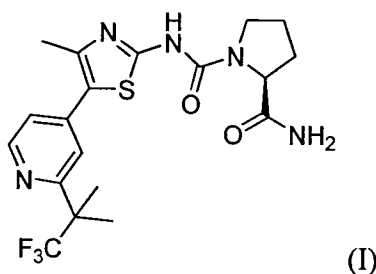
A CRYSTALLINE FORM OF (S)-PYRROLIDINE-1,2-DICARBOXYLIC ACID 2-AMIDE 1-(4-METHYL-5-[2-(2,2,2-TRIFLUORO-1,1-DIMETHYL-ETHYL)-PYRIDIN-4-YL]-THIAZOL-2-YL)-AMIDE AND ITS USE AS PI3K INHIBITOR

Field of the Invention

The present invention relates to specific solid forms of (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-(4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl)-amide, and its hydrates and solvates. The present invention further relates to processes for preparing said solid forms, pharmaceutical compositions comprising said solid forms, and methods of using said solid forms and pharmaceutical compositions to treat disease.

Background

(S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-(4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl)-amide, hereafter referred to as compound I,



is an alpha-selective phosphatidylinositol 3-kinase (PI3K) inhibitor. Compound I was originally described in WO 2010/029082, wherein the synthesis of its free base form was described. There is a need for additional solid forms of compound I, for use in drug substance and drug product development. It has been found that new solid forms of compound I can be prepared as one or more polymorph forms, including hydrate and solvate forms. These polymorph forms exhibit new physical properties that may be exploited in order to obtain new pharmacological properties, and that may be utilized in drug substance and drug product development.

Summary of the Invention

In one aspect, provided herein is a crystalline form of the compound of formula I, or a hydrate or solvate of the crystalline form of the compound of formula I, or a salt of the crystalline form of the compound of formula I, or a hydrate or solvate of a salt of the crystalline

form of the compound of formula I. In one embodiment, the crystalline form of the compound of formula I has the polymorph form A.

In another aspect, provided herein is a pharmaceutical composition comprising a crystalline compound of formula I. In one embodiment of the pharmaceutical composition, the crystalline compound of formula I has the polymorph form A.

In another aspect, provided herein is a process for the preparation of the polymorph form A, which comprises the following steps: (a) dissolving a compound of formula I in 70% aqueous acetone, (b) adding water to achieve lower solubility, and (c) keeping the temperature above 40 °C to form the polymorph form A.

In another aspect, provided herein is a method for the treatment of disorders mediated by PI3K, comprising administering to a patient in need of such treatment an effective amount of a crystalline compound of formula I (*e.g.*, polymorph form A).

In yet another aspect, provided herein is the use of a crystalline compound of formula I (*e.g.*, polymorph form A) for the preparation of a medicament for the treatment of disorders mediated by PI3K.

In still another aspect, provided herein is a method for the treatment of disorders selected from benign or malignant tumor; a cancer selected from sarcoma; lung; bronchus; prostate; breast (including sporadic breast cancers and sufferers of Cowden disease); pancreas; gastrointestinal cancer; colon; rectum; colon carcinoma; colorectal adenoma; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; glioma; glioblastoma; endometrial; melanoma; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary; multiple myeloma; esophagus; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; a carcinoma of the brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; melanoma; villous colon adenoma; a neoplasia; a neoplasia of epithelial character; lymphomas; a mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; tumor diseases, including solid tumors; a tumor of the neck or head; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Waldenstrom disease; as well as polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia,

asthma, COPD, ARDS, Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, autoimmune haematological disorders (*e.g.*, haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (*e.g.*, ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma, comprising administering to a patient in need of such treatment an effective amount of the crystalline compound of formula I (*e.g.*, polymorph form A).

In another aspect, provided herein is the use of the crystalline compound of formula I (*e.g.*, polymorph form A) for the preparation of a medicament for the treatment of the disorders listed above.

Brief Description of the Drawings

Figure 1 depicts the X-ray powder diffraction pattern of polymorph form A. **Figure 2** depicts the FT-IR spectrum of polymorph form A. **Figure 3** depicts the differential scanning calorimetry thermogram of polymorph form A.

Detailed Description of the Invention

Polymorph Forms and Properties

The present invention relates to a crystalline form of (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide). (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide), also referred to as the compound of formula I, or Compound I, was originally described in WO 2010/029082, the contents of which are incorporated herein by reference. Compound I is an inhibitor of PI3K (phosphatidylinositol 3-kinase), and shows an improved selectivity for PI3K alpha with respect to beta, delta and gamma subtypes in biochemical, as well as cellular, assays. Accordingly, Compound I, and pharmaceutical compositions comprising Compound I, can be used for the prevention, amelioration or treatment of diseases depending on PI3K (in particular PI3K alpha). As described herein, the free base of Compound I can be a crystalline form that exists as one or more polymorph forms. These polymorph forms (alternatively known in the art as polymorphic forms or crystal forms) differ with respect to their X-ray powder diffraction patterns, spectroscopic, physicochemical and pharmacokinetic properties, as well as their thermodynamic stability.

It is desirable to have access to different polymorph forms of crystalline Compound I, its hydrates or solvates, its salts and hydrates or solvates of its salts for several reasons. For example, distinct polymorph forms may incorporate distinct impurities upon crystallization, *i.e.* an impurity incorporated in polymorph form A is not necessarily also incorporated in another polymorph forms, such as a solvate form. Thus, the iterative preparation of distinct polymorph forms of Compound I may be used to increase the purity of the finally obtained form. In addition, distinct polymorph forms may exhibit different physical properties such as melting point, hygroscopicity, solubility, flow properties or thermodynamic stability, and therefore, distinct polymorph forms allow the choice of the most suitable form for a given use or aspect, *e.g.*, the use as an intermediate in the process of drug manufacture, in distinct administration forms such as tablets, capsules, ointments, suspensions or solutions, or in the manufacture of a drug form having optimum pharmacokinetic properties.

Thus, in one aspect, provided herein is a crystalline form of the compound of formula I, or a hydrate or solvate of the crystalline form of the compound of formula I.

In one embodiment, the compound of formula I has the polymorph form A. Polymorph form A can be defined by reference to one or more characteristic signals that result from analytical measurements including, but not necessarily limited to: the X-ray powder diffraction pattern of Figure 1, the FT-IR spectrum of Figure 2, or the differential scanning calorimetry thermogram of Figure 3. Polymorph form A can also be defined by reference to one or more of the following characteristic signals:

In one embodiment, the polymorph form A exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-Theta at angles of $17.1^{\circ} \pm 0.3^{\circ}$ and $20.4^{\circ} \pm 0.3^{\circ}$. In yet another embodiment, the polymorph form A exhibits characteristic peaks at angles of $4.2^{\circ} \pm 0.3^{\circ}$ and $21.7^{\circ} \pm 0.3^{\circ}$. In still another embodiment, the polymorph form A exhibits characteristic peaks at angles of $18.2^{\circ} \pm 0.3^{\circ}$ and $20.1^{\circ} \pm 0.3^{\circ}$. In another embodiment, the polymorph form A exhibits characteristic peaks at angles of $17.1^{\circ} \pm 0.3^{\circ}$, $20.4^{\circ} \pm 0.3^{\circ}$, $4.2^{\circ} \pm 0.3^{\circ}$, $21.7^{\circ} \pm 0.3^{\circ}$, $18.2^{\circ} \pm 0.3^{\circ}$ and $20.1^{\circ} \pm 0.3^{\circ}$. In a further embodiment, the polymorph form A exhibits an X-ray powder diffraction pattern substantially in accordance with Figure 1 and Table 1.

In one embodiment, the polymorph form A exhibits an FT-IR spectrum having characteristic peaks expressed in units of cm^{-1} at values of about 1693 and about 1668. In another embodiment, the polymorph form A exhibits additional peaks at values of about 1599 and about 1540. In still another embodiment, the polymorph form A exhibits an FT-IR spectrum substantially in accordance with Figure 2 with exception of the additional peaks of about 2925 and 2854. Figure 2 of the present application includes additional peaks of about 2925 and 2854 which correspond to the Nujol[®] mineral oil (Schering-Plough Corporation) used in the FT-IR measurement.

In one embodiment, the polymorph form A exhibits a differential scanning calorimetry thermogram having a characteristic peak expressed in units of $^{\circ}\text{C}$ at a temperature of about 203. In another embodiment, the polymorph form A exhibits a differential scanning calorimetry thermogram substantially in accordance with Figure 3.

In one embodiment, the polymorph form A contains less than 10% by weight total impurities. In another embodiment, the polymorph form A contains less than 5% by weight total impurities. In yet another embodiment, the polymorph form A contains less than 2% by weight total impurities.

5 As used herein, the term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

Crystallization

As discussed above, the present invention relates also to a process for the preparation of solid, preferably crystalline, forms of the compound of formula I, or its hydrates or solvates. The
15 precise conditions under which specific polymorphs are formed can be determined empirically and a number of methods are suitable in practice, including the crystallization conditions as described herein.

Crystallization-inducing conditions normally involve the use of an appropriate solvent, such as t-butylmethylether (TBME), ethyl acetate, tetrahydrofuran (THF), acetone, methanol,
20 ethanol, isopropanol or water or mixtures thereof. Conveniently, the amorphous compound is dissolved in a solvent, or in a solvent mixture. The solution may be produced by dissolving in the solvent any one or more amorphous forms of the compound, and solvates thereof, such as hydrates, methanولات, ethanolates, or isopropanolates. The resulting solution may be heated, cooled, or held at constant temperature. The resulting solution may be combined with another
25 solvent or solvent mixture. Crystals may then be formed by conversion from solution, crystallization taking place at a temperature of between about 0 °C and the boiling point of the solvent or solvent mixture.

The dissolution and crystallization may be carried out in various conventional ways that are known in the art.

Mixed solvents comprising a good solvent, in which the compound is readily soluble, and a poor solvent, in which it is more sparingly soluble, may also be employed provided that crystallization from the mixture is possible using the selected solvent mixture.

Alternatively, the difference in solubility of the crystals in different solvents may be used.

5 For example, an amorphous compound may be dissolved in a good solvent, followed by mixing with a poor solvent. The solution of the compound in the good solvent may be added to the poor solvent, or the poor solvent may be added to the solution of the compound in the good solvent. Examples of good solvents include methanol, ethanol and isopropanol, formic acid, acetic acid, ethyl acetate, tetrahydrofuran and acetone. An example of a poor solvent is *e.g.*, water.

10 In an alternative embodiment of the process of the invention, a solid compound is suspended in a solvent or solvent mixture in which the compound is incompletely soluble. In one embodiment, particles of the solid are dispersed, and remain incompletely dissolved in the solvent. The suspension may be kept at a temperature of normally about 0 °C or higher. Preferably the solids are maintained in a state of suspension by agitation (*e.g.*, by shaking or
15 stirring). In this manner, the original solid compound is transformed into a new crystal form, *i.e.* a polymorph. In certain embodiments, the original solid compound may be anhydrous, a hydrate, a solvate, or free of solvent.

In one aspect, provided herein is a process for the preparation of the polymorph form A, which comprises the following steps: (a) dissolving a compound of formula I in 50-90% aqueous
20 acetone, (b) adding water to achieve lower solubility, and (c) keeping the temperature above 30 °C to form the polymorph form A. Preferably, the compound of formula I is dissolved in 70% aqueous acetone in the above described step (a).

In one embodiment of the process, the temperature is in the range of 30-70 °C.

In another embodiment of the process, the temperature is in the range of 30-60 °C.

25 In yet another embodiment of the process, the temperature is in the range of 50-55 °C.

In still another embodiment of the process, the mixture is seeded with one or more crystals of polymorph form A.

As used herein, the term “seed” can be used as a noun to describe one or more crystals of a crystalline compound of formula I. The term “seed” can also be used as a verb to describe the
30 act of introducing said one or more crystals of a crystalline compound of formula I into an

environment (including, but not limited to *e.g.*, a solution, a mixture, a suspension, or a dispersion) thereby resulting in the formation of more crystals of the crystalline compound of formula I.

5 Methods of Treatment

The present invention also provides a method for preventing, ameliorating or treating conditions, disorders or diseases mediated by the activation of PI3K, especially PI3K α , *e.g.*, such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a crystalline compound of formula I,
10 especially polymorph form A.

The PI3K pathway is activated by several different mechanisms in cancers, as described, for example, by Engelman et al. (*J. Clin. Oncol.* 28, 2010, 1-10). Without being bound by theory, inhibitors of the PI3K signaling cascade, either alone or in combination with other therapeutics, are useful for the treatment of cellular proliferative diseases.

15 As used herein, the term “patient” refers to a mammal, preferably a human.

In one aspect, provided herein is a method for the treatment of disorders mediated by PI3K, comprising administering to a patient in need of such treatment an effective amount of a crystalline compound of formula I.

In one embodiment of the method, the PI3K is PI3K α .

20 In another embodiment of the method, the disorder is a cellular proliferative disease.

In yet another embodiment of the method, the disorder is selected from: benign or malignant tumor, or is a cancer selected from: sarcoma, lung, bronchus, prostate, breast (including sporadic breast cancers and sufferers of Cowden disease), pancreas gastrointestinal cancer, colon, rectum, colon carcinoma, colorectal adenoma, thyroid, liver, intrahepatic bile duct, hepatocellular, adrenal gland, stomach, gastric, glioma, glioblastoma, endometrial, melanoma,
25 kidney, renal pelvis, urinary bladder, uterine corpus, uterine cervix, vagina, ovary, multiple myeloma, esophagus; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia, myeloid leukemia, brain, a carcinoma of the brain, oral cavity and pharynx, larynx, small intestine, non-Hodgkin lymphoma, melanoma, villous colon
30 adenoma, a neoplasia, a neoplasia of epithelial character, lymphomas, a mammary carcinoma,

basal cell carcinoma, squamous cell carcinoma, actinic keratosis, tumor diseases, including solid tumors, a tumor of the neck or head, polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, and Walden stroem disease.

In still another embodiment of the method, the disorder is selected from polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, asthma, COPD, ARDS, Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, autoimmune haematological disorders (*e.g.*, haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (*e.g.*, ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

In one aspect, provided herein is a method for the treatment of the disorders listed above, comprising administering to a patient in need of such treatment an effective amount of a crystalline compound of formula I. In another aspect, provided herein is a method for the treatment of a cellular proliferative disease comprising administering to a patient in need of such treatment an effective amount of a compound of formula I having polymorph form A. The

cellular proliferative disease can be selected from: benign or malignant tumor, or is a cancer selected from: sarcoma, lung, bronchus, prostate, breast (including sporadic breast cancers and sufferers of Cowden disease), pancreas gastrointestinal cancer, colon, rectum, colon carcinoma, colorectal adenoma, thyroid, liver, intrahepatic bile duct, hepatocellular, adrenal gland, stomach, gastric, glioma, glioblastoma, endometrial, melanoma, kidney, renal pelvis, urinary bladder, uterine corpus, uterine cervix, vagina, ovary, multiple myeloma, esophagus; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia, myeloid leukemia, brain, a carcinoma of the brain, oral cavity and pharynx, larynx, small intestine, non-Hodgkin lymphoma, melanoma, villous colon adenoma, a neoplasia, a neoplasia of epithelial character, lymphomas, a mammary carcinoma, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, tumor diseases, including solid tumors, a tumor of the neck or head, polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, and Walden stroem disease.

In still another aspect, provided herein is a method for the treatment of polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, asthma, COPD, ARDS, Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, autoimmune haematological disorders (*e.g.*, haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (*e.g.*, ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina,

thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma, comprising administering to a patient in need of such treatment an effective amount of a compound of formula I having polymorph form A.

The present invention also provides for the use of a crystalline compound of formula I, especially polymorph form A, for the preparation of a medicament for the prevention, amelioration or treatment of conditions, disorders or diseases mediated by the activation of PI3K, especially PI3K α .

In one aspect, provided herein is the use of a crystalline compound of formula I for the preparation of a medicament for the treatment of disorders mediated by PI3K. In one embodiment of the use, the disorder is a cellular proliferative disease, such as the disorders listed above. In another aspect, provided herein is the use of a crystalline compound of formula I for the preparation of a medicament for the treatment of the disorders listed above.

Pharmaceutical Compositions

The compounds of the present invention are suitable as active agents in pharmaceutical compositions that are efficacious particularly for treating protein kinase-associated disorders, especially PI3K-associated disorders, *e.g.*, cancer. The pharmaceutical composition in various embodiments has a pharmaceutically effective amount of the crystalline compound of formula I, especially the polymorph form A, along with other pharmaceutically acceptable excipients, carriers, fillers, diluents and the like.

The language “pharmaceutically effective amount” or “pharmaceutically acceptable amount” of the compound is that amount necessary or sufficient to treat or prevent a PI3K-associated disorder, *e.g.*, prevent the various morphological and somatic symptoms of a protein kinase-associated disorder, especially a PI3K-associated disorder, and/or a disease or condition described herein. In an example, an effective amount of a compound of the invention is the amount sufficient to treat a PI3K-associated disorder in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the

particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an “effective amount.” One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

5 The regimen of administration can affect what constitutes a pharmaceutically effective amount. A compound of the invention can be administered to the subject either prior to or after the onset of a PI3K-associated disorder. Further, several divided dosages, as well as staggered dosages can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be
10 proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

 In one non-limiting embodiment, the phrase “pharmaceutically effective amount” refers to the amount of a compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, ameliorate, inhibit, prevent and/or treat a condition, or
15 a disorder or a disease (i) mediated PI3K, or (ii) associated with PI3K, or (iii) characterized by abnormal activity of PI3K; or (2) reduce or inhibit the activity of PI3K; or (3) reduce or inhibit the expression of PI3K. In still another non-limiting embodiment, the term “pharmaceutically effective amount” refers to the amount of a compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective
20 to at least partially reduce or inhibit the activity of PI3K; or at least partially reduce or inhibit the expression of PI3K.

 The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular organic compound. For example, the choice of the organic compound can affect what constitutes an “effective amount.” One of ordinary skill in
25 the art would be able to study the aforementioned factors and make the determination regarding the acceptable amount of the organic compound without undue experimentation.

 Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. Methods of use of compounds of the present invention include the

treatment of these diseases, and the manufacture of pharmaceutical preparations comprising compounds of the present invention for the treatment of these diseases.

The language “pharmaceutical composition” includes preparations suitable for administration to mammals, *e.g.*, humans. When the compounds of the present invention are administered as pharmaceuticals to mammals, *e.g.*, humans, they can be given *per se* or as a pharmaceutical composition containing, for example, 0.1% to 99.9% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The phrase “pharmaceutically acceptable carrier” is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate,

butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α -tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as

agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of

this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients
5 such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a
10 compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also
15 contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration
comprise one or more compounds of the invention in combination with one or more
pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions,
suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable
20 solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the
pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol,
25 propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents,
30 emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be

ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, *etc.*, administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral and/or IV administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral

administration” and “administered peripherally” as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

5 These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

10 Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

15 Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

20 The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

25 A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

30 In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective

dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day. An effective amount is that amount treats a PI3K-associated disorder.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

The present pharmaceutical compositions comprise one or more pharmacologically active substances. Thus, in one aspect, provided herein is a pharmaceutical composition comprising a crystalline compound of formula I.

In another aspect, provided herein is a pharmaceutical composition comprising the polymorph form A of the compound of formula I, and a pharmaceutically acceptable carrier or diluent.

In one embodiment, the pharmaceutical composition comprises less than 0.1% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In another embodiment, the pharmaceutical composition comprises less than 1% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In yet another embodiment, the pharmaceutical composition comprises less than 10.0% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In still another embodiment, the pharmaceutical composition comprises less than 50.0% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In another embodiment, the pharmaceutical composition comprises at least 50.0% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In yet another embodiment, the pharmaceutical composition comprises at least 75.0% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In still another embodiment, the

pharmaceutical composition comprises at least 99.0% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition. In yet another embodiment, the pharmaceutical composition comprises at least 99.9% by weight of polymorph form A based on the total weight of the compound of formula 1 in the composition.

5 In one embodiment, the pharmaceutical composition is formulated for oral administration. In another embodiment, the pharmaceutical composition is formulated for parenteral administration. In yet another embodiment, the pharmaceutical composition is formulated for topical administration.

10 Combinations

“Combination” refers to either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a crystalline compound of the formula I and a combination partner (*e.g.*, another drug as explained below, also referred to as “therapeutic agent” or “co-agent”) may be administered independently at the same time or separately within
15 time intervals, especially where these time intervals allow that the combination partners show a cooperative, *e.g.*, synergistic, effect. The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (*e.g.*, a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same
20 route of administration or at the same time. The term “pharmaceutical combination” as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, *e.g.*, a crystalline compound of formula I and a combination partner, are both administered to a patient simultaneously in the
25 form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, *e.g.*, a crystalline compound of formula I and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.*,
30 the administration of three or more active ingredients.

Thus, the crystalline compound of formula I, especially polymorph form A, is useful in combination with known anti-cancer agents. Such known anti-cancer agents include, but are not limited to, one or more compounds selected from the the group consisting of kinase inhibitors, anti-estrogens, anti androgens, other inhibitors, cancer chemotherapeutic drugs, alkylating agents, chelating agents , biological response modifiers, cancer vaccines, agents for antisense therapy as set forth below:

A. Kinase Inhibitors: Kinase inhibitors for use as anticancer agents in conjunction with the compound of the formula (I) include inhibitors of Epidermal Growth Factor Receptor (EGFR) kinases such as small molecule quinazolines, for example gefitinib (US 5457105, US 5616582, and US 5770599), ZD-6474 (WO 01/32651), erlotinib (Tarceva[®], US 5,747,498 and WO 96/30347), and lapatinib (US 6,727,256 and WO 02/02552); Vascular Endothelial Growth Factor Receptor (VEGFR) kinase inhibitors, including SU-11248 (WO 01/60814), SU 5416 (US 5,883,113 and WO 99/61422), SU 6668 (US 5,883,113 and WO 99/61422), CHIR-258 (US 6,605,617 and US 6,774,237), vatalanib or PTK-787 (US 6,258,812), VEGF-Trap (WO 02/57423), B43-Genistein (WO-09606116), fenretinide (retinoic acid p-hydroxyphenylamine) (US 4,323,581), IM-862 (WO 02/62826), bevacizumab or Avastin[®] (WO 94/10202), KRN-951, 3-[5-(methylsulfonylpiperadine methyl)-indolyl]-quinolone, AG-13736 and AG-13925, pyrrolo[2,1-f][1,2,4]triazines, ZK-304709, Veglin[®], VMDA-3601, EG-004, CEP-701 (US 5,621,100), Cand5 (WO 04/09769); Erb2 tyrosine kinase inhibitors such as pertuzumab (WO 01/00245), trastuzumab, and rituximab; Akt protein kinase inhibitors, such as RX-0201; Protein Kinase C (PKC) inhibitors, such as LY-317615 (WO 95/17182), and perifosine (US 2003171303); Raf/Map/MEK/Ras kinase inhibitors including sorafenib (BAY 43-9006), ARQ-350RP, LERafAON, BMS-354825 AMG-548, and others disclosed in WO 03/82272; Fibroblast Growth Factor Receptor (FGFR) kinase inhibitors; Cell Dependent Kinase (CDK) inhibitors, including CYC-202 or roscovitine (WO 97/20842 and WO 99/02162); Platelet-Derived Growth Factor Receptor (PDGFR) kinase inhibitors such as CHIR-258, 3G3 mAb, AG-13736, SU-11248 and SU6668; and Bcr-Abl kinase inhibitors and fusion proteins such as STI-571 or Gleevec[®] (imatinib).

B. Anti-Estrogens: Estrogen-targeting agents for use in anticancer therapy in conjunction with the compound of formula (I) include Selective Estrogen Receptor Modulators (SERMs) including tamoxifen, toremifene, raloxifene; aromatase inhibitors including Arimidex[®] or anastrozole; Estrogen Receptor Downregulators (ERDs) including Faslodex[®] or fulvestrant.

C. Anti-Androgens: Androgen-targeting agents for use in anticancer therapy in conjunction with the crystalline compound of formula I include flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids.

D. Other Inhibitors: Other inhibitors for use as anticancer agents in conjunction with the crystalline compound of formula I include protein farnesyl transferase inhibitors including tipifarnib or R-115777 (US 2003134846 and WO 97/21701), BMS-214662, AZD-3409, and FTI-277; topoisomerase inhibitors including merbarone and diflomotecan (BN-80915); mitotic kinesin spindle protein (KSP) inhibitors including SB-743921 and MKI-833; proteasome modulators such as bortezomib or Velcade[®] (US 5,780,454), XL-784; and cyclooxygenase 2 (COX-2) inhibitors including non-steroidal antiinflammatory drugs I (NSAIDs).

E. Cancer Chemotherapeutic Drugs: Particular cancer chemotherapeutic agents for use as anticancer agents in conjunction with the crystalline compound of formula I include anastrozole (Arimidex[®]), bicalutamide (Casodex[®]), bleomycin sulfate (Blenoxane[®]), busulfan (Myleran[®]), busulfan injection (Busulfex[®]), capecitabine (Xeloda[®]), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin[®]), carmustine (BiCNU[®]), chlorambucil (Leukeran[®]), cisplatin (Platinol[®]), cladribine (Leustatin[®]), cyclophosphamide (Cytosan[®] or Neosar[®]), cytarabine, cytosine arabinoside (Cytosar-U[®]), cytarabine liposome injection (DepoCyt[®]), dacarbazine (DTIC-Dome[®]), dactinomycin (Actinomycin D, Cosmegen), daunorubicin hydrochloride (Cerubidine[®]), daunorubicin citrate liposome injection (DaunoXome[®]), dexamethasone, docetaxel (Taxotere[®]), doxorubicin hydrochloride (Adriamycin[®], Rubex[®]), etoposide (Vepesid[®]), fludarabine phosphate (Fludara[®]), 5-fluorouracil (Adrucil[®], Efudex[®]), flutamide (Eulexin[®]), tezacitibine, Gemcitabine (difluorodeoxycytidine), hydroxyurea (Hydrea[®]), Idarubicin (Idamycin[®]), ifosfamide (IFEX[®]),

irinotecan (Camptosar[®]), L-asparaginase (ELSPAR[®]), leucovorin calcium, melphalan (Alkeran[®]), 6-mercaptopurine (Purinethol[®]), methotrexate (Folex[®]), mitoxantrone (Novantrone[®]), mylotarg, paclitaxel (Taxol[®]), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel[®]), tamoxifen citrate (Nolvadex[®]), teniposide (Vumon[®]), 6-thioguanine, thiotepa, tirapazamine (Tirazone[®]), topotecan hydrochloride for injection (Hycamptin[®]), vinblastine (Velban[®]), vincristine (Oncovin[®]), and vinorelbine (Navelbine[®]).

F. Alkylating Agents: Alkylating agents for use in conjunction with the crystalline compound of formula I include VNP-40101M or cloretizine, oxaliplatin (US 4,169,846, WO 03/24978 and WO 03/04505), glufosfamide, mafosfamide, etopophos (US 5,041,424), prednimustine; treosulfan; busulfan; iroflufen (acylfulvene); penclomedine; pyrazoloacridine (PD-115934); O6-benzylguanine; decitabine (5-aza-2-deoxycytidine); brostallicin; mitomycin C (MitoExtra); TLK-286 (Telcyta[®]); temozolomide; trabectedin (US 5,478,932); AP-5280 (Platinat formulation of Cisplatin); porfiromycin; and clearazide (meclorethamine).

G. Chelating Agents: Chelating agents for use in conjunction with the crystalline compound of formula I include tetrathiomolybdate (WO 01/60814); RP-697; Chimeric T84.66 (cT84.66); gadofosveset (Vasovist[®]); deferoxamine; and bleomycin optionally in combination with electroporation (EPT).

H. Biological Response Modifiers: Biological response modifiers, such as immune modulators, for use in conjunction with the crystalline compound of formula I include staurosporine and macrocyclic analogs thereof, including UCN-01, CEP-701 and midostaurin (see WO 02/30941, WO 97/07081, WO 89/07105, US 5,621,100, WO 93/07153, WO 01/04125, WO 02/30941, WO 93/08809, WO 94/06799, WO 00/27422, WO 96/13506 and WO 88/07045); squalamine (WO 01/79255); DA-9601 (WO 98/04541 and US 6,025,387); alemtuzumab; interferons (*e.g.*, IFN-a, IFN-b etc.); interleukins, specifically IL-2 or aldesleukin as well as IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, and active biological variants thereof having amino acid sequences greater than 70% of the native human sequence; altretamine (Hexalen[®]); SU 101 or leflunomide (WO 04/06834 and US 6,331,555);

imidazoquinolines such as resiquimod and imiquimod (US 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 5,352,784, 5,494,916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, and 5,525,612); and SMIPs, including benzazoles, anthraquinones, thiosemicarbazones, and tryptanthrins (WO 04/87153, WO 04/64759, and WO 04/60308).

5 **I. Cancer Vaccines:** Anticancer vaccines for use in conjunction with the crystalline compound of formula I include Avicine[®] (Tetrahedron Lett. 26:2269-70 (1974)); oregovomab (OvaRex[®]); Theratope[®] (STn-KLH); Melanoma Vaccines; GI-4000 series (GI-4014, GI-4015, and GI-4016), which are directed to five mutations in the Ras protein; GlioVax-1; MelaVax; Advexin[®] or INGN-201 (WO 95/12660); Sig/E7/LAMP-1, encoding HPV-16 E7; MAGE-3
10 Vaccine or M3TK (WO 94/05304); HER-2VAX; ACTIVE, which stimulates T-cells specific for tumors; GM-CSF cancer vaccine; and Listeria monocytogenes-based vaccines.

J. Antisense Therapy: Anticancer agents for use in conjunction with the crystalline compound of formula I also include antisense compositions, such as AEG-35156 (GEM-640); AP-12009 and AP-11014 (TGF-beta2-specific antisense oligonucleotides); AVI-4126; AVI-
15 4557; AVI-4472; oblimersen (Genasense[®]); JFS2; aprinocarsen (WO 97/29780); GTI-2040 (R2 ribonucleotide reductase mRNA antisense oligo) (WO 98/05769); GTI-2501 (WO 98/05769); liposome-encapsulated c-Raf antisense oligodeoxynucleotides (LErafAON) (WO 98/43095); and Sirna-027 (RNAi-based therapeutic targeting VEGFR-1 mRNA).

 The crystalline compound of formula I can also be combined in a pharmaceutical
20 composition with bronchodilatory or antihistamine drugs substances. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide, and tiotropium bromide, and β -2- adrenoreceptor agonists such as salbutamol, terbutaline, salmeterol, carmoterol, milveterol and, especially, formoterol or indacaterol. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride,
25 clemastine fumarate, promethazine, loratadine, desloratadine diphenhydramine and fexofenadine hydrochloride.

 The invention provides in a further aspect a combination comprising a crystalline compound of formula I and one or more compounds that are useful for the treatment of a thrombolytic disease, heart disease, stroke, etc. Such compounds include aspirin, a streptokinase,

a tissue plasminogen activator, a urokinase, a anticoagulant, antiplatelet drugs (e.g. PLAVIX; clopidogrel bisulfate), a statin (e.g., LIPITOR or Atorvastatin calcium), ZOCOR (Simvastatin), CRESTOR (Rosuvastatin), etc.), a Beta blocker (e.g., Atenolol), NORVASC (amlodipine besylate), and an ACE inhibitor (e.g., lisinopril).

5 The invention provides in a further aspect a combination comprising a crystalline compound of formula I and one or more compounds that are useful for the treatment of antihypertension. Such compounds include ACE inhibitors, lipid lowering agents such as statins, LIPITOR (Atorvastatin calcium), calcium channel blockers such as NORVASC (amlodipine besylate).

10 The invention provides in a further aspect a combination comprising a crystalline compound of formula I and one or more compounds selected from the group consisting of fibrates, beta-blockers, NEPI inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

 The invention provides in a further aspect a combination comprising a crystalline
15 compound of formula I and a compound suitable for the treatment of inflammatory diseases, including rheumatoid arthritis. Such compound may be selected from the group consisting of TNF- α inhibitors such as anti-TNF- α monoclonal antibodies (such as REMICADE, CDP-870) and D2E7 (HUMIRA) and TNF receptor immunoglobulin fusion molecules (such as ENBREL), IL-1 inhibitors, receptor antagonists or soluble IL-1R α (e.g. KINERET or ICE inhibitors),
20 nonsteroidal anti-inflammatory agents (NSAIDS), piroxicam, diclofenac, naproxen, flurbiprofen, fenoprofen, ketoprofen ibuprofen, fenamates, mefenamic acid, indomethacin, sulindac, apazone, pyrazolones, phenylbutazone, aspirin, COX-2 inhibitors (such as CELEBREX (celecoxib), PREXIGE (lumiracoxib)), metalloprotease inhibitors (preferably MMP-13 selective inhibitors), p2x7 inhibitors, α 2 α inhibitors, NEUROTIN, pregabalin, low dose methotrexate, leflunomide,
25 hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

 The invention provides in a further aspect a combination comprising a crystalline compound of formula I and a compound suitable for the treatment of osteoarthritis. Such compound may be selected from the group consisting of standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such

as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, lumiracoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The invention provides in a further aspect a combination comprising a crystalline compound of formula I and an antiviral agent and/or an antiseptis compound. Such antiviral agent may be selected from the group consisting of Viracept, AZT, acyclovir and famciclovir. Such antiseptis compound may be selected from the group consisting of Valant.

The invention provides in a further aspect a combination comprising a crystalline compound of formula I and one or more agents selected from the group consisting of CNS agents such as antidepressants (sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex; MAOB inhibitors (such as selegine and rasagiline); comP inhibitors (such as Tasmar); A-2 inhibitors; dopamine reuptake inhibitors; NMDA antagonists; Nicotine agonists; Dopamine agonists; and inhibitors of neuronal nitric oxide synthase).

The invention provides in a further aspect a combination comprising a crystalline compound of formula I and one or more anti-Alzheimer's drugs. Such anti-Alzheimer Drug may be selected from the group consisting of donepezil, tacrine, $\alpha 2 \delta$ inhibitors, NEUROTIN, pregabalin, COX-2 inhibitors, propentofylline or metryfonate.

The invention provides in a further aspect a combination comprising a crystalline compound of formula I and an osteoporosis agents and/or an immunosuppressant agent. Such osteoporosis agents may be selected from the group consisting of EVISTA (raloxifene hydrochloride), droloxifene, lasofoxifene or fosomax. Such immunosuppressant agents may be selected from the group consisting of FK-506 and rapamycin.

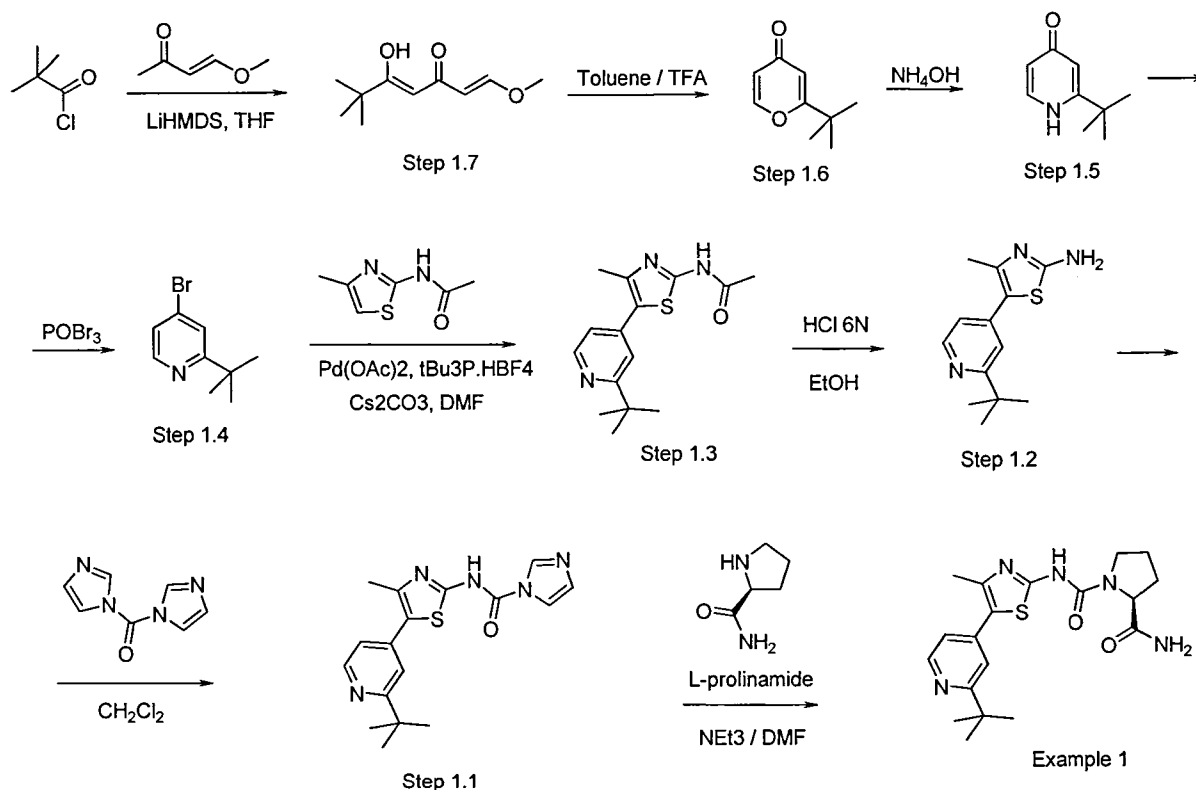
Kits

The present invention also provides kits for use by a consumer for treating disease. The kits comprise a) a pharmaceutical composition comprising a crystalline compound of formula I and a pharmaceutically acceptable carrier, vehicle or diluent; and, optionally, b) instructions

describing a method of using the pharmaceutical composition for treating the specific disease. Representative kits include a PI3K inhibitor compound (*e.g.*, a crystalline compound of formula I) and a package insert or other labeling including directions for treating a cellular proliferative disease by administering a PI3K inhibitory amount of the compound(s).

5 A “kit” as used in the instant application includes a container for containing the separate unit dosage forms such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a “refill” of tablets for placement into a different container), or a blister
10 pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

15 An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of
20 individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the
25 recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

*Exemplification of the Invention***Scheme 1.** Synthesis of (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-{[5-(2-*tert*-butyl-pyridin-4-yl)-4-methyl-thiazol-2-yl]-amide}

5

Example 1: Synthesis of (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-{[5-(2-*tert*-butyl-pyridin-4-yl)-4-methyl-thiazol-2-yl]-amide}

Triethylamine (1.54 mL, 11.1 mmol, 3 eq) is added to a solution of imidazole-1-carboxylic acid [5-(2-*tert*-butyl-pyridin-4-yl)-4-methyl-thiazol-2-yl]-amide (Step 1.1) (1.26 g, 3.7 mmol) and L-prolinamide (0.548 g, 4.8 mmol, 1.3 eq) in DMF (25 mL), under an argon atmosphere. The reaction mixture is stirred for 14 h at rt, quenched by addition of a saturated solution of NaHCO₃, and extracted with EtOAc. The organic phase is washed with a saturated solution of NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue is purified by silica gel column chromatography (DCM/MeOH, 1:0 → 94:6), followed by trituration in Et₂O to

afford 1.22 g of the title compound as an off-white solid: ESI-MS: 388.1 [M+H]⁺; t_R = 2.35 min (System 1); TLC: R_f = 0.36 (DCM/MeOH, 9:1).

Step 1.1: Imidazole-1-carboxylic acid [5-(2-tert-butyl-pyridin-4-yl)-4-methyl-thiazol-2-yl]-amide

5 A mixture of 5-(2-tert-butyl-pyridin-4-yl)-4-methyl-thiazol-2-ylamine (Step 1.2) (1 g, 4.05 mmol) and 1,1'-carbonyldiimidazole (0.984 g, 6.07 mmol, 1.5 eq) in DCM (50 mL) is stirred for 4 h at reflux and allowed to cool. The resulting precipitate is collected by filtration to provide 1.26 g of the title compound as white solid: ESI-MS: 340.2 [M-H]⁻; t_R = 2.85 min (System 1).

Step 1.2: 5-(2-tert-Butyl-pyridin-4-yl)-4-methyl-thiazol-2-ylamine

10 A mixture of N-[5-(2-tert-butyl-pyridin-4-yl)-4-methyl-thiazol-2-yl]-acetamide (Step 1.3) (2 g, 7 mmol), a 6N aqueous solution of HCl (10 mL) and EtOH (50 mL) is stirred for 2 h at 85°C, allowed to cool, quenched by addition of a saturated solution of NaHCO₃ and extracted with DCM/MeOH (9:1, v/v). The organic phase is washed with a saturated solution of NaHCO₃,
15 dried (Na₂SO₄), filtered and concentrated. The residue is purified by silica gel column chromatography (DCM/MeOH, 1:0 → 96:4) to afford 1.21 g of the title compound as a yellow solid: ESI-MS: 248.1 [M+H]⁺; TLC: R_f = 0.36 (DCM/MeOH, 9:1).

20 Step 1.3: N-[5-(2-tert-Butyl-pyridin-4-yl)-4-methyl-thiazol-2-yl]-acetamide

25 A mixture of 2-acetamido-4-methylthiazole (1.2 g, 7.7 mmol, 1.1 eq), cesium carbonate (4.55 g, 14 mmol, 2 eq), tri-tert-butylphosphonium tetrafluoroborate (0.406 g, 1.4 mmol, 0.2 eq), palladium (II) acetate (0.15 g, 0.7 mmol, 0.1 eq) and 4-bromo-2-tert-butyl-pyridine (Step 1.4) (1.5 g, 7 mmol) in DMF (50 mL) is stirred for 1.5 h at 90°C under an argon atmosphere, allowed to cool, quenched by addition of a saturated solution of NaHCO₃ and filtered through a pad of celite. The filtrate is extracted with EtOAc. The organic phase is washed with a saturated solution of NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue is purified by silica

gel column chromatography (DCM/MeOH, 1:0 → 97:3) to afford 2.02 g of the title compound as a yellow solid: ESI-MS: 290.1 [M+H]⁺; TLC: R_f = 0.35 (DCM/MeOH, 9:1).

Step 1.4: 4-Bromo-2-tert-butyl-pyridine

5 A mixture of 2-tert-butyl-1H-pyridin-4-one (Step 1.5) (4.25 g, 28 mmol) and POBr₃ (8.88 g, 31 mmol, 1.1 eq) is heated to 120°C, stirred for 15 min, allowed to cool, quenched by addition of a saturated solution of NaHCO₃ and extracted with DCM/MeOH (9:1, v/v). The organic phase is washed with a saturated solution of NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue is purified by silica gel column chromatography (Hex/EtOAc, 95:5) to
10 afford 5.18 g of the title compound as a yellow oil: ESI-MS: 214.0 / 216.0 [M+H]⁺; t_R = 2.49 min (System 1); TLC: R_f = 0.35 (Hex/EtOAc, 1:1).

Step 1.5: 2-tert-Butyl-1H-pyridin-4-one

A mixture of 2-tert-butyl-pyran-4-one (Step 1.6) (5.74 g, 37.7 mmol) and a 30% aqueous
15 solution of ammonium hydroxide (100 mL) is stirred for 1 h at reflux, allowed to cool and concentrated. The residue is triturated with MeOH (200 mL) and filtered. The filtrate is concentrated and the residue purified by silica gel column chromatography (DCM/MeOH/NH₃aq, 94:5:1 → 92:7:1) to afford 4.46 g of the title compound as a yellow solid: ESI-MS: 152.0 [M+H]⁺; t_R = 1.45 min (System 1); TLC: R_f = 0.11 (DCM/MeOH, 9:1).

20

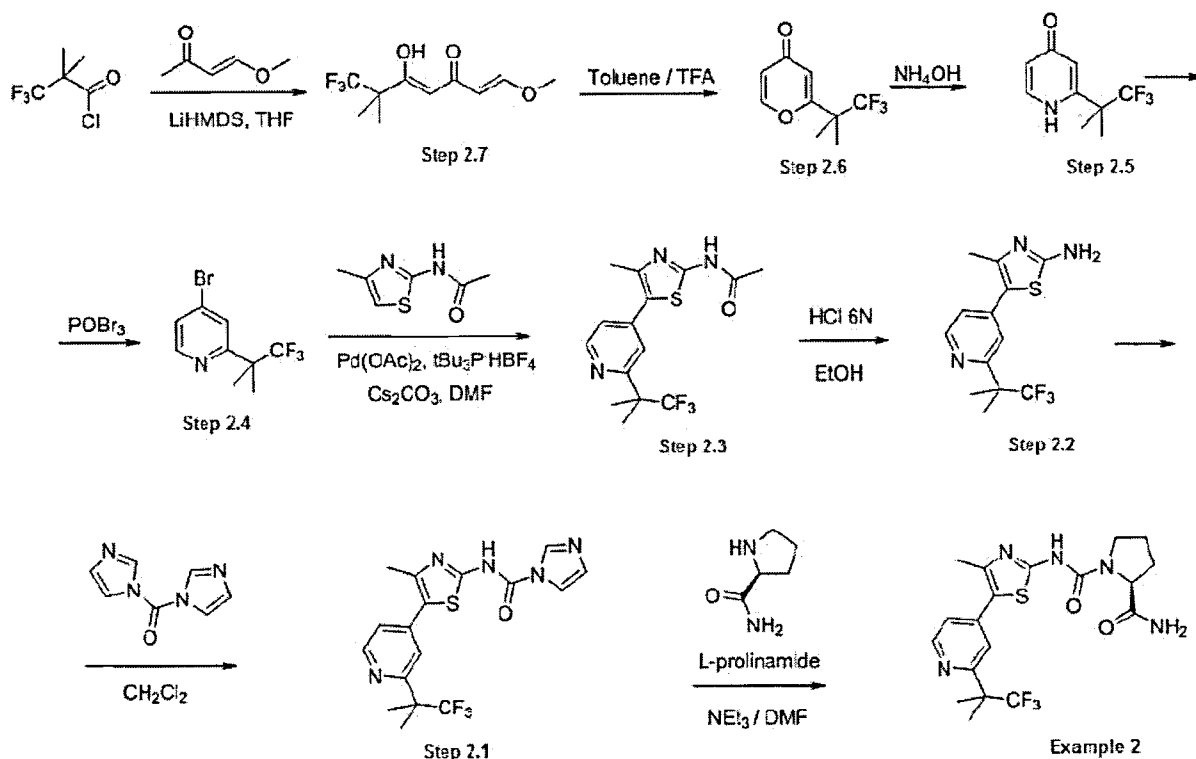
Step 1.6: 2-tert-Butyl-pyran-4-one

A mixture of 5-hydroxy-1-methoxy-6,6-dimethyl-hepta-1,4-dien-3-one (Step 1.7) (6.8 g, 36.9 mmol) and TFA (5.65 mL, 74 mmol, 2 eq) in benzene (250 mL) is stirred for 14 h at rt and concentrated. Purification of the residue by silica gel column chromatography (Hex/EtOAc, 1:0
25 → 75:25) provides 5.74 g of the title compound as a yellow oil: ESI-MS: 153.1 [M+H]⁺; t_R = 3.21 min (System 1); TLC: R_f = 0.22 (Hex/EtOAc, 1:1).

Step 1.7: 5-Hydroxy-1-methoxy-6,6-dimethyl-hepta-1,4-dien-3-one

LiHMDS (1M in THF, 100 mL, 2 eq) is added dropwise to a cold (-78°C) solution of 4-methoxy-3-buten-2-one (10 mL, 100 mmol, 2 eq) in THF (400 mL). After a 30 min stirring at -78°C, a solution of pivaloyl chloride (6.12 mL, 50 mmol) in THF (100 mL) is added. The
5 resulting mixture is allowed to warm to rt over 2 h and quenched by addition of a saturated solution of NH₄Cl. THF is removed under vacuum. The concentrated mixture is extracted with Et₂O. The organic phase is washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue is purified by silica gel column chromatography (Hex/EtOAc, 1:0 → 85:15) to afford 6.83 g of the title compound as a yellow oil: ESI-MS: 185.1 [M+H]⁺; TLC: R_f = 0.87
10 (Hex/EtOAc, 1:1).

Scheme 2. Synthesis of (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide)



Example 2: (S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide)

The title compound is prepared in analogy to the procedure described in Example 1 but with the following modifications. In Step 2.1 (corresponding to Step 1.1 of Example 1), the reaction mixture is stirred for 14 h at reflux. In Step 2.2 (corresponding to Step 1.2 of Example 1), the reaction mixture is stirred for 1 h at 85 °C and extracted with ethyl acetate after being quenched. In step 2.3 (corresponding to Step 1.3 of Example 1), the reaction mixture is stirred for 2.5 h at 120 °C. In Step 2.4 (corresponding to Step 1.4 of Example 1), the reaction mixture is stirred for 1 h at 83 °C and extracted with ethyl acetate after being quenched. In Step 2.5 (corresponding to Step 1.5 of Example 1), the reaction mixture is stirred for 1 h at 65 °C and trituration in methanol is not performed. In Step 2.6 (corresponding to Step 1.6 of Example 1),

the crude product is not purified. In Step 2.7 (corresponding to Step 1.7 of Example 1), 3,3,3-trifluoro-2,2-dimethyl-propionyl chloride is used.

Title compound: ESI-MS: 442.0 $[M+H]^+$; t_R = 3.02 min (System 1); TLC: R_f = 0.35 (DCM/MeOH, 9:1).

5

Example 3: Preparation of Polymorph Form A

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (10.0 g) was suspended in ethanol/water (85:15 v/v; 75 mL) and the mixture was heated to 75 °C. The solution was clear-filtered into a second flask and the first flask was then washed with ethanol/water (4:6 v/v; 20 mL), followed by water (10 mL). The clear solution was stirred at 75 °C for an additional 30 minutes. The clear solution was then cooled to 2 °C over 2 hours and the obtained thick suspension was stirred at 2 °C for an additional hour. The mixture was then filtered, and the flask and filter cake were washed with ethanol/water (1:1 v/v; 20 mL), followed by ethyl acetate (10 mL). The wet filter cake was returned to the flask and suspended in ethyl acetate (75 mL). the mixture was heated to 78 °C and was stirred under reflux for 1 hour. During this time, 15 mL ethyl acetate was distilled off. The mixture was then cooled to 2 °C over 2 hours and the suspension was stirred at 2 °C for an additional hour. The mixture was filtered, and the flask and filter cake were washed with cold ethyl acetate (12 mL). The filter cake was then dried under 1-50 mbar vacuum at 50 °C to yield the polymorph form A (7.3 g).

Tables

Table 1. List of most significant peaks of Figure 1 (Polymorph Form A)

2-Theta in deg	Intensity in %
4.2	79
8.5	19
9.3	25
10.5	13
15.5	12
16.8	36
17.1	100

18.2	36
20.1	54
20.4	87
21.0	34
21.3	27
21.7	50
22.7	10
24.9	10
25.1	15
25.6	11
26.2	20
26.5	16
27.0	33
27.9	10
31.2	11
33.0	11

The strongest line in the pattern is observed at an angle of diffraction of 2-Theta of 17.1° and has a relative intensity of 100%. X-ray powder diffraction measurement was obtained using a Bruker X-ray diffractometer with a CuK α radiation source; Step: 0.017°; Range: 2.00° - 40.00°;

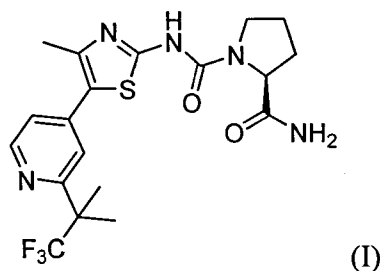
- 5 Constant scan rate: 0.3 s/step; All 2-Theta values +/- 0.3°.

Biological Activity

The biological activity of the compound of formula I is described in WO 2010/029082. This compound demonstrated activity against the phosphatidylinositol 3-kinase (PI3K).

Claims

1. A crystalline form of the compound of formula I,



or a hydrate or solvate of the crystalline form of the compound of formula I.

- 5 2. The compound of claim 1 in polymorph form A.
3. The compound of claim 2, which shows on X-ray powder diffraction peaks at an angle of diffraction 2Theta of $17.1^{\circ} \pm 0.3^{\circ}$ and $20.4^{\circ} \pm 0.3^{\circ}$.
4. The compound of claim 2, which shows on X-ray powder diffraction peaks at an angle of diffraction 2Theta of $4.2^{\circ} \pm 0.3^{\circ}$ and $21.7^{\circ} \pm 0.3^{\circ}$.
- 10 5. The compound of claim 2, which shows on X-ray powder diffraction peaks at an angle of diffraction 2Theta of $18.2^{\circ} \pm 0.3^{\circ}$ and $20.1^{\circ} \pm 0.3^{\circ}$.
6. The compound of any one of claims 1 or 2, which shows on X-ray powder diffraction peaks at an angle of diffraction 2Theta of $17.1^{\circ} \pm 0.3^{\circ}$, $20.4^{\circ} \pm 0.3^{\circ}$, $4.2^{\circ} \pm 0.3^{\circ}$, $21.7^{\circ} \pm 0.3^{\circ}$, $18.2^{\circ} \pm 0.3^{\circ}$ and $20.1^{\circ} \pm 0.3^{\circ}$.
- 15 7. The compound of any one of claims 1-6, which shows an FT-IR spectrum having peaks at values of about 1693 and about 1668 cm^{-1} .
8. The compound of any one of claims 7, which shows an FT-IR spectrum having further peaks at values of about 1599 and about 1540 cm^{-1} .

9. The compound of any one of claims 1-6, which shows an FT-IR spectrum substantially in accordance with Figure 2 with exclusion of the peaks at values of about 2925 and 2854 in the absence of Nujol®.
10. The compound of any one of claims 1-6, which shows a differential scanning calorimetry thermogram having a characteristic peak expressed in units of °C at a temperature of about 203.
11. A pharmaceutical composition comprising the polymorph form A of the compound of formula I according to claims 2-6, and a pharmaceutically acceptable carrier or diluent.
12. A pharmaceutical composition of claim 11, wherein the composition is formulated for oral administration in the form of a pill, capsule, lozenge or tablet.
13. A process for the preparation of the polymorph according to any one of claims 1-10, which comprises the following steps: (a) dissolving a compound of formula I in 50-90 % aqueous acetone, (b) adding water to achieve lower solubility, and (c) keeping the temperature above 30 degrees C to form the polymorph form A.
14. The process of claim 13, wherein said temperature is in the range of 30-70 degrees C.
15. A method for the treatment of disorders mediated by PI3K, comprising administering to a patient in need of such treatment an effective amount of the compound of any one of claims 1-10.
16. The method of claim 15, wherein the disorder is a cellular proliferative disease selected from the group consisting of benign or malignant tumor; a cancer selected from sarcoma; lung; bronchus; prostate; breast (including sporadic breast cancers and sufferers of Cowden disease); pancreas; gastrointestinal cancer; colon; rectum; colon carcinoma; colorectal adenoma; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; glioma; glioblastoma; endometrial; melanoma; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary; multiple myeloma; esophagus; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic

leukemia; myeloid leukemia; brain; a carcinoma of the brain; oral cavity and pharynx;
larynx; small intestine; non-Hodgkin lymphoma; melanoma; villous colon adenoma; a
neoplasia; a neoplasia of epithelial character; lymphomas; a mammary carcinoma; basal
cell carcinoma; squamous cell carcinoma; actinic keratosis; tumor diseases, including solid
5 tumors; a tumor of the neck or head; polycythemia vera; essential thrombocythemia;
myelofibrosis with myeloid metaplasia; and Walden stroem disease.

17. Use of a compound of any one of claims 1-10 for the preparation of a medicament for the
treatment of disorders mediated by PI3K.

18. The use of claim 17, wherein the disorder is a cellular proliferative disease.

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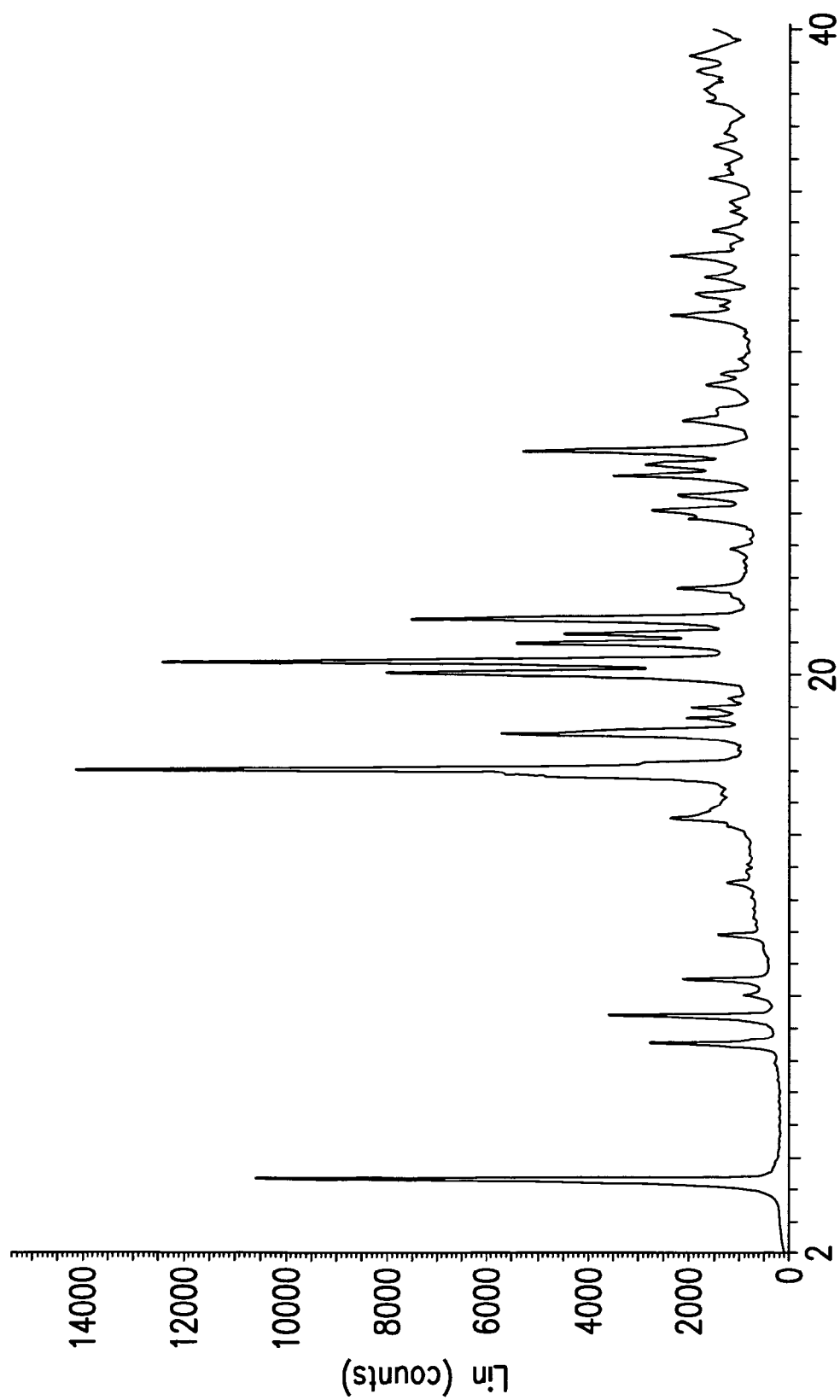


FIG.1

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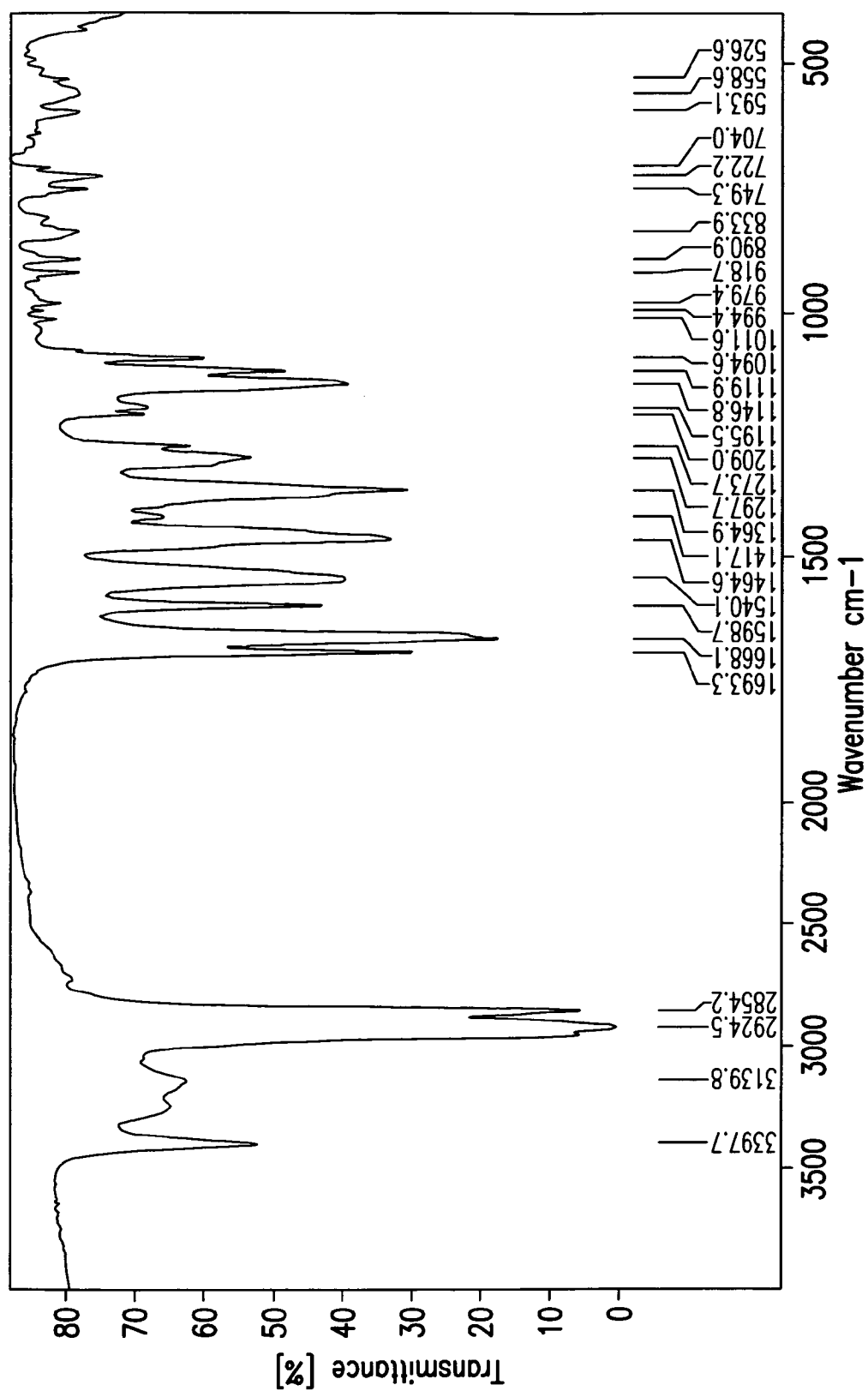


FIG. 2

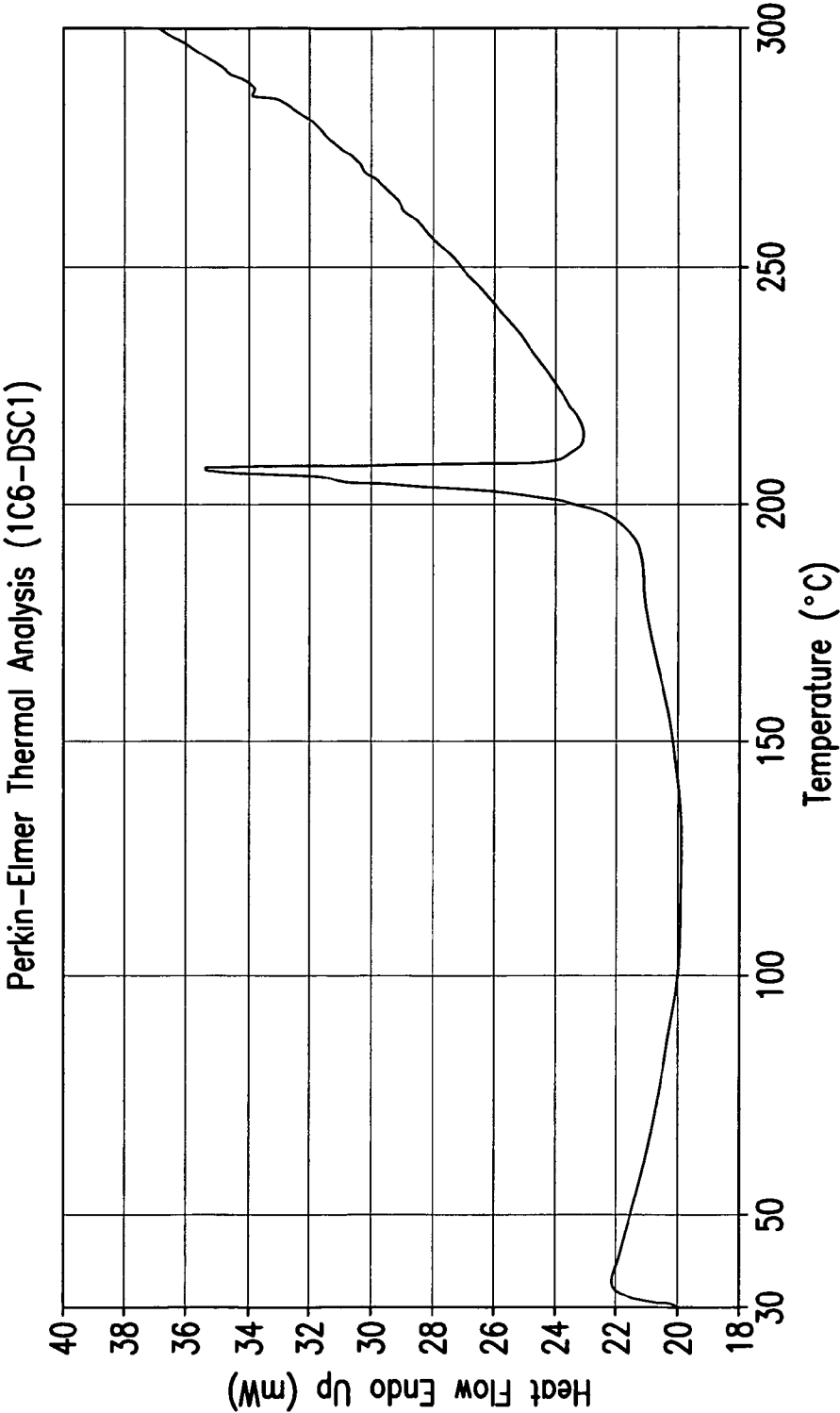


FIG.3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/063256

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/14 A61K31/4439 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/029082 A1 (NOVARTIS AG [CH]; CARAVATTI GIORGIO [CH]; FAIRHURST ROBIN ALEC [GB]; F) 18 March 2010 (2010-03-18) cited in the application page 55 - page 56; example 15 -----	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

20 September 2011

Date of mailing of the international search report

14/10/2011

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Fink, Dieter

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/063256

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WO 2010029082	A1	18-03-2010	
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