Solid Forms and Salts of Tetrahydro-Pyrido-Pyrimidine Derivatives

FIELD OF THE INVENTION

The invention relates to novel solid forms and salts of tetrahydro-pyrido-pyrimidine derivatives, processes for their preparation and their use in pharmaceutical compositions.

BACKGROUND OF THE INVENTION

The international patent application PCT/EP2011/061393, published as WO2012/004299 discloses substituted tetrahydro-pyrido-pyrimidine derivatives that are suitable for the treatment of a disorder or disease which is mediated by the activity of the PI3K enzymes. PCT/EP2011/061393 discloses {(*S*)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone and 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one and methods of making these compounds.

These compounds are useful for the treatment, either alone or in combination, with one or more other pharmacologically active compounds, of PI3K-related diseases including but not limited to autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection, cancers eg of hematopoietic origin or solid tumors.

These compounds are also useful for treatment, either alone or in combination, with one or more other pharmacologically active compounds, includes methods of treating conditions, diseases or disorders in which one or more of the functions of B cells such as antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren‘s syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease.

SUMMARY OF THE INVENTION

The invention relates to crystalline anhydrous forms, crystalline solvate forms and/or salt forms including crystalline salt forms of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or salt forms including crystalline salt forms of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on; pharmaceutical compositions and combinations including these forms. The invention further relates to methods of using these forms, including their pharmaceutical compositions and combinations for the treatment of diseases mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform.

It is well known that the crystalline form of the active pharmaceutical ingredient (API) of a particular drug is often an important determinant of the drug's ease of preparation, hygroscopicity, stability, solubility, storage stability, ease of formulation, rate of dissolution in gastrointestinal fluids and in vivo bioavailability. Crystalline forms occur where the same composition of matter crystallizes in a different lattice arrangement resulting in different thermodynamic properties and stabilities specific to the particular crystalline form. Crystalline forms may also include different hydrates or solvates of the same compound. In deciding which form is preferable, the numerous properties of the forms are compared and the preferred form chosen based on the many physical property variables. It is entirely possible that one form can be preferable in some circumstances where certain aspects such as ease of preparation, stability, etc. are deemed to be critical. In other situations, a different form may be preferred for greater dissolution rate and/or superior bioavailability. It is not yet possible to predict whether a particular compound or salt of a compound will form polymorphs, whether any such polymorphs will be suitable for commercial use in a therapeutic composition, or which polymorphs will display such desirable properties.

DESCRIPTION OF THE DRAWINGS

Figure 1 discloses the X-ray Powder Diffraction Pattern of Example 1 citrate salt

Figure 2 discloses the X-ray Powder Diffraction Pattern of Example 1 fumarate salt

Figure 3 discloses the X-ray Powder Diffraction Pattern of Example 1 napadisylate salt

Figure 4 discloses the X-ray Powder Diffraction Pattern of Example 67 phosphate salt

Figure 5 discloses the X-ray Powder Diffraction Pattern of Example 67 HCl salt

Figure 6 discloses the X-ray Powder Diffraction Pattern of Example 67 hippurate salt

Figure 7 discloses the X-ray Powder Diffraction Pattern of Example 1 anhydrous form

Figure 8 discloses the X-ray Powder Diffraction Pattern of Example 1 trihydrate

Figure 9 discloses the X-ray Powder Diffraction Pattern of Example 67 anhydrous form

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention relates to an anhydrous crystalline form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone.

In another embodiment, the anhydrous crystalline form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 7.5, 10.9, 11.7, 14.3, 15.1, 15.8, 16.7, 17.7, 18.9, 20.5, 21.8, 22.5, 23.3, 24.2, 24.6, 25.0, 25.6, 26.2, 27.0, 28.0, 29.1, 32.8 and 34.6.

In another embodiment, the invention relates to a trihydrate crystalline form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone.

In another embodiment, the trihydrate crystalline form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 6.6, 8.9, 13.3, 14.5, 15.0, 16.5, 17.5, 17.7, 18.2, 20.0, 21.6, 22.6, 23.8, 24.4, 26.7, 27.5, 27.8, 29.2, 33.3, 33.9, 35.7 and 38.8.

In another embodiment, the invention relates to a salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, wherein the anion is selected from citrate, fumarate or napadisylate.

In another embodiment, the invention relates to a salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, wherein the anion is selected from citrate.

In another embodiment, the invention relates to a citrate salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, in form of a monohydrate.

In another embodiment, the monohydrate citrate salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-

pyran-4-yl)-methanone is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.7, 11.5, 12.1, 14.3, 15.4, 17.2, 17.9, 19.3, 20.2, 20.7, 21.9, 23.3, 23.9, 25.5, 27.0, 27.7, 29.8 and 30.3.

In another embodiment, the invention relates to a salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, wherein the anion is selected from fumarate.

In another embodiment, the invention relates to a fumarate salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, in form of a monohydrate.

In another embodiment, the monohydrate fumarate salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 6.0, 6.5, 9.8, 12.3, 13.1, 15.6, 17.7, 19.1, 19.7, 23.9, 24.7, 24.9, 25.2, 26.4 and 27.0.

In another embodiment, the invention relates to a salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, wherein the anion is selected from napadisylate.

In another embodiment, the invention relates to a napadisylate salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, in form of a monohydrate.

In another embodiment, the monohydrate napadisylate salt of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 4.3, 8.5, 9.4, 12.2, 12.9, 13.5, 15.0, 15.6, 16.0, 17.7, 18.9, 19.3, 20.0, 20.8, 21.2, 22.0, 23.0, 24.5 and 26.5.

In another embodiment the invention relates to an anhydrous crystalline form of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one

In another embodiment, the anhydrous crystalline form of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 7.9, 9.6, 11.5, 13.4, 15.2, 15.9, 16.8, 17.6, 18.7, 20.0, 20.6, 22.0, 22.4, 22.7, 23.4, 23.9, 24.5, 25.1, 25.8 and 26.7.

In another embodiment, the invention relates to a salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, wherein the anion is selected from phosphate, chloride or hippurate.

In another embodiment, the invention relates to a salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, wherein the anion is selected from phosphate.

In another embodiment, the invention relates to a phosphate salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, in anhydrous form.

In another embodiment, the anhydrous phosphate salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.2, 9.8, 10.3, 11.6, 14.9, 15.5, 15.9, 16.6, 19.5, 20.7, 21.5, 22.1, 23.3, 25.8, 26.4, 27.2 and 28.2.

In another embodiment, the invention relates to a salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, wherein the anion is selected from chloride.

In another embodiment, the invention relates to a hydrochloride salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, in anhydrous form.

In another embodiment, the anhydrous hydrochloride salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.6, 11.0, 11.3, 11.8, 14.7, 17.1, 18.7, 19.4, 22.0, 22.6, 23.1, 23.7, 24.9 and 25.5.

In another embodiment, the invention relates to a salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, wherein the anion is selected from hippurate.

In another embodiment, the invention relates to a hippurate salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, in anhydrous form.

In another embodiment, the anhydrous hippurate salt of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one is characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.2, 7.5, 10.3, 10.9, 11.8, 13.1, 16.1, 16.7, 17.7, 18.4, 21.2, 23.2, 24.2 and 26.2.

Unless otherwise specified, the term “form of the invention” refers to a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on.

As used herein, the term "a”, "an”, "the” and similar terms used in the context of the present invention, especially in the context of the claims, are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language, *e.g.* "such as”, provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

As used herein, the term “combination” refers to either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on and a combination partner (e.g. an other drug as explained below, also referred to as “therapeutic agent” or “co-agent”) may be administered independently at the same time or separately within 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 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 anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on 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. the administration of three or more active ingredients.

As used herein, the term “polymorph” refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal.

As used herein, the term “solvate” refers to a crystalline form of a molecule, atom, and/or ions that further comprises molecules of a solvent or solvents incorporated into the crystalline lattice structure. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. For example, a solvate with a nonstoichiometric amount of solvent molecules may result from partial loss of solvent from the solvate. Solvates may occur as dimers or oligomers comprising more than one molecule or Compound ABC within the crystalline lattice structure.

Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In another embodiment, the invention relates to the the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on of the present invention as pharmaceutical. The invention thus provides:

- a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, as pharmaceutical / for use as pharmaceutical;

- a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, as medicament / for use as medicament;

- a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for use in therapy;

- a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for the prevention and/or treatment of conditions, diseases or disorders

which are mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform;

- the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for the manufacture of a medicament for the prevention and/or treatment of conditions, diseases or disorders which are mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform;

- A crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for use in the prevention and/or treatment of conditions, diseases or disorders which are mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform;

- the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for the prevention and/or treatment of conditions, diseases or disorders which are mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform;

- the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein for the inhibition of the PI3K, enzymes, preferably of the PI3Kδ isoform ;

- the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for the treatment of a disorder or disease selected from autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection, cancers eg of hematopoietic origin or solid tumors.

- the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for the treatment of a disorder or disease selected from antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren‘s syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; ; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease.

- the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein, for the treatment of a disorder or disease selected from rheumatoid arthritis (RA), pemphigus vulgaris (PV), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple

sclerosis (MS), myasthenia gravis (MG), Sjögren's syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis) , goodpasture's syndrome, transplant rejection and cancers of haematopoietic origin.

- a method of modulating the activity of the PI3K enzymes, preferably the PI3Kδ isoform, in a subject, comprising the step of administering to a subject a therapeutically effective amount of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as definded herein;

- a method for the treatment of a disorder or disease mediated by the PI3K enzymes, preferably by the PI3Kδ isoform. comprising the step of administering to a subject a therapeutically effective amount of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as definded herein;

- a method for inhibition of the PI3K enzymes, preferably the PI3Kδ isoform, in a cell, comprising contacting said cell with an effective amound of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein.

As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

The term "administration" or "administering" of the subject compound means providing a form of the invention to a subject in need of treatment. Administration “in combination with” one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order, and in any route of administration.

Suitably, the invention relates to the treatment, either alone or in combination, with one or more other pharmacologically active compounds, of PI3K-related diseases including but not limited to autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection, cancers eg of hematopoietic origin or solid tumors.

The invention also relates to the treatment, either alone or in combination, with one or more other pharmacologically active compounds, includes methods of treating conditions, diseases or disorders in which one or more of the functions of B cells such as antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren‘s syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria,

allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease.

The invention includes methods of treating conditions, diseases or disorders in which one or more of the functions of neutrophils, such as superoxide release, stimulated exocytosis, or chemoatractic migration are abnormal or are undesirable including rheumatoid arthritis, sepsis, pulmonary or resporatory disorders such as asthma, inflammatory dermatoses such as psoriasis and others.

The invention includes methods of treating conditions, diseases or disorders in which one or more of the functions of basophil and mast cells such as chemoatractic migration or allergen-IgE-mediated degranulation are abnormal or are undesirable including allergic diseases (atopic dermatitis, contact dermatitis, allergic rhinitis) as well as other disorders such as COPD, asthma or emphysema.

The invention includes methods of treating conditions, diseases or disorders in which one or more of the functions of T cells such as cytokine production or cell-mediated cytotoxicity abnormal or are undesirable including rheumatoid arthritis, multiple sclerosis, acute or chronic rejection of cell tissue or organ grafts or cancers of haematopoietic origin.

Further, the invention includes methods of treating neurodegenerative diseases, cardiovascular diseases and platelet aggregation.
Further, the invention includes methods of treating skin diseases such as porphyria cutanea tarda, polymorphous light eruption, dermatomyositis, solar urticaria, oral lichen planus, panniculitis, scleroderma, urticarial vasculitis.

Further, the invention includes methods of treating chronic inflammatory diseases such as sarcoidosis, granuloma annulare.

In other embodiments, the condition or disorder (e.g. PI3K-mediated) is selected from the group consisting 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 haematogical 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 opthalmopathy, 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 another embodiment, the compounds of the present invention are useful in the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarhropathies including ankolsing spondylitis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enterophathics arthritis, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies. Specific auto-immune diseases for which antibodies of the invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopa-thic thrombocytopenia), acquired hemophilia A, cold agglutinin disease, cryoglobulinemia, thrombotic thrombocytopenic purpura, Sjögren’s syndrome, systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, anti-neutrophil cytoplasmic antibody- associated vasculitis, IgM mediated neuropathy, opsoclonus myoclonus syndrome, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson

syndrome, pemphigus vulgaris, pemphigus foliacius, idio-pathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Graves' disease, sarcoidosis, multiple sclerosis, neuromyelitis optica, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior, intermediate and posterior as well as panuveitis), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephro-tic syndrome or minimal change nephropathy), tumors, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

In another embodiment, the compounds of the present invention are useful in the treatment of conditions or disorders selected from the group consisting of, primary cutaneous B-cell lymphoma, immunobullous disease, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa acquisita, chronic graft versus host disease, dermatomyositis, systemic lupus erythematosus, vasculitis, small vessel vasculitis, hypocomplementemic urticarial vasculitis, antineutrophil cytoplasmic antibody-vasculitis, cryoglobulinemia, Schnitzler syndrome, Waldenstrom's macroglobulinemia, angioedema, vitiligo, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, multiple sclerosis, cold agglutinin disease, autoimmune hemolytic anemia, antineutrophil cytoplasmic antibody—associated vasculitis, graft versus host disease, cryoglobulinemia and thrombotic thrombocytopenic.

In a further embodiment, the invention relates to a process or a method for the treatment of one of the disorders or diseases mentioned hereinabove, especially a disease which responds to the inhibition of the PI3K enzymes. A crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on, can be administered as such or in the form of pharmaceutical compositions, prophylactically or therapeutically, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human, requiring such treatment, the compounds especially being used in the form of pharmaceutical compositions.

In a further embodiment, the invention relates to the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-

(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on, as such or in the form of a pharmaceutical composition with at least one pharmaceutically acceptable carrier, for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, mediated by the PI3K enzymes.

In a further embodiment, the invention relates to the use of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on, for the preparation of a pharmaceutical composition for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, especially a disorder or disease selected from autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection, cancers eg of hematopoietic origin or solid tumors.

In another embodiment, the invention relates to pharmaceutical compositions comprising a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on of the present invention. The invention thus provides

- a pharmaceutical composition comprising (i.e. containing or consisting of) a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-onas defined herein and one or more carriers / excipients;

- a pharmaceutical composition comprising a therapeutically effective amount of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-

d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-onas defined herein, and one or more pharmaceutically acceptable carriers / excipients.

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The present invention provides a pharmaceutical composition comprising a form of the present invention and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired
d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art. Suitable compositions for oral administration include an effective amount of a form of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a form of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the form of the invention optionally with carriers, optionally a rate controlling barrier to deliver the form of the invention of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder, either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids, from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds of the present invention.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers,*e. g.*, vials, blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the form of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium;

and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

Suitable excipients / carriers may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.
Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like.
Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.
Compressed gases may be used to disperse a compound of of the present invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight, and individual condition, the individual pharmacokinetic data, and the mode of administration. The amount of the form of the present invention in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-99.99 wt% of a form of the present invention based on the total formulation, with the balance being one or more suitable pharmaceutical excipients.

Pharmaceutical compositions comprising a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-onas defined herein in association with at least one pharmaceutical acceptable carrier (such as excipient a and/or diluent) may be manufactured in conventional manner, e.g. by means of conventional mixing, granulating, coating, dissolving or lyophilising processes.

In a further embodiment, the invention relates to a pharmaceutical composition for administration to a warm-blooded animal, especially humans or commercially useful mammals suffering from a disease which responds to an inhibition of the PI3K enzymes, comprising an effective quantity of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on for the inhibition of the PI3K enzymes, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier.

In a further embodiment, the invention relates to a pharmaceutical composition for the prophylactic or especially therapeutic management of a disorder or disease selected from autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection, cancers eg of hematopoietic origin or solid tumors; of a warm-blooded animal, especially a human or a commercially useful mammal requiring such treatment.

In another embodiment, the invention relates to combinations comprising a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on and one or more additional active ingredients. The invention thus provides

- a combination in particular a pharmaceutical combination, comprising a therapeutically effective amount of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on and one or more therapeutically active agents, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic agent, e.g. as indicated below;

- a combined pharmaceutical composition, adapted for simultaneous or sequential administration, comprising a therapeutically effective amount of a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on as defined herein; therapeutically effective amount(s) of one or more combination partners e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic agent, e.g. as indicated below; one or more pharmaceutically acceptable excepients;

- a combined pharmaceutical composition as defined herein (i) as pharmaceutical, (ii) for use in the treatment of a disease mediated by the PI3K enzymes, (iii) in a method of treatment of a disease mediated by the PI3K enzymes.

By “combination”, there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g. synergistic effect.

The term "a therapeutically effective amount" of a form of the present invention refers to an amount of the form of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the form of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by the dysregulation of PI3K delta, or (ii) associated with the dysregulation of PI3K delta, or (iii) characterized by the dysregulation of the PI3K delta; or (2) reducing or inhibiting the activity of the PI3K delta. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the form of the present invention that, when administered to a cell, or a tissue, or a

non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting PI3K delta.

The a crystalline anhydrous form, a crystalline solvate form or a salt form including a crystalline salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone or a salt form including a crystalline salt form of 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-on may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, e.g a malignant cell anti-proliferative agent. For example, the compounds of the present invention may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578, AP23573, TAFA-93, biolimus-7 or biolimus-9; an ascomycin having immuno-suppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid or salt; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; a PKC inhibitor, e.g. as disclosed in WO 02/38561 or WO 03/82859, e.g. the compound of Example 56 or 70; a JAK3 kinase inhibitor, e.g. N-benzyl-3,4-dihydroxy-benzylidene-cyanoacetamide α-cyano-(3,4-dihydroxy)-]N-benzylcinnamamide (Tyrphostin AG 490), prodigiosin 25-C (PNU156804), [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P131), [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P154), [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] WHI-P97, KRX-211, 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate (also called CP-690,550), or a compound as disclosed in WO 04/052359 or WO 05/066156; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD52, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antihistamines; or antitussives, or a bronchodilatory agent; or an angiotensin receptor blockers; or an anti-infectious agent.

Where the compounds of the present invention are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth.

A form of the present invention may also be used to advantage in combination with each other or in combination with other therapeutic agents, especially other antiproliferative agents. Such antiproliferative agents include, but are not limited to, aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active agents; alkylating agents; histone deacetylase inhibitors; compounds, which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; agents used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors; temozolomide (TEMODAL®); and leucovorin.

The term "aromatase inhibitor", as used herein, relates to a compound which inhibits the estrogen production, i.e., the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to, steroids, especially atamestane, exemestane and formestane; and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketoconazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g., under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g., under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g., under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g., breast tumors.

The term "anti-estrogen", as used herein, relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to, tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g., under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g., under the trademark EVISTA. Fulvestrant can be formulated as disclosed in U.S. Patent No. 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g., under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g., breast tumors.

The term "anti-androgen", as used herein, relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g., as disclosed in U.S. Patent No. 4,636,505.

The term "gonadorelin agonist", as used herein, includes, but is not limited to, abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Patent No. 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZOLADEX. Abarelix can be formulated, e.g., as disclosed in U.S. Patent No. 5,843,901.

The term "topoisomerase I inhibitor", as used herein, includes, but is not limited to, topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO 99/17804). Irinotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor", as used herein, includes, but is not limited to, the anthracyclines, such as doxorubicin, including liposomal formulation, e.g., CAELYX; daunorubicin; epirubicin; idarubicin; nemorubicin; the anthraquinones mitoxantrone and losoxantrone; and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g., in the form as it is marketed, e.g., under the trademark ETOPOPHOS. Teniposide can be administered, e.g., in the form as it is marketed, e.g., under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark FARMORUBICIN. Idarubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g., in the form as it is marketed, e.g., under the trademark NOVANTRON.

The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing agents and microtublin polymerization inhibitors including, but not limited to, taxanes, e.g., paclitaxel and docetaxel; vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate; vincristine, especially vincristine sulfate and vinorelbine; discodermolides; cochicine; and epothilones and derivatives thereof, e.g., epothilone B or D or derivatives thereof. Paclitaxel may be administered, e.g., in the form as it is marketed, e.g., TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g., under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g., under the trademark VINBLASTIN R.P. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g., under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in U.S. Patent No. 5,010,099. Also included are epothilone derivatives which are disclosed in WO 98/10121, U.S. Patent No. 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are epothilone A and/or B.

The term "alkylating agent", as used herein, includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially *N*-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU; capecitabine; gemcitabine; DNA demethylating agents, such as 5-azacytidine and decitabine; methotrexate and edatrexate; and folic acid antagonists, such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark GEMZAR. Also included is the monoclonal antibody trastuzumab which can be administered, e.g., in the form as it is marketed, e.g., under the trademark HERCEPTIN.

The term "platin compound", as used herein, includes, but is not limited to, carboplatin, *cis*-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g., under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds", as used herein, includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g., a *N*-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the IGF-IR receptor, such as those compounds disclosed in WO 02/092599;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase;

h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g., imatinib;

i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family and their gene-fusion products, e.g., BCR-Abl kinase, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g., a *N*-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, PD180970, AG957, NSC 680410 or PD173955 from ParkeDavis;

j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK and Ras/MAPK family members, or PI(3) kinase family,

or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in U.S. Patent No. 5,093,330, e.g., midostaurin; examples of further compounds include, e.g., UCN-01; safingol; BAY 43-9006; Bryostatin 1; Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds, such as those disclosed in WO 00/09495; FTIs; PD184352; or QAN697 (a P13K inhibitor);

k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810, AG 99, Tyrphostin AG 213, Tyrphostin AG 1748, Tyrphostin AG 490, Tyrphostin B44, Tyrphostin B44 (+) enantiomer, Tyrphostin AG 555, AG 494, Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester, NSC 680410, adaphostin; and

l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or hetero-dimers), such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g., EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g., the compound of Example 39, or in EP 0 564 409; WO 99/03854; EP 0520722; EP 0 566 226; EP 0 787 722; EP 0 837 063; U.S. Patent No. 5,747,498; WO 98/10767; WO 97/30034; WO 97/49688; WO 97/38983 and, especially, WO 96/30347, e.g., compound known as CP 358774; WO 96/33980, e.g., compound ZD 1839; and WO 95/03283, e.g., compound ZM105180, e.g., trastuzumab (HERCEPTIN), cetuximab, Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3; and 7*H*-pyrrolo-[2,3-*d*]pyrimidine derivatives which are disclosed in WO 03/013541.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g., unrelated to protein or lipid kinase inhibition, e.g., thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are, e.g., inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, e.g., okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are e.g. retinoic acid, α- γ- or δ-tocopherol or α- γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor, as used herein, includes, but is not limited to, e.g., Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g., 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid or lumiracoxib.

The term "bisphosphonates", as used herein, includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark SKELID. "Pamidronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity, such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor", as used herein, refers to compounds which target, decrease or inhibit heparin sulphate degradation. The term includes, but is not limited to, PI-88.

The term "biological response modifier", as used herein, refers to a lymphokine or interferons, e.g., interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g., H-Ras, K-Ras or N-Ras, as used herein, refers to compounds which target, decrease or inhibit the oncogenic activity of Ras, e.g., a "farnesyl transferase inhibitor", e.g., L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity

of telomerase are especially compounds which inhibit the telomerase receptor, e.g., telomestatin.

The term "methionine aminopeptidase inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are, e.g., bengamide or a derivative thereof.

The term "proteasome inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, e.g., PS-341 and MLN 341.

The term "matrix metalloproteinase inhibitor" or "MMP inhibitor", as used herein, includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g., hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "agents used in the treatment of hematologic malignancies", as used herein, includes, but is not limited to, FMS-like tyrosine kinase inhibitors, e.g., compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-*D*-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, e.g., compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g., PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors", as used herein, includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative, other geldanamycin related compounds, radicicol and HDAC inhibitors.

The term "antiproliferative antibodies", as used herein, includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erlotinib (Tarceva™), bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 antibody. By antibodies is meant, e.g., intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

For the treatment of acute myeloid leukemia (AML), compounds of the present invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds the present invention can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications.

The above-mentioned compounds, which can be used in combination with a compound the present invention, can be prepared and administered as described in the art, such as in the documents cited above.

A form of the present invention may also be used to advantage in combination with known therapeutic processes, e.g., the administration of hormones or especially radiation.

A form of the present invention may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a form of the present invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic, effect or any combination thereof. 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 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 form of the present inventionand a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. a form of the present invention 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. the administration of three or more active ingredients.

Experimental details:

Insofar as the production of the starting materials is not particularly described, the compounds of the present invention are known or may be prepared analogously to methods known in the art or as described hereafter.

The following examples are illustrative of the invention without any limitation.

Abbreviations:

AcOH	acetic acid
aq	aqueous
Ar	aryl
BOC	*tert*-butyl-carbonate
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
br.s.	broad singlet
$CDCl_3$	chloroform-d
CDI	1,1'-carbonyldiimidazole
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
Cs_2CO_3	cesium carbonate
d	doublet
dd	doublet of doublets
DIPEA	*N*-ethyldiisopropylamine
DME	1,4-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DBU	1,8-diaza-7-bicyclo[5.4.0]undecene
DMSO	dimethylsulfoxide
dt	doublet of triplets
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
eq.	equivalent
EtOAc	ethyl acetate
FCC	flash column chromatography
h	hour
HBTU	(2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid

HOBT	benztriazol-1-ol
HPLC	high pressure liquid chromatography
HT	high throughput
H_2O	water
Hyflo	Hyflo Super Cel Medium
Isolute® SCX-2	polymer supported sulfonic acid macroporous polystyrene
K	kelvin
K_2CO_3	potassium carbonate
LC	liquid chromatography
M	molar
MeCN	acetonitrile
MeOD	methanol-d4
MeOH	methanol
2-Me-THF	2-methyltetrahydrofuran
MgSO4	magnesium sulfate
MHz	mega herz
MS	mass spectroscopy
m	multiplet
mBar	millibar
mL	millilitre
mm	millimeter
mM	millimolar
min.	minute
mw	microwave
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
$NaHCO_3$	sodium hydrogen carbonate
NaO^tBu	sodium *tert*-butoxide
NEt_3	triethylamine
NH_3	ammonia
NH_4OH	concentrated solution of ammonia in water possessing a specific gravity of 0.88
NMP	N-methylpyrrolidinone
NMR	nuclear magnetic resonance
OBD	optimum bed density
$Pd(OAc)_2$	palladium acetate
$Pd(OH)_2/C$	palladium hydroxide on carbon

$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
$Pd_2(dba)_3.CHCl_3$	tris(dibenzylideneacetone)dipalladium chloroform complex
PL-HCO_3 MP	polymer supported hydrogen carbonate macroporous polystyrene
PL-SO_3H MP	polymer supported sulfonic acid macroporous polystyrene
rt	room temperature
Rt	retention time
s	singulet
SCX-2	polymer supported sulfonic acid macroporous polystyrene
t	triplet
TBME	*tert*-butylmethyl ether
tBuOK	potassium tert-butoxide
tert-BuONa	sodium tert-butoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography
X-Phos	dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine

Microwave equipment used is a Biotage Initiator®

All compounds are named using AutoNom.

LCMS Methods used:

LC method 1 (Rt [(1)]): The retention times (Rt) were obtained on a Agilent HPLC system with an Ascentis®Express column C18 30 x 2.1mm, 2.7µm (Supelco) applying a gradient (H_2O+0.05% formic acid+3.75 mM Ammonium acetate) / (CH_3CN+0.04% formic acid) 90/10 to 5/95 over 3.7 min and 1.2 mL/min as solvent flow and then 5/95 over 0.7 min with 1.4 mL/min as solvent flow and 40°C for the oven temperature. Detection method UV 220-400 nm – MS.

LC method 2 (Rt [(2)]): The retention times (Rt) were obtained on a Agilent HPLC system with an Ascentis®Express column C18 30 x 2.1mm, 2.7µm (Supelco) applying a gradient (H_2O+0.05% formic acid+3.75 mM Ammonium acetate) / (CH_3CN+0.04% formic acid) 95/5 to 5/95 over 3.7 min and 1.2 mL/min as solvent flow and then 5/95 over 0.7 min with 1.4 mL/min as solvent flow and 40°C for the oven temperature. Detection method UV 220-400 nm – MS.

LC method 3 (Rt [(3)]): The retention times (Rt) were obtained on a Agilent HPLC system with an Ascentis®Express column C18 30 x 2.1mm, 2.7µm (Supelco) applying a gradient (H_2O+0.05% formic acid+3.75 mM Ammonium acetate) / (CH_3CN+0.04% formic acid) 99/1

over 0.5 min and 1.2 mL/min as solvent flow then 99/1 to 5/95 over 1.7 min and 1.2 mL/min as solvent flow and then 5/95 over 0.7 min with 1.4 mL/min as solvent flow and 40°C for the oven temperature. Detection method UV 220-400 nm – MS.

LC method 4 (Rt $^{(4)}$): The retention times (Rt) were obtained on a Agilent HPLC system with an Ascentis®Express column C18 30 x 2.1mm, 2.7µm (Supelco) applying a gradient (H_2O+0.05% formic acid+3.75 mM Ammonium acetate) / (CH_3CN+0.04% formic acid) 90/10 to 5/95 over 1.7 min and 1.2 mL/min as solvent flow and then 5/95 over 0.7 min with 1.4 mL/min as solvent flow and 40°C for the oven temperature. Detection method UV 220-400 nm – MS.

LC method 6 (Rt $^{(6)}$): The retention times (Rt) were obtained on a Agilent HPLC system with an Ascentis®Express column C18 30 x 2.1mm, 2.7µm (Supelco) applying a gradient (H_2O+TFA) / (CH_3CN+0.04% TFA) 99/1 over 0.5 min and 1.2 mL/ min as solvent flow then 99/1 to 5/95 over 1.7 min and 1.2 mL/min as solvent flow and then 5/95 over 0.7 min with 1.4 mL/min as solvent flow and 40°C for the oven temperature. Detection method UV 220-400 nm – MS.

LC method 7 (Rt $^{(7)}$): The retention times (Rt) were obtained on a Waters Agilent HPLC system with an Ascentis®Express column C18 30 x 2.1mm, 2.7µm (Supelco) applying a gradient (H_2O+0.05% TFA) / (CH_3CN+0.04% TFA) 90/10 to 5/95 over 1.7 min and 1.2 mL/min as solvent flow and then 5/95 over 0.7 min with 1.4 mL/min as solvent flow and 40°C for the oven temperature. Detection method UV 220-400 nm – MS.

Purification method:

Preparative reverse phase Gilson HPLC

- Method A: Column SunFire prep C18 OBD 5µm, 30 x 100mm from WATERS, with H_2O + 0.1% TFA and Acetonitrile + 0.1% TFA as mobile phase. Detection method UV 220-400 nm

- Method B: Column Atlantis prep T3 OBD 5µm, 30 x 150mm from WATERS, with H_2O + 0.1% TFA and Acetonitrile + 0.1% TFA as mobile phase. Detection method UV 220-400 nm

- Method C: Column XTerra RP18 OBD 5µm, 19 x 50mm from WATERS, with H_2O + 0.1% TFA and Acetonitrile + 0.1% TFA as mobile phase. Detection method UV 220-400 nm

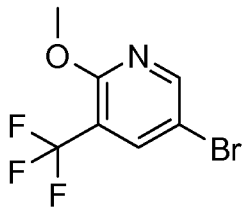
X-ray Powder Diffraction

Instrumentation:

Method X1	
Instrument	Bruker AXS, D8 Advance
Irradiation	CuKα (30 kV, 40 mA)
Detector	PSD (Vantec) detector
Scan range	2°- 40° (2 theta value)

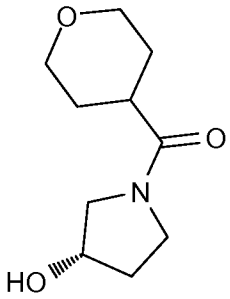
Method X2	
Instrument	Bruker D8 GADDS Discover
Irradiation	CuKα (40 kV, 40 mA)
Detector	HI-STAR Area detector
Scan range	6°- 40° (2 theta value)

Preparation of intermediate compounds



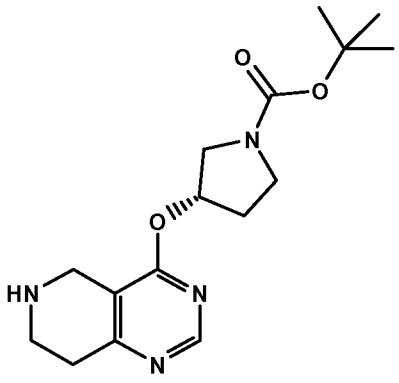
Intermediate 1: 5-Bromo-2-methoxy-3-trifluoromethyl-pyridine

To 2-methoxy-3-(trifluoromethyl)pyridine (20.0 g, 113.0 mmol) and 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (43.6 g, 152.0 mmol) was added TFA (80 mL) and the resulting mixture stirred at rt for 18h under argon. The TFA was removed *in vacuo* (50 mbar, 45°C) and the residue suspended in tert-butyl methyl ether (200 mL). The resulting colourless solid was removed by filtration and washed with tert-butyl methyl ether (50 mL). The filtrate was concentrated *in vacuo* and suspended in EtOAc (50 mL) The insoluble colourless solid was removed by filtration and washed with EtOAc (50 mL).The filtrate was concentrated *in vacuo*, diluted with heptane/ tert-butyl methyl ether (5/1, 20 mL) and the insoluble colourless solid was removed by filtration. The filtrate was purified by column chromatography on silica gel with heptane / EtOAc, 100/0 to 90/10. The crude product was filtered through a plug of $NaHCO_3$ (20g) and the filtrate evaporated *in vacuo* to give a golden oil (27.9 g). The oil was dissolved in heptanes (20 mL) and purified by filtered through a plug of silica gel (80 g), eluting with heptane to give 5-bromo-2-methoxy-3-(trifluoromethyl)pyridine as a colourless oil (22.5g, 74% yield). ^{1}H-NMR (400 MHz, DMSO-d_6, 298 K): δ ppm 4.03 (s, 3H) 7.95 (d, 1H) 8.4 (d, 1H).



Intermediate 3: ((*S*)-3-Hydroxy-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone

The (*S*)-pyrrolidin-3-ol hydrochloride (3.69g, 29.9 mmol) and triethylamine (6.65 g, 9.16 mL, 65.7 mmol) were put in CH_2Cl_2 (15 mL). The suspension was cooled at ~3°C. To this mixture, a solution of tetrahydro-pyran-4-carbonyl chloride (4.67g, 29.9 mmol) in CH_2Cl_2 (15 mL) was added slowly. Then the resulting reaction mixture was stirred for 1.5h at 3-10°C. The reaction mixture was then concentrated to give a powder. To this powder, addition of EtOAc (100 mL). The solid was filtered and washed with EtOAc. The recovered filtrate was then concentrated to give ((*S*)-3-hydroxy-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone as beige powder. (6.77 g, 98% yield). ^{1}H-NMR (400 MHz, Methanol-d4, 298 K): δ ppm 1.59-2.15 (m, 6H) 2.69-2.86 (m, 1H) 3.43-3.75 (m, 6H) 3.94-4.00 (m, 2H) 4.37-4.48 (m, 1H). LCMS: [M+H]+= 199.9, $Rt^{(6)}$= 0.86 min



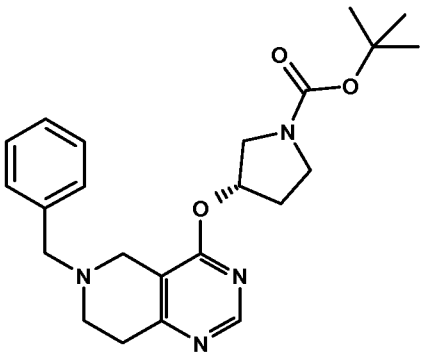
Intermediate 7: (*S*)-3-(5,6,7,8-Tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

$Pd(OH)_2$ /C (1.2 g, 1.71 mmol) was flushed with argon, (*S*)-3-(6-Benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (10.95 g, 26.7 mmol) dissolved in methanol (25 mL) was added followed by the addition of ammonium formate (1.68 g, 26.7 mmol). The reaction mixture was refluxed for 1h, cooled down to room temperature, filtered through a celite pad and concentrated under vacuum. Purification by

flash chromatography on silica gel (CH_2Cl_2 then TBME then TBME/MeOH 100/0 to 90/10 then TBME/MeOH/NH_4OH 85/15/5) gave (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (7.39 g, 87% yield) as a yellow sticky oil. ^1H NMR (400 MHz, methanol-d4, 298K) δ ppm 1.46-1.46 (m, 9 H) 2.10 - 2.30 (m, 2 H) 2.78-2.83 (m, 2 H) 3.11-3.14 (m, 2 H) 3.41 - 3.60 (m, 3 H) 3.65-3.72 (m, 1 H) 3.78 (s, 2 H) 5.68 (m, 1 H) 8.52 (s, 1 H). LCMS: $[M+H]^+$=321.2, Rt $^{(2)}$= 0.87 min

Aternative sythesis for intermediate 7:

$Pd(OH)_2$ /C (1.54 g, 2.2 mmol) was flushed with nitrogen, (*S*)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.5 g, 20.67 mmol) dissolved in methanol (50 mL) was added followed by the addition of triethylammonium formate (7.9 g, 53.7 mmol). The reaction mixture was refluxed for 1h, cooled down to room temperature, filtered through a celite pad and the filtrate was partitioned between 2-Me-THF (50 mL) and water (20 mL). The upper organic phase was collected and the bottom aqueous phase was re-extracted with 2-Me-THF (10 mL). All the organic layers were combined and concentrated under vacuum to provide (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (6.2 g, 94 % yield) as a yellow gum.



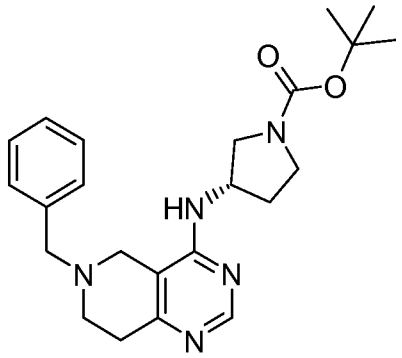
(S)-3-(6-Benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (*S*)-3-hydroxypyrrolidine-1- carboxylic acid tert-butyl ester (0.94 g, 5.01 mmol) in THF (20 mL) was added under argon NaH (0.23 g, 5.78 mmol). The mixture was stirred at rt for 25 min., then 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (1 g, 3.85 mmol) was added and stirring continued at rt for 4h. The mixture was quenched with H_2O, extracted with CH_2Cl_2. The organic layer was filtered and evaporated to dryness. Purification by flash chromatography on silica gel (heptanes / ethyl acetate, 1/1) gave the *(*S)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.35 g, 85% yield) as a yellow gum. ^1H NMR (400 MHz, DMSO-d6, 298K) δ ppm 1.39 (s, 9 H) 2.00 - 2.20 (m, 2 H) 2.35-2.81 (m, 4 H) 3.36-3.63 (m, 6 H) 3.70

(br.s, 2 H) 5.50-5.59 (m, 1 H) 7.25-7.37 (m, 5H) 8.56 (s, 1 H). LCMS: [M+H]+= 411.6, Rt [(7)]= 1.00 min

Alternative synthesis for *(S)-3-(6-Benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester*

To a solution of (*S*)-3-hydroxypyrrolidine-1- carboxylic acid tert-butyl ester (6.21 g, 33.16 mmol) and 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (9 g, 34.65 mmol) in 2-Me-THF (100 mL) was added under nitrogen tBuOK (8.17 g, 72.95 mmol). The mixture was stirred at rt for 25 min. The mixture was quenched with H_2O. The organic layer was washed with brine. The resulting organic solution was concentrated in vacuo to provide *(*S)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (12.6 g, 89% yield) as a yellow gum.

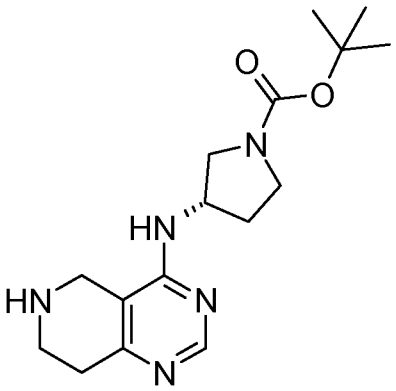


Intermediate 22: (*S*)-3-(6-Benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester

6-Benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (5.0 g, 19.06 mmol), (*S*)-tert-butyl 3-aminopyrrolidine-1-carboxylate (4.11 g, 20.96 g) and triethylamine (3.98 mL, 28.6 mmol) were heated in a sealed vial at 120°C for 42h. The mixture was allowed to cool, diluted with tert-butyl methyl ether (100 mL) and the resulting suspension stirred for 10 min. The mixture was diluted with water (50 mL) and the organic layer separated. The organic layer was washed with brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a brown gum. The residue was purified by column chromatography on silica gel with EtOAc / MeOH, 98/2 to 82/18 to give (*S*)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester as a pale yellow foam (7.36 g, 93% yield). ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 1.48 (s, 9H) 2.10-2.31 (m, 2H) 2.80-2.96 (m, 4H) 3.15-3.87 (m, 8H) 4.44-4.77 (m, 1H) 5.62-5.73 (m, 1H) 7.29-7.45 (m, 5H) 8.50 (s, 1H). LCMS: [M+H]+=410.0, Rt [(6)]= 1.39 min.

Alternative synthesis for intermediate 22:

(*S*)-tert-Butyl-3-aminopyrrolidine-1-carboxylate (50 g, 192.5 mmol) was added to 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (39.440 g, 211.8 mmol) in NMP (200 mL) solution followed by the addition of K_2CO_3 (39.9 g, 288.8 mmol). The mixture was heated to 120°C for 20h. The mixture was allowed to cool, partitioned between water (300 mL) and ethylacetate (500 mL). the bottom aqueous phase was discarded and the upper organic phase was washed with brine (150 mL) and concentrated in vacuo to provide crude (*S*)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester as a pale yellow foam (76.44 g, 97% yield).



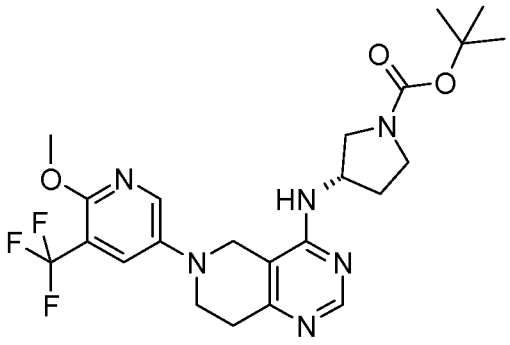
Intermediate 23: (*S*)-3-(5,6,7,8-Tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (*S*)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate 22**) (30.1 g, 73.5 mmol) in MeOH (100 mL) was added 20% palladium hydroxide on carbon (3.3 g) then ammonium formate (4.63 g, 73.5 mmol) and the mixture heated at reflux for 1h. Added ammonium formate (0.38 g, 6.02 mmol) and continued heating at reflux for 30 min. The reaction mixture was allowed to cool and filtered through a celite pad, washing with MeOH (50 mL) then CH_2Cl_2 (50 mL). The filtrate was evaporated in vacuo to give a brown oil. Dissolved in CH_2Cl_2 (100 mL), added solid $NaHCO_3$ (10 g) and filtered through a celite pad. The filtrate was evaporated *in vacuo* to give a brown oil. Dissolved in EtOAc (50 mL) and a solid precipitated which was filtered to give (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester as a beige solid (15.55 g, 66% yield). ^{1}H-NMR (400 MHz, DMSO-d_6, 298 K): δ ppm 1.40 (s, 9H) 1.81-1.98 (m, 1H) 2.05-2.17 (m, 1H) 2.92 (t, 2H) 3.10-3.46 (m, 5H) 3.49-3.63 (m, 3H) 4.47-4.63 (m, 1H) 6.46 (d, 1H, N-H) 8.25 (s, 1H). LCMS: [M+H]+= 320.0, Rt $^{(6)}$= 1.29 min.

Alternative synthesis for intermediate 23:

$Pd(OH)_2$ /C (6.60 g, 5.3 mmol) was flushed with nitrogen, (*S*)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate**

22) dissolved in methanol (164 mL) was added followed by the addition of triethylammonium formate (28.4 g, 188.0 mmol). The reaction mixture was refluxed for 1h, cooled down to room temperature, filtered through a celite pad and the filtrate was concentrated under vacuum. the residue was recrystallized with methyl tert-butyl ether (200 mL) and heptanes (50 mL) to provide (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester as a beige solid (25.7 g, 85% yield).



Intermediate 24: (*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a glass vial was added (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate 23**) (3.5 g, 10.96 mmol), 5-bromo-2-methoxy-3-(trifluoromethyl)pyridine (**intermediate 1**) (3.09 g, 12.05 mmol), sodium tert-butoxide (1.58 g, 16.44 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.502 g, 0.548 mmol), 2-di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl (0.225 g, 0.657 mmol) and anhydrous *tert*-butanol (6 mL). The vial was flushed with a stream of argon for 15 sec and capped. The mixture was heated with stirring for 5h at 100°C. Allowed to cool and partitioned between EtOAc (100 mL) and water (20 mL) and filtered the biphasic mixture through a celite pad. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purified by flash column chromatography through Biotage® amino silica gel eluting with heptane / EtOAc, 100/0 to 0/100 then EtOAc/MeOH (90/10) to give (*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester as a yellow foam (4.00 g, 74% yield). LCMS: [M+H]+=495.2, Rt $^{(3)}$= 1.59 min.

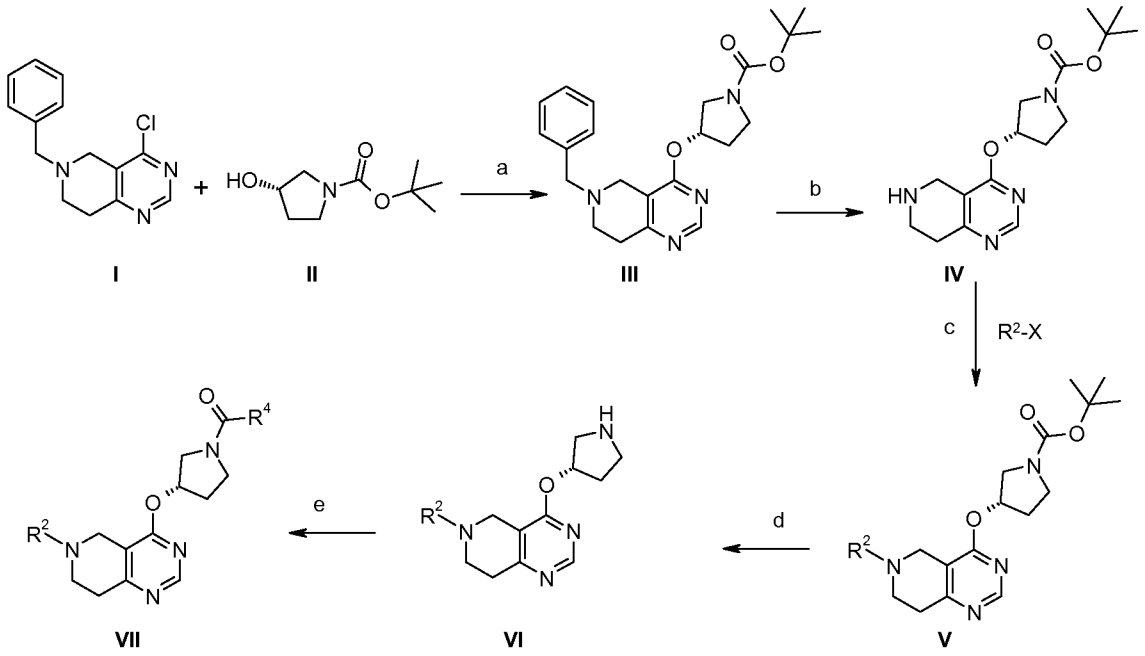
Alternative synthesis for intermediate 24:

To a glass flask was added (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate 23**) (6.331 g, 15.86 mmol), 5-bromo-2-methoxy-3-(trifluoromethyl)pyridine (**intermediate 1**) (4.465 g, 17.442 mmol), sodium tert-butoxide (2.29 g, 23.78 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.726 g, 0.793 mmol), di-tert-butyl(2'-methylbiphenyl-2-yl)phosphine (0.297 g, 0.951 mmol) and

anhydrous *tert*-butanol (30 mL). The flask was flushed with a stream of nitrogen for 15 sec and capped. The mixture was heated with stirring for 4h under reflux. The mixture was allowed to cool to rt and partitioned between EtOAc (100 mL) and water (20 mL). The biphasic mixture was filtered the through a celite pad. The organic layer was separated and concentrated *in vacuo* to give crude (*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester as a yellow foam (7.46 g, 95% yield).

Preparation of examples

Scheme 1



a) (*S*)-3-(6-Benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester **III** is firstly prepared by reacting 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine with (*S*)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester in the presence of a suitable base such as sodium hydride (NaH) and polar organic solvent such as THF or dioxane under inert gas conditions at room temperature. b) N-debenzylation is performed under customary transfer hydrogenation conditions, using among the possible palladium catalysts, preferably palladium hydroxide on carbon $Pd(OH)_2$ /C and among the possible formate salt preferably ammonium formate and organic solvent such as preferably methanol. The reaction is preferably carried out under refluxing conditions. c) Buchwald-Hartwig cross coupling between (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester **IV** and aryl bromide of the general formula R^2-X where X=Bromo or Iodo is performed under customary Buchwald-Hartwig conditions using such a ligand such as X-Phos or 2-di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl with a palladium catalyst such as $Pd_2(dba)_3$ or $Pd_2(dba)_3.CHCl_3$ or $Pd(OAc)_2$, preferably $Pd_2(dba)_3$ with X-Phos, base such as preferably Cs_2CO_3 or preferably *tert*-BuONa, and organic solvent such as preferably dioxane or preferably THF. The reaction is preferably stirred at a temperature of approximately 80-120°C, preferably 120°C. The reaction may preferably carry out under an inert gas such as nitrogen or argon. d) N-BOC deprotection is performed under customary BOC deprotection conditions using among the possible acid preferably trifluoro-

acetic acid or HCl and suitable organic solvent such as CH_2Cl_2 or diethyl ether. The reaction is preferably performed at room temperature. e)

Reaction of compounds of general formula **VI** with an acid chloride of formula $R^4C(O)Cl$ or carboxylic acid of formula $R^4C(O)OH$. Those skilled in the art will appreciate that there are many known ways of preparing amides. For example, see Mantalbetti, C.A.G.N and Falque, V., Amide bond formation and peptide coupling, Tetrahedron, 2005, 61(46), pp10827-10852 and references cited therein. The examples provided herein are thus not intended to be exhaustive, but merely illustrative.

The following general methods i – v have been used.

i. To a vigorously stirring solution of the acid chloride (1.3 eq.) in CH_2Cl_2 was added simultaneously portionwise excess sat. $NaHCO_3$(aq) and a solution of the amine of general formula **VI** (1.0 eq.) in CH_2Cl_2 at rt. The resulting biphasic mixture was stirred vigorously at rt for 2h. The organic layer was separated, dried ($MgSO_4$), concentrated *in vacuo* and purified by either reverse phase chromatography, normal phase chromatography or crystallisation.

ii. To the amine of general formula **VI** (1.0 eq.) in CH_2Cl_2 was added the acid chloride (1.1 eq.) and triethylamine (3.0 eq.) at rt. The reaction mixture was stirred at room temperature for 1h. The reaction mixture was concentrated under vacuum and subsequently partitioned between water and a suitable organic solvent and purified either reverse phase chromatography, normal phase chromatography or crystallisation.

iii. To the carboxylic acid (1.0 eq.) and HBTU (1.2 eq.) in DMF was added triethylamine (4.0 eq.). The mixture was stirred for 20 min and then the amine of general formula **VI** (1.0 eq.) in DMF was added. The mixture was allowed to stir overnight at room temperature and subsequently partitioned between water and a suitable organic solvent. The organic phase was separated, dried ($MgSO_4$), concentrated *in vacuo* and purified by either reverse phase chromatography, normal phase chromatography or crystallisation.

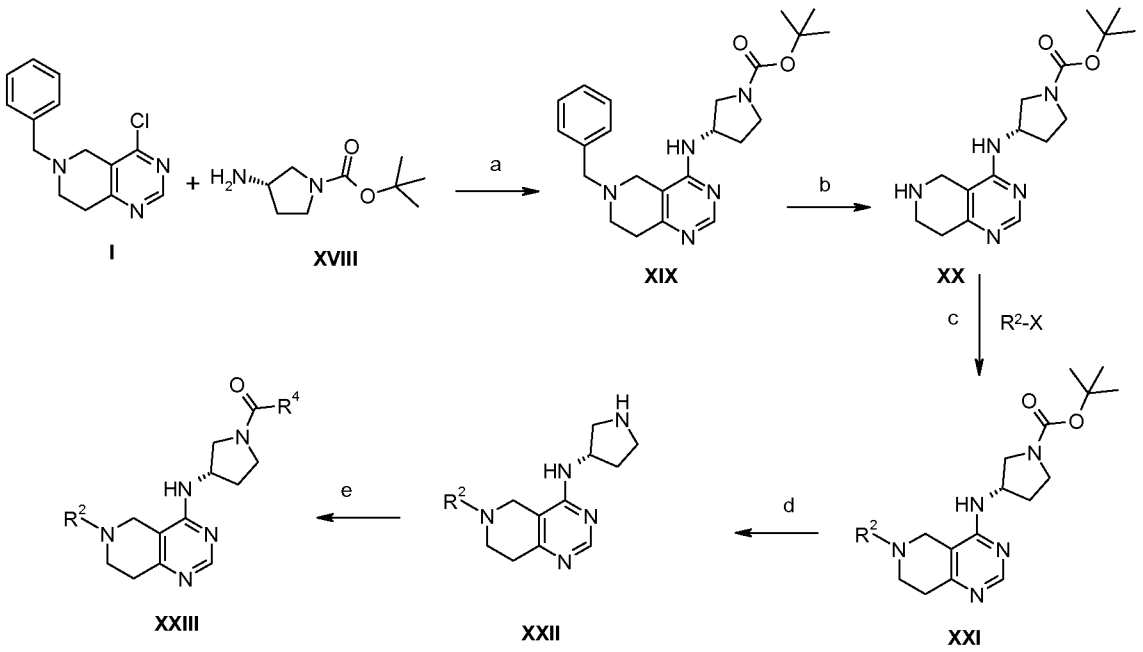
iv. To the carboxylic acid (1.0 eq.) and the amine general formula **VI** (1.0 eq.) in DMF was added DCC (1.2 eq.) in DMF. The reaction mixture was stirred at rt for 18h and concentrated *in vacuo* and purified by either reverse phase chromatography, normal phase chromatography or crystallisation.

v. To the carboxylic acid (1.1 eq.) and the amine general formula **VI** (1.0 eq.) in CH_2Cl_2 was added benztriazol-1-ol (1.1 eq.) and EDC (1.6 eq.). The reaction mixture was stirred at rt for

18h and subsequently partitioned between water and a suitable organic solvent. The organic phase was separated, dried ($MgSO_4$), concentrated *in vacuo* and purified by either reverse phase chromatography, normal phase chromatography or crystallization.

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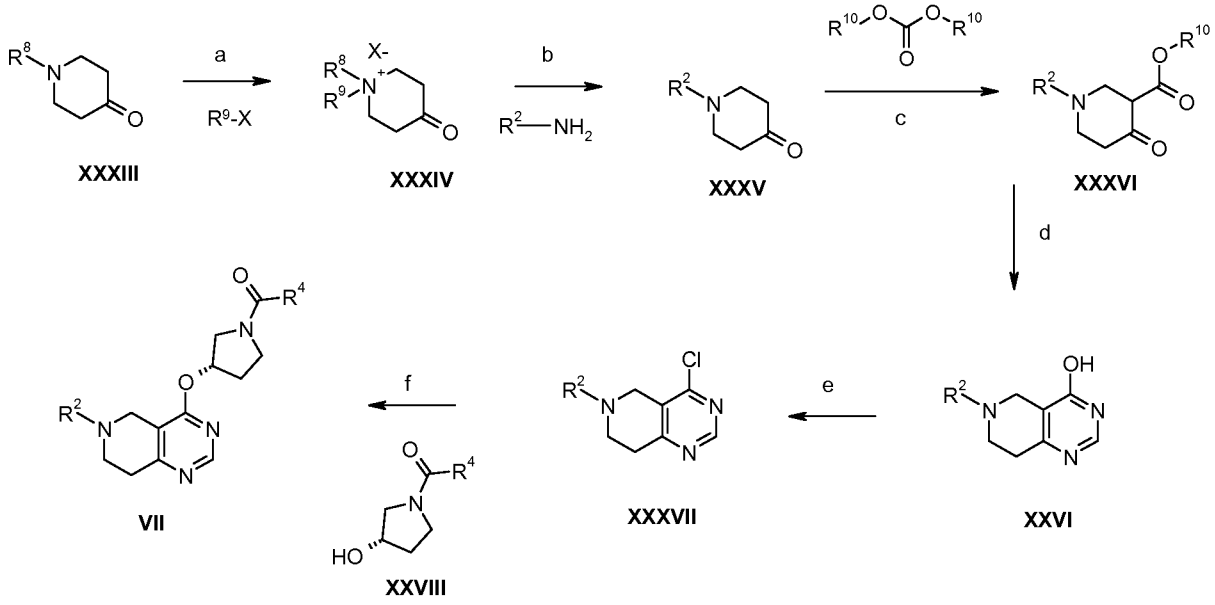
Scheme 4



a) (*S*)-3-(6-Benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester **XIX** is firstly prepared by reacting 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine with (*S*)-3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester in the presence of a suitable base such as triethylamine or N,N-diisopropylethylamine at elevated temperature (e.g. 120°C) for 24-48h. Typical conditions comprise of 1.0 eq. of 6-benzyl-4-chloro-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine, 1.0 eq. of (*S*)-3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester and 1.5 eq. of triethylamine at 120°C for 48h. b) Removal of the benzyl protecting group is performed using standard methodology as described in "Protecting groups in Organic Synthesis" by T.W. Greene and P. Wutz, 3rd edition, 1999, John Wiley and Sons. Typical conditions comprise of 1.0 eq.t of (S)-3-(6-benzyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester **XIX**, 1.1 – 8.0 eq. of ammonium formate and 20% (w/w) palladium hydroxide $Pd(OH)_2/C$ (catalyst) heated under reflux in methanol. c) (*S*)-3-(5,6,7,8-Tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester **XX** is reacted with halide R^2-X (where R2 is defined above and X is halo and preferably bromo or iodo), in the presence of a suitable base such as sodium *tert*-butoxide or cesium carbonate and a suitable catalyst system such as $Pd_2(dba)_3$ with 2-di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl or $Pd_2(dba)_3$ with X-Phos in a suitable solvent such as anhydrous *tert*-butanol or anhydrous dioxane, heated at elevated temperture (e.g. 100°C). The reaction may preferably be carried out under an inert gas such as nitrogen or argon. Typical conditions comprise of 1 eq. of (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester **XX**, 1-

1.5 eq. of R2-X, 1.5-2.0 eq. of sodium *tert*-butoxide, 5-10 mol% $Pd_2(dba)_3$ and 5-10 mol% 2-di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl in anhydrous *tert*-butanol at 100°C for 5-24 hours under an atmosphere of argon. d) N-Boc deprotection is performed under customary Boc deprotection conditions with a suitable acid such as trifluoroactetic acid in a suitable solvent such as CH_2Cl_2 at room temperature. Typical conditions comprise of 1 eq. of compound of general formula **XII** in excess trifluoroacetic acid in CH_2Cl_2 at room temperature for 1-3 h. e) Reaction of compounds of general formula **XXII** with an acid chloride of formula $R^4C(O)Cl$ or carboxylic acid of formula $R^4C(O)OH$ using general methods i – v as decribed in Scheme 1, step e. Those skilled in the art will appreciate that there are many known ways of preparing amides. For example, see Mantalbetti, C.A.G.N and Falque, V., Amide bond formation and peptide coupling, Tetrahedron, **2005**, 61(46), pp10827-10852 and references cited therein. The examples provided herein are thus not intended to be exhaustive, but merely illustrative.

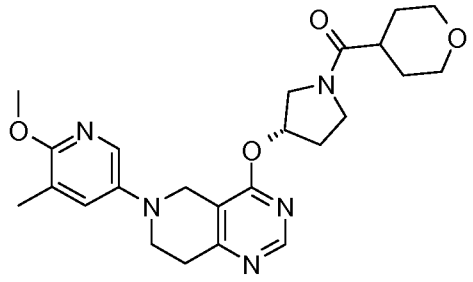
Scheme 8



a) Quaternarization of the tertiary amine of general formula **XXXIII** (where R^8 = alkyl e.g. benzyl) with compound of general formula R^9-X (where R^9 = alkyl e.g. methyl and X = Bromo or Iodo) under customary conditions using in particular acetone as organic solvent. b) Alkylation of amine of general formula R^2-NH2 with quaternary amine **XXXIV** was performed by using base such a in particular K_2CO_3 and organic solvent such as in particular a 2/1 mixture of ethanol and water and heating the reaction mixture at 80-100°C, in particular 80°C. c) Compound of general formula **XXXV** was reacted with base such as in particular NaH and compound of general formula $(R^{10}O)_2CO$ (where R^{10} = alkyl e.g. carbonic acid dimethyl ester). The reaction mixture is stirred under high temperature (90°C). d) Pyrimidine

ring formation was obtained by reacting the compound of general formula **XXXVI** with formamidine acetate with a base such as sodium methoxide and organic solvent such as methanol at elevated temperature such as 90°C for 2-18h. e) Compound of general formula **XXVI** was reacted with phosphoryl chloride in presence of base such as triethylamine in organic solvent such as toluene at elevated temperature such as 100°C for 12-18h. f) Alcohol of general formula **XXVIII** is reacted with Compound of general formula **XXXVII** under customary conditions by deprotonation of the secondary alcohol using sodium hydride (NaH) and organic solvent THF under inert gas conditions at room temperature.

Where it is stated that compounds were prepared in the manner described for an earlier example, the skilled person will appreciate that reaction times, number of equivalents of reagents and reaction temperatures may be modified for each specific reaction, and that it may nevertheless be necessary or desirable to employ different work-up or purification conditions.

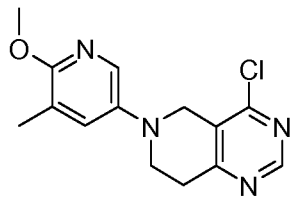


Example 1: {(*S*)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone

Synthesis of Example 1 - Method 1a (according to Scheme 8)

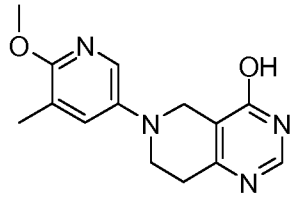
Sodium hydride (60% in dispersion oil, 17.88 mg, 0.447 mmol) was added under argon to a solution of **intermediate 3** (75 mg, 0.378 mmol) in 2mL of dry THF. The suspension was stirred under an atmosphere of argon at ambient temperature for 15 min. 4-Chloro-6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (100 mg, 0.344 mmol) was added and stirred at rt for an additional 3 hours. The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification by flash-chromatography on silica gel (CH_2Cl_2/MeOH 95/5) gave {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone

as a light yellow gum (115 mg, 74% yield). ^{1}H-NMR (400 MHz, methanol-d4, 298K) δ ppm 1.59-1.87 (m, 4H) 2.20 (s, 3H) 2.27-2.43 (m, 2H) 2.74-2.91 (m, 1H) 2.97-3.03 (m, 2H) 3.42-4.14 (m, 15H) 5.75-5.86 (m, 1H) 7.39-7.43 (m, 1H) 7.63-7.68 (m, 1H) 8.57-8.61 (m, 1H). LCMS: $[M+H]^+$=454.2, Rt [(3)]= 1.46min.



4-Chloro-6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine

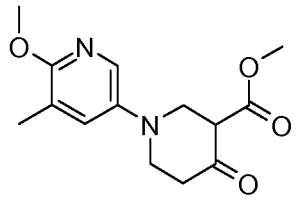
A mixture of 6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ol (650 mg, 2.387 mmol), phosphoroxy chloride (0.334 mL, 3.58 mmol), triethylamine (0.665 mL, 4.77 mmol) and toluene (12 mL) was heated at 100°C for 16h. The mixture was neutralized with the addition of solid sodium bicarbonate, filtered and the solution was concentrated in vacuum. The remaining black residue was taken up in CH_2Cl_2 and water, the layers were separated and the organic phase washed with brine, dried over sodium sulfate, filtered and concentrated to give a dark brown solid. The solid was triturated in ethylacetate, filtered and dried under high vacuum to yield 4-chloro-6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (630 mg, 91% yield) as a tan solid. ^{1}H-NMR (400 MHz, DMSO-d6, 298K) δ ppm 2.15 (s, 3H) 3.03 (t, 2H) 3.53 (t, 2H) 3.82 (s, 3H) 4.26 (s, 2H) 7.49 (dd, 1H) 7.74 (d, 1H) 8.85 (s, 1H). LCMS: $[M+H]^+$=291.1, Rt [(4)]= 0.97min.



6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ol

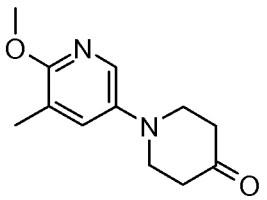
A mixture of 6'-methoxy-5'-methyl-4-oxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-3-carboxylic acid methyl ester (900 mg, 3.23 mmol), formamidine acetate (521 mg, 4.85 mmol), sodium methoxide (5.4 Molar) in methanol (2.395 mL, 12.94 mmol) and methanol (4 mL) was heated to 90°C for 3h. The mixture was allowed to cool down to rt, diluted in CH_2Cl_2, neutralized with acetic acid (0.741 mL, 12.94 mmol) and quenched with H_2O. The layers were separated and

aqueous was washed twice with CH_2Cl_2, organics were combined, washed with brine, dried over sodium sulfate, filtered and evaporated to give a yellow solid. The solid was triturated in ethylacetate to yield 6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ol (669 mg, yield 76%) as a white powder. ^{1}H-NMR (400 MHz, DMSO-d6, 298K) δ ppm 2.14 (s, 3H) 2.72 (t, 2H) 3.39 (t, 2H) 3.81 (s, 3H) 3.90 (s, 2H) 7.42 (d, 1H) 7.67 (d, 1H) 8.07 (s, 1H) 12.46 (br.s., 1H). LCMS: $[M+H]^+$=273.1, Rt $^{(3)}$= 1.30min.



6'-Methoxy-5'-methyl-4-oxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-3-carboxylic acid methyl ester

To a stirred suspension of sodium hydride (60%,153 mg, 6.36 mmol) in dimethyl carbonate (3.82 mL, 45.4 mmol) at room temperature was slowly added 6'-methoxy-5'-methyl-2,3,5,6-tetrahydro-[1,3']bipyridinyl-4-one (1 g, 4.54 mmol). The reaction mixture was heated to reflux (90°C) for 1h and then cooled to room temperature. The mixture was partitioned between CH_2Cl_2 and water and a solution of 1N HCl was added cautiously. The aqueous layer was separated and washed with an addition portion of CH_2Cl_2. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and evaporated to give the crude product, which was purified by flash-chromatography on silica gel (heptane / ethylacetate 3/1) to afford 6'-methoxy-5'-methyl-4-oxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-3-carboxylic acid methyl ester (975 mg, yield 77%) as a white solid. ^{1}H-NMR (400 MHz, DMSO, 298K) (mixture of keto and enol tautomers observed) δ ppm 2.12 (s, 6H) 2.36-2.69 (m, 4H) 3.26-3.96 (m, 20H) 7.34-7.77 (m, 4H) 11.84 (s, 1H). LCMS: $[M+H]^+$=279.1, Rt $^{(3)}$=1.51min (tautomer 1) and 1.70min (tautomer 2).



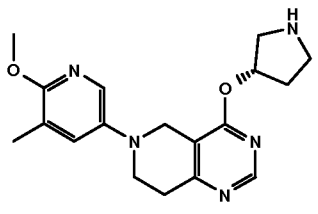
6'-Methoxy-5'-methyl-2,3,5,6-tetrahydro-[1,3']bipyridinyl-4-one

A slurry of iodide salt 1-benzyl-1-methyl-4-oxo-piperidinium (Ref: Tortolani, R.; Org. Lett., Vol. 1, No 8, 1999) (3.61 g, 10.86 mmol) in water (10 mL) was added slowly to a refluxing solution of 2-methoxy-5-amino-3-picolin (1 g, 7.24 mmol) and potassium carbonate (0.140 g, 1.013 mmol) in ethanol (20 mL). The reaction mixture was heated to reflux for an additional 3h. The reaction mixture was cooled to rt and partitioned between CH_2Cl_2 and water. The organic layer was separated and washed with an addition portion of CH_2Cl_2. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give the crude product which was purified by flash-chromatography on silica gel (heptane/ethylacetate 1/1) to afford 6'-methoxy-5'-methyl-2,3,5,6-tetrahydro-[1,3']bipyridinyl-4-one (1.15 g, yield 72%) as a light yellow gum. ^{1}H-NMR (400 MHz, DMSO, 298K) δ ppm 2.12 (s, 3H) 2.42 (t, 4H) 3.46 (t, 4H) 3.80 (s, 3H) 7.40 (d, 1H) 7.71 (d, 1H). LCMS: $[M+H]^+$=221.1, Rt $^{(3)}$= 1.41min.

Synthesis of Example 1 - Method 1b (according to Scheme 1)

Step 3

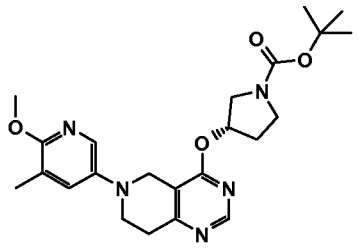
To a mixture 6-(6-methoxy-5-methyl-pyridin-3-yl)-4-((*S*)-pyrrolidin-3-yloxy)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (639 mg, 1.87 mmol) in CH_2Cl_2 (5 mL) was added the acid chloride tetrahydo-2H-pyran-4-carbonyl chloride (306 mg, 2.06 mmol) and triethylamine (0.522 mL, 3.74 mmol) at rt. The reaction mixture was stirred at rt for 10 min. The reaction mixture was concentrated under vacuum. Purification by preparative reverse phase Gilson HPLC (Method A) and subsequent neutralization of the combined fractions by extraction with CH_2Cl_2/1N NaOH, separation of the organic phase through a phase separation tube and evaporated gave {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone (432 mg, 51% yield) as a white powder. ^{1}H-NMR (400 MHz, DMSO-d6, 298K) δ ppm 1.50-1.65 (m, 4H) 2.10-2.32 (m, 5H) 2.62-2.78 (m, 1H) 2.85-2.95 (m, 2H) 3.30-3.95 (m, 13H) 4.0-4.20 (m, 2H) 5.61-5.72 (m, 1H) 7.42 (br, 1H) 7.68 (m, 1H) 8.60-8.61 (m, 1H) . LCMS: $[M+H]^+$=454.2, Rt $^{(1)}$= 1.42min.



6-(6-Methoxy-5-methyl-pyridin-3-yl)-4-((S)-pyrrolidin-3-yloxy)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine

Step 2

(*S*)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (2.05 g, 4.63 mmol) was dissolved in TFA / CH_2Cl_2 (1/2) and stirred at rt for 1h. The reaction mixture was concentrated under vacuum, the residue was diluted with CH_2Cl_2, the organic layer washed with NaOH 1N then brine, dried over Na_2SO_4, filtered and evaporated to give 6-(6-methoxy-5-methyl-pyridin-3-yl)-4-((*S*)-pyrrolidin-3-yloxy)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine. ^1H NMR (400 MHz, $CDCl_3$, 298K) δ ppm 2.20-2.30 (m, 2 H), 2.22 (s, 3 H) ,3.00-3.06 (t, 2 H), 3.09-3.18 (m, 1 H), 3.22-3.37 (m, 3 H), 3.45-3.50 (t, 2 H), 3.95 (s 3 H), 4.10 (s, 2 H), 4.20-4.65 (br.s 1 H), 5.63-5.69 (m, 1 H), 7.21-7.252 (m, 1 H), 7.70-7.74 (m, 1 H), 8.60 (s, 1 H). LCMS: $[M+H]^+$=341.9, Rt $^{(7)}$= 0.61min.



(S)-3-[6-(6-Methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

Step 1

X-Phos (0.96 g, 2.01 mmol, 0.3 eq.), $Pd_2(dba)_3$ (0.615 g, 0.672 mmol, 0.1eq.), Cs_2CO_3 (4.38 g, 13.44 mmol, 2 eq.) were combined and flushed 10 min with Argon. To this mixture, a solution of (*S*)-3-(5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate 7**) (2.15 g, 6.72 mmol) in dioxane (6 mL) and 5-bromo-2-methoxy-3-methylpyridine (1.76 g, 8.73 mmol) were added at rt and the reaction mixture was stirred at 120°C for 2h. The reaction was cooled down to rt, the reaction mixture filtered over Hyflo, AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was dissolved in dioxane (6 mL) and added to a glass vial containing 5-bromo-2-methoxy-3-methylpyridine (1.76 g, 8.73 mmol), X-Phos (0.96 g, 2.01 mmol), $Pd_2(dba)_3$ (0.615 g, 0.672 mmol), Cs_2CO_3 (4.38 g, 13.44 mmol). The vial was capped and the reaction mixture was stirred at 120°C for 2h. The reaction was cooled down to rt, the reaction mixture filtered over Hyflo, AcOEt was added and the organic

layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography on silica gel (CH_2Cl_2 then TBME then TBME/MeOH 99/1 to 90/10) gave (*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester as a yellow foam (2.05 g, 69% yield). ^{1}H NMR (400 MHz, DMSO-d6, 298K) δ ppm 1.35-1.44 (br.s., 9H) 2.07-2.23 (m, 2 H), 2.14 (s, 3 H) ,2.87-2.93 (m, 2 H), 3.39-3.68 (m, 6 H), 3.81 (s, 3 H), 4.03-4.08 (m, 2 H), 5.56-5.63 (m, 1 H), 7.41-7.46 (m, 1 H), 7.67-7.73 (m, 1 H), 8.60 (s, 1 H). LCMS: $[M+H]^+$=342.2, Rt $^{(2)}$= 0.94min.

Crystallization of Example 1 by heating and cooling in acetonitrile

1 part of Example 1 (eg. 100 mg) was mixed with 5 parts of acetonitrile (0.5 mL for each 100 mg of compound) with stirring. A solution was obtained by heating up to 40-60°C. The mixture was then allowed to slowly cooled down to RT. After further cooling overnight (5°C), precipitation was observed. In case no precipitation is not observed, the volume of ethanol can be reduce using a nitrogen stream and repeating the overnight cooling step. The mixture was centrifuged to remove the ethanol. The solid was dried under vacuum at 25°C and 70 mbar. A crystalline anhydrous form of Example 1 with a MP of 131°C was obtained. This crystalline form was also observed under other other methods and/or solvents, such as heating and cooling in ethanol, acetone, ethyl acetate, isopropanol, by slurry in heptane, or by antisolvent addition in THF or 3-methyl-1-butanol using heptane as antisolvent. These results show the reproducibility and scalability of the crystalline form as well as suggests that the same form can be prepared under different experimental conditions than the ones described above.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 1 anhydrous form (Method X2):

2-Theta in deg	Intensity in %
7.5	56
10.9	12.5
11.7	25.1
14.3	23.8
15.1	100
15.8	40.9
16.7	22.1
17.7	65.1
18.9	28.9
20.5	24.7

21.8	26
22.5	28.3
23.3	31.3
24.2	76.1
24.6	51.8
25.0	41.3
25.6	20.4
26.2	20.8
27.0	14.2
28.0	17.5
29.1	16.1
32.8	14
34.6	11.4

Crystallization of trihydrate form of Example 1 by slurry in water

Slurry of Example 1 in water e.g., 1 part of Example 1 in 10 parts of water, at RT produced a trihydrate form of Example 1. The crystals were separated by centrifugation and dried at room environment.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 1 trihydrate form (Method X2):

2-Theta in deg	**Intensity in %**
6.6	24.3
8.9	7.9
13.3	100
14.5	18.3
15.0	12.6
16.5	12.4
17.5	15.7
17.7	17.2
18.2	9.8
20.0	10.7
21.6	11.7
22.6	20.3
23.8	11.4
24.4	15.2
26.7	26.5

27.5	18.7
27.8	16.6
29.2	9.8
33.3	9
33.9	7.6
35.7	8.2
38.8	7

Preparation of citrate salt of Example 1

0.5 g of Example 1 (assay 91.8%) were dissolved in 5 mL of methylethylketone and 0.25 mL of water and heated at 60°C. 213 mg of citric acid were added at 50°C and the mixture was allowed to cool down to RT within 30 min. Crystallization occurs at 45°C. The mixture was stirred for 16 h at RT. The crystals were collected by filtration. The filter cake was washed 3 times with 1 mL of methylethylketone and afterwards dried for 16 h at 50°C and ca. 10 mbar vacuum. Elementary analysis of the citrate salt showed a 1:1 (monohydrate) form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 1 citrate salt (Method X1):

2-Theta in deg	**Intensity in %**
5.7	62
11.5	100
12.1	4
14.3	4
15.4	12
17.2	21
17.9	31
19.3	25
20.2	37
20.7	8
21.9	5
23.3	11
23.9	36
25.5	28
27.0	5
27.7	6
29.8	8
30.3	7

Preparation of fumarate salt of Example 1

0.5 g Example 1 (assay 91.8%) were dissolved in 15 mL of acetonitrile and 0.2 mL of water and heated at 76°C. 129 mg of fumaric acid were added at 60°C. The solution was allowed to cool down to RT within 30 min. The salt precipitated and the suspension was stirred for 16 h at RT. The crystals were collected by filtration. The filter cake was washed 3 times with 1 mL of acetonitrile and afterwards dried for 16 h at 50°C and ca. 10 mbar vacuum. Elementary analysis of the fumarate salt showed a 1:1 (monohydrate) form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 1 fumarate salt (Method X1):

2-Theta in deg	Intensity in %
6.0	100
6.5	12
9.8	8
12.3	10
13.1	14
15.6	22
17.7	16
19.1	21
19.7	27
23.9	40
24.7	6
24.9	10
25.2	5
26.4	11
27.0	4

Preparation of napadisylate salt of Example 1

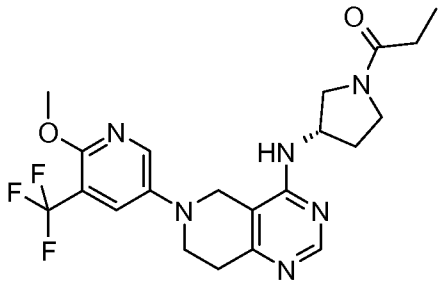
0.5 g Example 1 (assay 91.8%) were dissolved in 5 mL of ethanol absolute and 0.25 mL of water at 60°C. 250 mg of naphthalendisulfonic acid were added at 50°C and the mixture was allowed to cool down to RT within 30 min. Crystallization occurs at 40°C. The mixture was stirred for 16 h at RT. The crystals were collected by filtration. The filter cake was washed 3 times with 1 mL of ethanol and afterwards dried for 16 h at 50°C and ca. 10 mbar vacuum. Elementary analysis of the napadisylate salt showed a 2:1 (monohydrate) form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 1 napadisylate salt (Method X1):

2-Theta in deg	Intensity in %
4.3	100

8.5	3
9.4	6
12.2	12
12.9	12
13.5	37
15.0	26
15.6	12
16.0	11
17.7	28
18.9	23
19.3	11
20.0	11
20.8	3
21.2	5
22.0	9
23.0	41
24.5	39
26.5	20

Example 67 was prepared according the general procedure described in scheme 4



Example 67: 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one

To a solution of (*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate 24**) (13.4 g, 27.1 mmol) in CH_2Cl_2 (100 mL), was added TFA (41.8 mL) and the mixture stirred at rt for 1h. Concentrated *in vacuo* and partitioned between 2M NaOH(aq) (300 mL) and CH_2Cl_2 (200 mL). The organic phase was separated and the aqueous phase extracted

with CH_2Cl_2 (2 x 200 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a brown foam. The foam was dissolved in CH_2Cl_2 (50 mL) and was added simultaneously portionwise with sat.$NaHCO_3$(aq) (50 mL) to a vigourously stirring solution of propionyl chloride (2.63 g, 28.5 mmol) in CH_2Cl_2 (50 mL) at rt. The resulting biphasic mixture was stirred at rt for 1h. Further propionyl chloride (0.566g, 6.12 mmol) was added and continued stirring vigorously for 20 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown gum. The gum was stirred in EtOAc (100 mL) and the resulting solid filtered (9.4 g). The mother liquors were concentrated *in vacuo* and purified by column chromatography through a Biotage® amino silica gel eluting with EtOAc / MeOH, 100/0 to 90/10 to give a yellow foam which was then stirred in EtOAc (20 mL) and the resulting solid filtered (870 mg). Both batches of solids were combined and stirred in refluxing EtOAc (50 mL) for 1h. Filtered to give 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one as a colourless solid (9.42 g, 76% yield). ^{1}H NMR (400 MHz, DMSO-d6, 298K) δ ppm 0.95-1.05 (m, 3H) 1.87-2.32 (m, 4H) 2.77-2.86 (m, 2H) 3.25-3.88 (m, 6H) 3.93 (s, 3H) 3.98 (s, 2H) 4.55-4.80 (m, 1H) 6.70-6.80 (m, 1H, N-H) 7.86-7.92 (m, 1H) 8.27-8.33 (m, 1H) 8.33-8.37 (m, 1H) LCMS: [M+H]+=451.0, Rt $^{(6)}$= 1.49 min.

Alternative synthesis for example 67

A solution of (*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester (**intermediate 24**) (29.04 g, 58.73 mmol) in 2-Me-THF (100 mL) was dropwise added into aqueous HCl solution (150 mL, 31 %) over 15 min. The reaction mixture was partitioned between water (300 mL) and isopropyl acetate (100 mL) and the upper organic phase was discarded. The aqueous phase was partitioned between 25% NaOH (aq) (200 g) and 2-Me-THF (200 mL), and the organic phase was collected and dried. Triethylamine (16.32 mL, 117.48 mmol) was added into the organic phase followed by dropwise addition of propionyl chloride (6.0 g, 64.6 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1h. The reaction mixture was washed with water (110 mL) and the resulting organic phase was concentrated *in vacuo* to give a brown gum. The residue was recrystallized with isopropanol and methyl tert-butyl ether to give 1-{(*S*)-3-[6-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one as a colourless solid (17.2 g, 65% yield).

Crystallization of Example 67 by heating in acetonitrile/water

2.0 g of Example 67 (4.440 mol) were dissolved in 10 mL of acetonitrile and 0.5 mL of water at 75°C. The solution was allowed to cool down to rt within 30 min resulting in a suspension. The mixture was stirred for 16 h at rt. The crystals were collected by filtration. The filter cake

was washed 2 times with 1 mL of acetonitrile and afterwards dried for 16 h at 24°C and ca. 10 mbar vacuum. Elementary analysis of the material showed a waterless form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 67 anhydrous form Method X1):

2-Theta in deg	Intensity in %
7.9	31
9.6	88
11.5	29
13.4	8
15.2	7
15.9	100
16.8	57
17.6	9
18.7	20
20.0	8
20.6	40
22.0	32
22.4	53
22.7	26
23.4	17
23.9	23
24.5	41
25.1	20
25.8	13
26.7	31

Preparation of phosphate salt of Example 67

2.0 g of Example 67 (4.440 mol) were dissolved in 10 mL of acetonitrile and 0.5 mL of water at 75°C. 512 mg of ortho-phosphoric acid 85% (4.440 mol) were added at 70°C. Crystallization occurs quickly at 70°C. The suspension was allowed to cool down to rt within 30 min. The suspension was diluted with 10 ml acetonitrile and stirred for 16 h at rt. The crystals were collected by filtration. The filter cake was washed 3 times with 1 mL of acetonitrile and afterwards dried for 16 h at 24°C and ca. 10 mbar vacuum. Elementary analysis of the phosphate salt showed a 1:1 (waterless) form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 67 phosphate salt (Method X1):

2-Theta in deg	Intensity in %

5.2	51
9.8	56
10.3	19
11.6	100
14.9	14
15.5	48
15.9	11
16.6	65
19.5	54
20.7	62
21.5	10
22.1	21
23.3	57
25.8	18
26.4	29
27.2	20
28.2	13

Preparation of hydrochloride salt of Example 67

2.0 g of Example 67 (4.440 mol) were dissolved in 20 mL of acetonitrile and 1.0 mL of water at 70°C. 459 mg of hydrochloric acid 37% (4.440 mol) were added at 70°C. Crystallization occurs quickly at 70°C. The suspension was allowed to cool down to rt within 30 min and stirred for 16 h at rt. The crystals were collected by filtration. The filter cake was washed 3 times with 1 mL of acetonitrile and afterwards dried for 16 h at 24°C and ca. 10 mbar vacuum. Elementary analysis of the HCl salt showed a 1:1 (waterless) form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 67 hydrochloride salt (Method X1):

2-Theta in deg	**Intensity in %**
5.6	100
11.0	18
11.3	42
11.8	12
14.7	33
17.1	13
18.7	19
19.4	29
22.0	23

22.6	28
23.1	50
23.7	28
24.9	29
25.5	15

Preparation of hippurate salt of Example 67

0.4 g of Example 67 (0.888 mmol) were dissolved in 8 mL of acetonitrile and 0.2 mL of water at 70°C. 167 mg of hippuric acid (0.888 mmol) were added at 70°C. The solution was allowed to cool down to rt within 30 min. Crystallization occurs at 40°C. The suspension was stirred for 16 h at rt. The crystals were collected by filtration. The filter cake was washed 3 times with 1 mL of acetonitrile and afterwards dried for 16 h at 50°C and ca. 10 mbar vacuum. Elementary analysis of the hippurate salt showed a 1:1 (waterless) form.

List of most significant peaks from X-ray Powder Diffraction Pattern of Example 67 hippurate salt (Method X1):

2-Theta in deg	Intensity in %
5.2	76
7.5	100
10.3	60
10.9	63
11.8	9
13.1	16
16.1	44
16.7	26
17.7	49
18.4	38
21.2	49
23.2	74
24.2	67
26.2	28

Biological evaluation

The activity of a compound according to the present invention can be assessed by the *in vitro & in vivo* methods described in the international patent application PCT/EP2011/061393, published as WO2012/004299 in the section 'Biological assays' in points 1 to 3, pages 167 to 179.

Enzymatic Assay

Example	PI3K alpha (uM)	PI3K delta (uM)
1	2.0378	0.015
67	0.262	0.023

Buffered solutions are used in the enzymatic assay and as a consequence the forms of the present invention should generate same or comparable IC_{50} values as the corresponding amorphous free base.

Cellular Assays

Example	Cell PI3Kδ / IC50 [umol l-1]	mCD86 / IC50 CD86 [nmol l-1]
1	0.153	94.9
67	0.047	48.3

SRBC Assay

	Plaques/spleen
Example **1** 10mg/kg bid	12608 ± 4986
Vehicle (0.5% CMC 0.5%Tween80)	168363 ± 49142

Claims:

1. The anhydrous crystalline form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone.

2. The anhydrous crystalline form according to claim 1, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 7.5, 10.9, 11.7, 14.3, 15.1, 15.8, 16.7, 17.7, 18.9, 20.5, 21.8, 22.5, 23.3, 24.2, 24.6, 25.0, 25.6, 26.2, 27.0, 28.0, 29.1, 32.8 and 34.6.

3. The trihydrate crystalline form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone.

4. The trihydrate crystalline form according to claim 3, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 6.6, 8.9, 13.3, 14.5, 15.0, 16.5, 17.5, 17.7, 18.2, 20.0, 21.6, 22.6, 23.8, 24.4, 26.7, 27.5, 27.8, 29.2, 33.3, 33.9, 35.7 and 38.8.

5. A salt form of {(*S*)-3-[6-(6-methoxy-5-methyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone, wherein the anion is selected from citrate, fumarate or napadisylate.

6. A salt form according to claim 5, wherein the anion is citrate.

7. A salt according to claim 6 in form of a monohydrate.

8. A salt form according to claim 7, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.7, 11.5, 12.1, 14.3, 15.4, 17.2, 17.9, 19.3, 20.2, 20.7, 21.9, 23.3, 23.9, 25.5, 27.0, 27.7, 29.8 and 30.3.

9. A salt form according to claim 5, wherein the anion is fumarate.

10. A salt according to claim 9 in form of a monohydrate.

11. A salt form according to claim 10, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 6.0, 6.5, 9.8, 12.3, 13.1, 15.6, 17.7, 19.1, 19.7, 23.9, 24.7, 24.9, 25.2, 26.4 and 27.0.

12. A salt form according to claim 5, wherein the anion is napadisylate.

13. A salt according to claim 12 in form of a monohydrate.

14. A salt form according to claim 13, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 4.3, 8.5, 9.4, 12.2, 12.9, 13.5, 15.0, 15.6, 16.0, 17.7, 18.9, 19.3, 20.0, 20.8, 21.2, 22.0, 23.0, 24.5 and 26.5.

15. A salt form of 1-{(*S*)-3-[6-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4-ylamino]-pyrrolidin-1-yl}-propan-1-one, wherein the anion is selected from phosphate, chloride or hippurate.

16. A salt form according to claim 15, wherein the anion is phosphate.

17. A salt according to claim 16 in anhydrous form.

18. A salt form according to claim 17, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.2, 9.8, 10.3, 11.6, 14.9, 15.5, 15.9, 16.6, 19.5, 20.7, 21.5, 22.1, 23.3, 25.8, 26.4, 27.2 and 28.2.

19. A salt form according to claim 15, wherein the anion is chloride.

20. A salt according to claim 19 in anhydrous form.

21. A salt form according to claim 20, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.6, 11.0, 11.3, 11.8, 14.7, 17.1, 18.7, 19.4, 22.0, 22.6, 23.1, 23.7, 24.9 and 25.5.

22. A salt form according to claim 15, wherein the anion is hippurate.

23. A salt according to claim 22, in anhydrous form.

24. A salt form according to claim 23, characterized by an X-Ray powder diffraction pattern comprising the following peaks given at degrees 2-Theta +/- 0.2 degrees: 5.2, 7.5, 10.3, 10.9, 11.8, 13.1, 16.1, 16.7, 17.7, 18.4, 21.2, 23.2, 24.2 and 26.2.

25. A form according to anyone of claims 1 to 24, for use as pharmaceutical.

26. A combination comprising a therapeutically effective amount of a form according to anyone of claims 1 to 24, and one or more therapeutically active agents.

27. Use of a form according to anyone of claims 1 to 24, for the manufacture of a medicament for the treatment of a diseases or disorders which are mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform.

28. A form according to anyone of claims 1 to 24, for use in the treatment of a diseases or disorders which are mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform.

29. A pharmaceutical composition comprising a therapeutically effective amount of a form according to anyone of claims 1 to 24, and one or more pharmaceutically acceptable carriers.

30. A method of modulating the activity of the PI3K enzymes, preferably of the PI3Kδ isoform , in a subject, comprising the step of administering to a subject a therapeutically effective amount of a form according to anyone of claims 1 to 24.

31. Use of a form according to anyone of claims 1 to 24, for the treatment of a disorder or a disease in a subject mediated by the activity of the PI3K enzymes, preferably by the activity of the PI3Kδ isoform