

**PHARMACEUTICAL COMPOSITIONS AND SOLID FORMS OF COMPOUND 1 WITH
FUMARATE FOR THE TREATMENT OF INFLAMMATORY DISORDERS**

FIELD OF THE INVENTION

[0001] The present invention relates to novel pharmaceutical compositions and novel solid forms of compounds useful in the treatment of inflammatory diseases, and/or diseases associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23. The invention also relates to the preparation of the pharmaceutical compositions, to the preparation of the solid forms, to the preparation of Compound 1, to the use of the pharmaceutical compositions and solid forms in the treatment of inflammatory diseases, and/or diseases associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, and to pharmaceutical unit dosage compositions comprising the compositions and solid forms.

BACKGROUND

[0002] Janus kinases (JAKs) are cytoplasmic tyrosine kinases that transduce cytokine signaling from membrane receptors to STAT transcription factors. Four JAK family members are described, JAK1, JAK2, JAK3 and TYK2. Upon binding of the cytokine to its receptor, JAK family members auto- and/or transphosphorylate each other, followed by phosphorylation of STATs that then migrate to the nucleus to modulate transcription. JAK-STAT intracellular signal transduction serves the interferons, most interleukins, as well as a variety of cytokines and endocrine factors such as EPO, TPO, GH, OSM, LIF, CNTF, GM-CSF and PRL (Vainchenker, Dusa, and Constantinescu 2008).

[0003] The combination of genetic models and small molecule JAK inhibitor research revealed the therapeutic potential of JAK inhibitors (JAKinibs) (Babon et al. 2014). The last decade has seen the development of JAKinibs with various degrees of selectivity profiles versus the JAK family members. In particular, whereas targeting multiple JAK may not be detrimental (Broekman, Giovannetti, and Peters 2011), developing selective JAKinibs would be very desirable to develop treatment course tailored to the needs of the patient despite the challenge it represents (Fabian et al. 2005). For example, whereas JAK2 inhibition has proven useful in the treatment of polycythemia and myelofibrosis, undesirable effect associated with JAK2 inhibition were observed (O'Shea and Plenge, 2012) thus rendering compounds with JAK2 inhibition components unsuitable for the treatment of non-JAK2 mediated diseases.

[0004] Using TYK2 knock out mice, it has been shown that IL-6, IL-10, IL-11, IL12, IL-13, IL-19, IL-20, IL-22, IL-23, IL-27, IL-28, IL-29, IL-31, IL-35 and/or type I interferons signaling are dependent on TYK2 (Schwartz et al. 2016). However, it has recently been shown that whereas JAK1 is a key driver in IFN α , IL-6, IL-10 and IL-22 signaling, TYK2 is involved in type I interferons (including IFN α , INF β), IL-23 and IL-12 signaling (Gillooly et al. 2016; Sohn et al. 2013). Since the activity of IL-12 and IL-23 is particularly increased in patients with auto-immune diseases (O'Shea and Plenge, 2012) such as psoriasis and/or inflammatory bowel disorders, selective TYK2 inhibition may be particularly advantageous in the

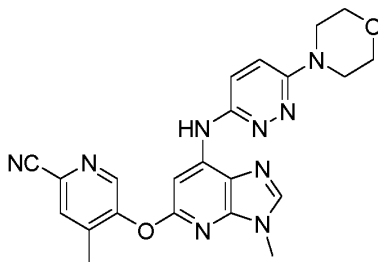
treatment of these diseases while avoiding JAK2 dependent erythropoietin (EPO) and thrombopoietin (TPO) signaling (Neubauer et al. 1998; Parganas et al. 1998).

[0005] Furthermore, TYK2 has been reported as a target for multiple autoimmune disorders, providing protection against inflammatory diseases as well as type 2 diabetes with a limited impact on the immune system (Dendrou et al. 2016).

[0006] Accordingly, there is an ongoing unmet medical need for the development of new and improved therapies in the treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23. In particular, diseases such as systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease.

[0007] In this context, new drugs are being developed, in particular Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl)amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile).

[0008] Compound 1 is a small molecule inhibitor of JAK, a family of tyrosine kinases, more particularly TYK2, and is currently under investigation as a drug for the treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23. The identification and synthesis of Compound 1 (also known as Cpd 1) have previously been described in WO2019076716.



Cpd 1

[0009] An important characteristic of various bioactive substances (for example, but without limitation, pharmaceuticals, medicines and biocides, usually referred to as drugs) is their “bioavailability” or active concentration in a form which can be absorbed and utilized by a target organ or organism. In many cases, bioavailability is related to drug solubility in water, which may depend on many parameters such as acid-basic properties, crystalline form, and/or polymorphism.

[0010] Drugs in their free base form may be poorly soluble in water, but the presence of acidic sites (for example carboxylic acids, phenols, sulfonic acids) or basic sites (for example amino groups, basic nitrogen

centres) can be used advantageously to produce salts of the drug. The resulting ionic compounds become much more soluble in water by virtue of their ionic character and lower dissolution energy, and thus may improve bioavailability. A guideline of 50 µg/mL for aqueous solubility is provided by Lipinski *et al* (Lipinski et al. 2001).

[0011] Salt forming agents are available in large number, and salt selection must be carefully designed. The aim of the salt selection is to identify the best salt form suitable for development, and is based primarily on four main criteria: aqueous solubility at various pH, high degree of crystallinity, low hygroscopicity, and optimal chemical stability (Stahl et al. 2011).

[0012] A cocrystal (or co-crystal) is the aggregation of two or more chemical entities in a crystalline lattice through non-covalent interactions. Over the last decade, cocrystals have are a potential alternate solid form of pharmaceuticals. Cocrystalline forms includes solvates, solid solutions, eutectics, salts, ionic liquids, solid dispersions, supramolecular gelators (Row, Kaur, and Cherukuvada 2016).

[0013] Polymorphism is a solid-state property of some molecules (and molecular complexes) wherein a single molecule may give rise to a variety of distinct crystal structures with different physical properties which may be characterized by determining melting point, thermal behaviors using thermogravimetric analysis (TGA), or differential scanning calorimetry (DSC), X-ray pattern diffraction (XRPD), infrared absorption fingerprint, and/or solid state (¹³C) NMR spectrum.

[0014] If a suitable solid form, such as a crystalline or polymorphic form of a drug or salt thereof can be identified, further investigations can be performed to identify alternative solid forms both qualitatively and quantitatively. The availability of such solid forms is highly unpredictable and can require a combination of intuition, careful empirical design, perseverance and serendipity. On top of the challenges associated with even finding one or more defined solid forms, the properties of any forms thus discovered need to be carefully evaluated to see if one or more of them is actually suitable for pharmaceutical development. In a first aspect, crystallinity of drug can affect, among other physical and mechanical properties, solubility, dissolution rate, flowability, hardness, compressibility, and/or melting point. In a second aspect, a crystalline form may have advantages over the amorphous form, for example, purification to the high degree of purity required by most regulatory authorities could be more efficient and therefore cost less for the crystalline form than for the amorphous solid. In addition, handling of the crystalline form could be improved over the amorphous form, which could be oily, or sticky for example, and in practice, drying of a crystalline material which has a well-defined drying or desolvation temperature could in some cases be more easily controlled, than for the amorphous solid which could have a greater affinity for organic solvents and variable drying temperature. Finally, downstream processing of the crystalline drug can in some cases permit enhanced process control. In a third aspect, physical and chemical stability, and/or shelf-life could be improved for certain crystalline forms over amorphous forms.

[0015] Further pharmacokinetic and pharmacodynamic properties of a drug could be linked to a particular solid or crystalline structural form, and it could be paramount to produce and retain the same form from production to administration to the patient. Therefore the obtention of salts, crystalline and/or co-crystalline forms over amorphous materials, whilst challenging, is highly desirable (Hilfiker et al. 2006).

[0016] Thus, herein are provided, *inter alia*, novel pharmaceutical compositions and novel solid forms of the invention, such as cocrystalline and/or salt forms of Compound 1, and specific crystalline forms thereof, methods of preparing pharmaceutical compositions and/or solid forms and/or Compound 1, and pharmaceutical unit dosage compositions comprising the compositions and/or solid forms. The novel compositions and solid forms have desirable pharmacological properties, with a good pharmaceutical profile, in particular improved *in vivo* exposure over existing forms.

DESCRIPTION OF THE DRAWINGS

[0017] FIGURE 1A shows the ¹H-NMR spectrum of HCl salt form of Compound 1.

[0018] FIGURE 1B shows the ¹H-NMR spectrum of Compound 1 (green) and the ¹H-NMR spectrum of HCl salt form of Compound 1 (red).

[0019] FIGURE 1C shows the XRPD for HCl salt form of Compound 1.

[0020] FIGURE 1D shows the DSC curve for HCl salt form of Compound 1.

[0021] FIGURE 1E shows the TGA curve for HCl salt form of Compound 1.

[0022] FIGURE 1F shows the DVS curve for HCl salt form of Compound 1.

[0023] FIGURE 2A shows the ¹H-NMR spectrum of mesylate salt form of Compound 1.

[0024] FIGURE 2B shows the ¹H-NMR spectrum of Compound 1 (green) and the ¹H-NMR spectrum of mesylate salt form of Compound 1 (red).

[0025] FIGURE 2C shows the XRPD for mesylate salt form of Compound 1.

[0026] FIGURE 2D shows the DSC curve for mesylate salt form of Compound 1.

[0027] FIGURE 2E shows the TGA curve for mesylate salt form of Compound 1.

[0028] FIGURE 2F shows the DVS curve for mesylate salt form of Compound 1.

[0029] FIGURE 3A shows the ¹H-NMR spectrum of maleate cocrystal form of Compound 1.

[0030] FIGURE 3B shows the ¹H-NMR spectrum of Compound 1 (green) and the ¹H-NMR spectrum of maleate cocrystal form of Compound 1 (red).

[0031] FIGURE 3C shows the DSC curve for maleate cocrystal form of Compound 1.

[0032] FIGURE 4A shows the ¹H-NMR spectrum of phosphate cocrystal form A of Compound 1.

[0033] FIGURE 4B shows the DSC curve for phosphate form A of Compound 1.

[0034] FIGURE 4C shows the TGA curve for phosphate cocrystal form A of Compound 1.

[0035] FIGURE 4D shows the DVS curve for phosphate cocrystal form A of Compound 1.

[0036] FIGURE 4E shows the XRPD for phosphate cocrystal form A of Compound 1.

[0037] FIGURE 5A shows the ¹H-NMR spectrum of phosphate cocrystal form B of Compound 1.

[0038] FIGURE 5B shows the DSC curve for phosphate form B of Compound 1.

[0039] FIGURE 5C shows the TGA curve for phosphate cocrystal form B of Compound 1.

[0040] FIGURE 6A shows the ^1H -NMR spectrum of fumarate cocrystal form of Compound 1. ^1H NMR (400MHz, DMSO- d_6) δ ppm: 13.13(s, 1H), 9.84 (s, 1H), 8.53 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.64 (d, J = 9.7 Hz, 1H), 7.43 (d, J = 9.7 Hz, 1H), 3.63 (s, 2H), 3.77 – 3.65 (m, 4H), 3.61 (s, 3H), 3.49 – 3.40 (m, 4H), 2.31 (s, 3H).

[0041] FIGURE 6B shows the ^1H -NMR spectrum of Compound 1 (top) and the ^1H -NMR spectrum of fumarate cocrystal form of Compound 1 (bottom). Top: ^1H NMR (400 MHz, DMSO- d_6) δ ppm: 9.86 (s, 1H), 8.53 (s, 1H), 8.20 (s, 1H), 8.19 (s, 1H), 8.15 – 8.08 (m, 1H), 7.64 (d, J = 9.7 Hz, 1H), 7.43 (d, J = 9.7 Hz, 1H), 3.75 (t, J = 4.8 Hz, 4H), 3.61 (s, 3H), 3.50 – 3.42 (m, 4H), 2.31 (d, J = 0.7 Hz, 3H). Bottom ^1H NMR (400MHz, DMSO- d_6) δ ppm: 13.13(s, 1H), 9.84 (s, 1H), 8.53 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.64 (d, J = 9.7 Hz, 1H), 7.43 (d, J = 9.7 Hz, 1H), 3.63 (s, 2H), 3.77 – 3.65 (m, 4H), 3.61 (s, 3H), 3.49 – 3.40 (m, 4H), 2.31 (s, 3H).

[0042] FIGURE 6C shows the XRPD for fumarate cocrystal form of Compound 1.

[0043] FIGURE 6D shows the DSC curve for fumarate cocrystal form of Compound 1. Sample 1.7 mg. Integral -336.00 mJ, normalized -197.65 Jg $^{-1}$; onset 253.90 °C, peak 259.72 °C, endset 262.42 °C.

[0044] FIGURE 6E shows the TGA curve for fumarate cocrystal form of Compound 1. Sample 1.94 mg, step -0.2946%, -5.74147e $^{-03}$ mg.

[0045] FIGURE 6F shows the DVS curve for fumarate cocrystal form of Compound 1. The line with white circles represents Sorption #1, the line with black squares represents Desorption #1, and the line with white triangles represent Sorption #2.

[0046] FIGURE 7A shows the DSC-TGA curve for L-tartrate cocrystal form of Compound 1.

[0047] FIGURE 7B shows the DVS curve for L-tartrate cocrystal form of Compound 1.

[0048] FIGURE 7C shows the XRPD for L-tartrate cocrystal form of Compound 1.

[0049] FIGURE 7D shows the ^1H -NMR spectrum of L-tartrate cocrystal form of Compound 1.

[0050] FIGURE 8A shows the DSC-TGA curve for L-malate cocrystal form of Compound 1.

[0051] FIGURE 8B shows the DVS curve for L-malate cocrystal form of Compound 1.

[0052] FIGURE 8C shows the XRPD for L-malate cocrystal form of Compound 1.

[0053] FIGURE 8D shows the ^1H -NMR spectrum of L-malate cocrystal form of Compound 1.

[0054] FIGURE 9A shows the DSC-TGA curve for saccharinate cocrystal form of Compound 1.

[0055] FIGURE 9B shows the DVS curve for saccharinate cocrystal form of Compound 1.

[0056] FIGURE 9C shows the XRPD for saccharinate cocrystal form of Compound 1.

[0057] FIGURE 9D shows the ¹H-NMR spectrum of saccharinate cocrystal form of Compound 1.

[0058] FIGURE 10A shows the XRPD for the hydrate of Compound 1 (Form A).

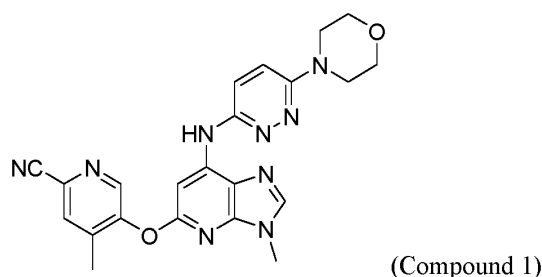
[0059] FIGURE 10B shows the XRPD for anhydrous Compound 1 (Form C).

[0060] FIGURE 11A shows the XRPD for the amorphous composition comprising Compound 1 and fumaric acid.

SUMMARY OF THE INVENTION

[0061] Herein are provided, inter alia, solid forms of the invention, useful in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23. In particular, the compound comprised in a solid form of the invention inhibits JAK, a family of tyrosine kinases, and more particularly TYK2. Herein are also provided inter alia, pharmaceutical compositions comprising a solid form of the invention and methods for the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23 by administering a solid form of the invention.

[0062] Accordingly, in a first and second aspect of the invention, there are provided pharmaceutical compositions and solid forms, respectively, of Compound 1:



[0063] In a further aspect, a solid form of the invention is a crystalline form. In a particular aspect, the solid form of the invention is a cocrystal form. In a more particular aspect, a solid form of the invention is a cocrystal form comprising two components. In a further particular aspect, a solid form of the invention is a cocrystal form comprising two components in a 1 to 1 ratio. In another aspect, a solid form of the invention is a cocrystal form comprising Compound 1 and fumaric acid in a 1 to 1 ratio. In another aspect,

a solid form of the invention is amorphous. In another aspect, a solid form of the invention is anhydrous. In another aspect, a solid form is solvated. In another aspect, a solid form is unsolvated.

[0064] In a particular aspect, solid forms of the invention are provided inter alia for use in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23. In a particular aspect, the solid forms of the invention are provided inter alia for use in the prophylaxis and / or treatment of systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease.

[0065] Furthermore, it has also been unexpectedly demonstrated that a solid form of the invention exhibits improved bioavailability compared to other solid state forms of Compound 1.

[0066] In a further aspect, are provided inter alia, pharmaceutical compositions comprising a solid form of the invention, and a pharmaceutical carrier, excipient or diluent. In a particular aspect, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the solid form of the invention. In a more particular aspect, the further therapeutically active ingredient is an agent for the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23.

[0067] Moreover, the solid forms of the invention, useful in pharmaceutical compositions and in treatment methods provided herein, are pharmaceutically acceptable as prepared and used.

[0068] In a further aspect, is provided inter alia, a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, which method comprises administering an effective amount of the pharmaceutical composition or solid form of the invention as described herein.

[0069] Herein are also provided inter alia, pharmaceutical compositions comprising a solid form of the invention, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular aspect, the pharmaceutical composition is for use in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23.

[0070] In additional aspects, herein are provided inter alia, methods for synthesizing the solid forms of the invention, with representative synthetic protocols and pathways disclosed later on herein.

[0071] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

DEFINITIONS

[0072] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0073] Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein.

[0074] The articles ‘a’ and ‘an’ may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example ‘an analogue’ means one analogue or more than one analogue.

[0075] The term ‘cocrystal’ or ‘co-crystal’ refers to a crystalline material composed of Compound 1 and a co-crystal former (‘coformer’) in the same crystal lattice. The terms “cocrystal” and “co-crystal” are used interchangeably herein.

[0076] Reference to a certain ‘dose’ or ‘dosage’ refers to the equivalent weight of free base Compound 1 being administered, *i.e.* not including the weight of any salt, solvate or cocrystal counterpart or component.

[0077] ‘Palladium precursor’ means a substance comprising palladium that requires further activation or reaction to produce an active catalyst. Examples of palladium precursor are Pd(π -cinnamyl)Cl dimer, Pd(OAc)₂, Pd(Cl)₂, Pd₂(dba)₃, Pd(dba)₂, Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd(acac)₂ and Pd(PhCN)₂Cl₂.

[0078] ‘Pharmaceutically acceptable’ means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0079] ‘Pharmaceutically acceptable salt’ refers to a salt of a solid form of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts

formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.* an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[0080] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a solid form of the invention is administered.

[0081] As used herein, the term 'pharmaceutical composition' means a mixture comprising a pharmaceutically acceptable active ingredient, in combination with suitable pharmaceutically acceptable excipients. In particular, the pharmaceutically acceptable ingredient is a solid form of the invention.

[0082] Pharmaceutical excipients are substances other than the pharmaceutically acceptable active ingredient which have been appropriately evaluated for safety and which are intentionally included in an oral solid dosage form. For example, excipients can aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. Examples of excipients include, for example but without limitation inert solid diluents (bulking agent *e.g.* lactose), binders (*e.g.* starch), glidants (*e.g.* colloidal silica), lubricants (*e.g.* non-ionic lubricants such as vegetable oils), disintegrants (*e.g.* starch, polyvinylpyrrolidone), coating better polymers (*e.g.* hydroxypropyl methylcellulose), colorants (*e.g.* iron oxide), and/or surfactants (*e.g.* non-ionic surfactants). (Rowe et al. 2009).

[0083] As used herein, the term 'pharmaceutical formulation' means the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product. Examples of formulation include enteral formulations (tablets, capsules), parenteral formulations (liquids, lyophilized powders), or topical formulations (cutaneous, inhalable).

[0084] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a solid form of the invention is administered.

[0085] 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The solid forms of the invention may be prepared *e.g.* in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0086] The terms ‘inert solid diluent’ or ‘solid diluent’ or ‘diluent’ refer to materials used to produce appropriate dosage form size, performance and processing properties for tablets and/or capsules. An inert solid diluent can be also referred to as filler or filler material. Particular examples of diluents include cellulose powdered, silicified microcrystalline cellulose acetate, compressible sugar, confectioner’s sugar, corn starch and pregelatinized starch, dextrates, dextrin, dextrose, erythritol, ethylcellulose, fructose, fumaric acid, glyceryl palmitostearate, inhalation lactose, isomalt, kaolin, lactitol, lactose, anhydrous, monohydrate and corn starch, spray dried monohydrate and microcrystalline cellulose, maltodextrin, maltose, mannitol, medium-chain triglycerides, microcrystalline cellulose, polydextrose, polymethacrylates, simethicone, sorbitol, pregelatinized starch, sterilizable maize, sucrose, sugar spheres, sulfobutylether β -cyclodextrin, talc, tragacanth, trehalose, or xylitol. More particular examples of diluents include cellulose powdered, silicified microcrystalline cellulose acetate, compressible sugar, corn starch and pregelatinized starch, dextrose, fructose, glyceryl palmitostearate, anhydrous, monohydrate and corn starch, spray dried monohydrate and microcrystalline cellulose, maltodextrin, maltose, mannitol, medium chain triglycerides, microcrystalline cellulose, polydextrose, sorbitol, starch, pregelatinized, sucrose, sugar spheres, trehalose, or xylitol.

[0087] ‘Lubricant’ refers to materials that prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Particular examples of lubricants include canola oil, hydrogenated castor oil, cottonseed oil, glyceryl behenate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, medium-chain triglycerides, mineral oil, light mineral oil, octyldodecanol, poloxamer, polyethylene glycol, polyoxyethylene stearates, polyvinyl alcohol, starch, or hydrogenated vegetable oil. More particular examples of lubricants include magnesium stearate, glyceryl behenate, glyceryl monostearate, or hydrogenated vegetable oil.

[0088] ‘Disintegrant’ refers to material that swells when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution. Particular examples of disintegrants include alginic acid, powdered cellulose, chitosan, colloidal silicon dioxide, corn starch and pregelatinized starch, crospovidone, glycine, guar gum, low-substituted hydroxypropyl cellulose, methylcellulose, microcrystalline cellulose, croscarmellose sodium or povidone.

[0089] The term ‘colorant’ describes an agent that imparts color to a formulation. Particular examples of colorants include iron oxide, or synthetic organic dyes (US Food and Drug administration, Code of Federal Regulations, Title 21 CFR Part73, Subpart B).

[0090] The term ‘plasticizing agent’ or ‘plasticizer’ refers to an agent that is added to promote flexibility of films or coatings. Particular examples of plasticizing agent include polyethylene glycols or propylene glycol.

[0091] The term ‘pigment’ refers to an insoluble colouring agent.

[0092] The term ‘film-coating agent’ or ‘coating agent’ or ‘coating material’ refers to an agent that is used to produce a cosmetic or functional layer on the outer surface of a dosage form. Particular examples of film-coating agent include glucose syrup, maltodextrin, alginates, or carrageenan.

[0093] ‘Glidant’ refers to materials that are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce diwall friction. Particular examples of glidants include powdered cellulose, colloidal silicon dioxide, hydrophobic colloidal silica, silicon dioxide, or talc. More particular examples of glidants include colloidal silicon dioxide, hydrophobic colloidal silica, silicon dioxide, or talc.

[0094] ‘Flavouring agents’ refers to material that can be used to mask unpleasant tasting active ingredients and improve the acceptance that the patient will complete a course of medication. Flavourings may be natural (e.g. fruit extract) or artificial. Non-limiting examples of flavouring agents include mint, cherry, anise, peach, apricot, liquorice, raspberry, or vanilla.

[0095] ‘Prodrugs’ refers to compounds, including derivatives of the solid form of the invention, which have cleavable groups and become by solvolysis or under physiological conditions pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0096] ‘Subject’ includes humans. The terms ‘human’, ‘patient’ and ‘subject’ are used interchangeably herein.

[0097] ‘Effective amount’ means the amount of a solid form of the invention that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The “effective amount” can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0098] ‘Preventing’ or ‘prevention’ refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.* causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset).

[0099] The term ‘prophylaxis’ is related to ‘prevention’ and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0100] ‘Treating’ or ‘treatment’ of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (*i.e.* arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment ‘treating’ or ‘treatment’ refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, ‘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 a further embodiment, “treating” or “treatment” relates to slowing the progression of the disease.

[0101] As used herein the term ‘allergic disease(s)’ refers to the group of conditions characterized by a hypersensitivity disorder of the immune system including, allergic airway disease (*e.g.* asthma, rhinitis), sinusitis, eczema and hives, as well as food allergies or allergies to insect venom.

[0102] As used herein the term ‘asthma’ as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate the cause.

[0103] As used herein the term ‘inflammatory disease(s)’ refers to the group of conditions including, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, allergic airway disease (*e.g.* asthma, rhinitis), chronic obstructive pulmonary disease (COPD), inflammatory liver diseases (*e.g.* primary biliary cholangitis (PBC), and/or primary sclerosing cholangitis (PSC)), inflammatory bowel diseases (*e.g.* Crohn’s disease, ulcerative colitis), endotoxin-driven disease states (*e.g.* complications after bypass surgery or chronic endotoxin states contributing to *e.g.* chronic cardiac failure), and related diseases involving cartilage, such as that of the joints. Particularly the term refers to rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases. More particularly the term refers to rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and inflammatory bowel diseases. Most particularly the term refers to rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases.

[0104] As used herein the term ‘metabolic disease(s)’ refers to the group of conditions involving the body’s ability to process certain nutrients and vitamins. Metabolic disorders include phenylketonuria (PKU), type II diabetes, hyperlipidemia, gout, and rickets. A particular example of metabolic disorders is type II diabetes and/or obesity.

[0105] As used herein the term ‘autoinflammatory diseases(s)’ refers to the group of diseases including Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçets, Systemic-Onset Juvenile Idiopathic Arthritis (SJIA) or Still’s disease.

[0106] As used herein the term ‘autoimmune disease(s)’ refers to the group of diseases including obstructive airways disease, including conditions such as COPD, asthma (*e.g.* intrinsic asthma, extrinsic asthma, dust asthma, infantile asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperresponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, Sjogren’s syndrome, multiple sclerosis, psoriasis, dry eye disease, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), thyroiditis (Hashimoto’s and autoimmune thyroiditis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (*e.g.* Crohn’s disease and ulcerative colitis), interferonopathy, atherosclerosis and amyotrophic lateral sclerosis. Particularly the term refers to COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus, interferonopathy, and inflammatory bowel disease.

[0107] As used herein the term ‘proliferative disease(s)’ refers to conditions such as cancer (e.g. uterine leiomyosarcoma or prostate cancer), myeloproliferative disorders (e.g. polycythemia vera, essential thrombocytosis and myelofibrosis), leukemia (e.g. acute myeloid leukemia, acute and chronic lymphoblastic leukemia), multiple myeloma, psoriasis, restenosis, scleroderma or fibrosis. In particular the term refers to cancer, leukemia, multiple myeloma and psoriasis.

[0108] As used herein, the term ‘cancer’ refers to a malignant or benign growth of cells in skin or in body organs, for example but without limitation, breast, prostate, lung, kidney, pancreas, stomach or bowel. A cancer tends to infiltrate into adjacent tissue and spread (metastasis) to distant organs, for example to bone, liver, lung or the brain. As used herein the term cancer includes both metastatic tumour cell types (such as but not limited to, melanoma, lymphoma, leukemia, fibrosarcoma, rhabdomyosarcoma, and mastocytoma) and types of tissue carcinoma (such as but not limited to, colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer, renal cancer, gastric cancer, glioblastoma, primary liver cancer, ovarian cancer, prostate cancer and uterine leiomyosarcoma). In particular, the term ‘cancer’ refers to acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymblastoma, ependymoma, esophageal cancer, Ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenstrom macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, asopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sezary syndrome, skin cancer,

small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

[0109] As used herein the term 'leukemia' refers to neoplastic diseases of the blood and blood forming organs. Such diseases can cause bone marrow and immune system dysfunction, which renders the host highly susceptible to infection and bleeding. In particular the term leukemia refers to acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL).

[0110] As used herein the term 'transplantation rejection' refers to the acute or chronic rejection of cells, tissue or solid organ allo- or xenografts of e.g. pancreatic islets, stem cells, bone marrow, skin, muscle, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus, or graft-versus-host diseases.

[0111] As used herein the term 'diseases involving impairment of cartilage turnover' includes conditions such as osteoarthritis, psoriatic arthritis, juvenile rheumatoid arthritis, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, Tietze syndrome or costal chondritis, fibromyalgia, osteochondritis, neurogenic or neuropathic arthritis, arthropathy, endemic forms of arthritis like osteoarthritis deformans endemica, Meleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis. In a particular embodiment, the term refers to ankylosing spondylitis.

[0112] As used herein the term 'congenital cartilage malformation(s)' includes conditions such as hereditary chondrolysis, chondrodysplasias and pseudochondrodysplasias, in particular, but without limitation, microtia, anotia, metaphyseal chondrodysplasia, and related disorders.

[0113] As used herein the term 'disease(s) associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23 includes conditions such as systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, multiple sclerosis, trisomy 21, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.

[0114] As used herein the term 'solid form(s) of the invention', and equivalent expressions, are meant to embrace solid forms herein described, amorphous or crystalline, which expression includes the pharmaceutically acceptable salts, crystals and cocrystals, and their respective solvates, e.g. hydrates, and the solvates of the pharmaceutically acceptable salts/cocrystals/crystals where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0115] A solid state form, such as a crystal form or an amorphous form, may be referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a FIGURE. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. It is well-known in the art that the graphical data potentially provides a "fingerprint" containing additional technical information defining further the respective solid state form which cannot otherwise be only described by reference to

numerical values or peak positions. The skilled person will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and/or peak positions due to certain factors including variations in instrument, sample concentration and/or purity.

[0116] Other derivatives of the solid forms of the invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgard, H, 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the solid forms of the invention are particularly useful prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particular such prodrugs are the C₁₋₈ alkyl, C₂₋₈ alkenyl, C₆₋₁₀ optionally substituted aryl, and (C₆₋₁₀ aryl)-(C₁₋₄ alkyl) esters of the solid forms of the invention.

[0117] All isotopic forms of the solid forms of the invention are also included, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the "natural isotopic form") or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an "unnatural variant isotopic form"). It is understood that an atom may naturally exist as a mixture of mass numbers. The term "unnatural variant isotopic form" also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an "uncommon isotope") has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or > 99% by number of the atoms of that atomic number (the latter embodiment referred to as an "isotopically enriched variant form"). The term "unnatural variant isotopic form" also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

[0118] An unnatural variant isotopic form of a compound may thus contain one or more artificial or uncommon isotopes such as deuterium (²H or D), carbon-11 (¹¹C), carbon-13 (¹³C), carbon-14 (¹⁴C), nitrogen-13 (¹³N), nitrogen-15 (¹⁵N), oxygen-15 (¹⁵O), oxygen-17 (¹⁷O), oxygen-18 (¹⁸O), phosphorus-32 (³²P), sulphur-35 (³⁵S), chlorine-36 (³⁶Cl), chlorine-37 (³⁷Cl), fluorine-18 (¹⁸F), iodine-123 (¹²³I), iodine-125 (¹²⁵I) in one or more atoms or may contain an increased proportion of said isotopes as compared with the proportion that predominates in nature in one or more atoms.

[0119] Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ³H, and carbon-14, i.e. ¹⁴C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Unnatural variant isotopic forms which incorporate deuterium i.e. ²H or D may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced

dosage requirements, and hence may be preferred in some circumstances. Further, unnatural variant isotopic forms may be prepared which incorporate positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0120] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

[0121] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e. as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[0122] 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[0123] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0124] The compound comprised in a solid form of the invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

[0125] Unless indicated otherwise, the description or naming of a compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

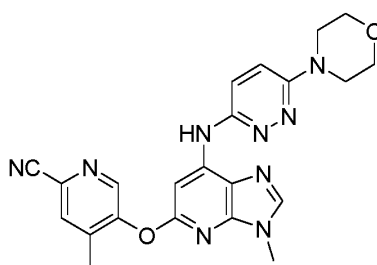
[0126] It will be appreciated that solid forms of the invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION

[0127] Herein are provided, inter alia, solid forms of the invention, useful in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of

IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23. In particular, the pharmaceutical composition or solid form of the invention comprising Compound 1 inhibit JAK, a family of tyrosine kinases, and more particularly TYK2. Herein are also provided inter alia, pharmaceutical compositions comprising a solid form of the invention and methods for the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23 by administering a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention comprising Compound 1.

[0128] Accordingly, herein are provided inter alia, pharmaceutical compositions and solid forms of the invention comprising Compound 1:



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[0129] In one embodiment, a solid form of the invention is a cocrystal. In another embodiment, a pharmaceutical composition of the invention comprises Compound 1 and fumaric acid. In a particular embodiment, a solid form of the invention is a fumarate cocrystal. In a more particular embodiment, a solid form of the invention is a fumarate cocrystal where Compound 1 and fumaric acid are present in a 1:1 ratio.

[0130] In one embodiment, Compound 1 is present in a natural isotopic form.

[0131] In one embodiment, Compound 1 is in an unnatural variant isotopic form. In a specific embodiment, the unnatural variant isotopic form is a form in which deuterium (*i.e.* ^2H or D) is incorporated where hydrogen is specified in the chemical structure in one or more atoms of a Compound 1. In one embodiment, the atoms of Compound 1 are in an isotopic form which is not radioactive. In one embodiment, one or more atoms of Compound 1 are in an isotopic form which is radioactive. Suitably radioactive isotopes are stable isotopes. Suitably the unnatural variant isotopic form is a pharmaceutically acceptable form.

[0132] In one embodiment, Compound 1 is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, Compound 1 is provided whereby two or more atoms exist in an unnatural variant isotopic form.

[0133] Unnatural isotopic variant forms can generally be prepared by conventional techniques known to those skilled in the art or by processes described herein e.g. processes analogous to those described in the

accompanying Examples for preparing natural isotopic forms. Thus, unnatural isotopic variant forms could be prepared by using appropriate isotopically variant (or labelled) reagents in place of the normal reagents employed in the Examples.

[0134] In one embodiment Compound 1 is not an isotopic variant.

HCl salt form of Compound 1

[0135] One solid form is the HCl salt form of Compound 1 and exhibits peaks on a XRPD spectrum. A particular form of this solid form is the HCl salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 4.8, 6.0, 7.6, 8.7, 9.2, 9.7, 11.7, 11.9, 12.3, 14.2, 14.5, 15.0, 16.4, 18.0, 19.2, 21.4, 22.5, 23.6, 24.1 or 25.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 1C. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 4.8, 6.0, 7.6, 8.7, 9.2, 9.7, 11.7, 11.9, 12.3, 14.2, 14.5, 15.0, 16.4, 18.0, 19.2, 21.4, 22.5, 23.6, 24.1 or 25.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 1C.

[0136] A particular form of this solid form is the HCl salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15 or more peaks at the following positions: 4.8, 6.0, 7.6, 8.7, 9.2, 9.7, 11.7, 11.9, 12.3, 14.2, 14.5, 15.0, 16.4, 18.0, 19.2, 21.4, 22.5, 23.6, 24.1 or 25.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15 or more peaks at the following positions: 4.8, 6.0, 7.6, 8.7, 9.2, 9.7, 11.7, 11.9, 12.3, 14.2, 14.5, 15.0, 16.4, 18.0, 19.2, 21.4, 22.5, 23.6, 24.1 or 25.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 1C.

[0137] One solid form is the HCl salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 4.8, 6.0, 7.6, 9.7 and 11.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0138] One solid form is the HCl salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 4.8, 6.0, 7.6, 9.7 and 11.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0139] One solid form is the HCl salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 4.8, 6.0, 7.6, 8.7, 9.2, 9.7, 11.7, 11.9, 12.3, 14.2, 14.5, 15.0, 16.4, 18.0, 19.2, 21.4, 22.5, 23.6, 24.1 and 25.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 4.8, 6.0, 7.6, 8.7, 9.2, 9.7, 11.7, 11.9, 12.3, 14.2, 14.5, 15.0, 16.4, 18.0, 19.2, 21.4, 22.5, 23.6, 24.1 and 25.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 1C.

[0140] One solid form is the HCl salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 1C.

[0141] One solid form is the HCl salt form of Compound 1 and may be characterized by an ^1H NMR spectrum substantially as depicted in FIGURE 1A.

[0142] One solid form is the HCl salt form of Compound 1 and may be characterized by a DSC curve substantially in accordance with FIGURE 1D.

[0143] One solid form is the HCl salt form of Compound 1 and may be characterized by a TGA curve substantially in accordance with FIGURE 1E.

[0144] One solid form is the HCl salt form of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 1F.

Mesylate salt of Compound 1

[0145] One solid form is the mesylate salt form of Compound 1 and exhibits peaks on a XRPD spectrum. A particular form of this solid form is the mesylate salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 8.5, 9.3, 9.8, 11.3, 12.1, 15.1, 15.2, 16.7, 17.0, 17.2, 17.5, 17.7, 18.7, 20.4, 22.1, 22.5, 22.6, 25.3, 25.6 or 26.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 2C. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 8.5, 9.3, 9.8, 11.3, 12.1, 15.1, 15.2, 16.7, 17.0, 17.2, 17.5, 17.7, 18.7, 20.4, 22.1, 22.5, 22.6, 25.3, 25.6 or 26.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 2C.

[0146] A particular form of this solid form is the mesylate salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 8.5, 9.3, 9.8, 11.3, 12.1, 15.1, 15.2, 16.7, 17.0, 17.2, 17.5, 17.7, 18.7, 20.4, 22.1, 22.5, 22.6, 25.3, 25.6 or 26.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 8.5, 9.3, 9.8, 11.3, 12.1, 15.1, 15.2, 16.7, 17.0, 17.2, 17.5, 17.7, 18.7, 20.4, 22.1, 22.5, 22.6, 25.3, 25.6 or 26.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 2C.

[0147] One solid form is the mesylate salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 8.5, 12.1, 15.1, 15.2, 16.7 and 25.3 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0148] One solid form is mesylate salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 8.5, 12.1, 15.1, 15.2, 16.7 and 25.3 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0149] A particular form of this solid form is the mesylate salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 8.5, 9.3, 9.8, 11.3, 12.1, 15.1, 15.2, 16.7, 17.0, 17.2, 17.5, 17.7, 18.7, 20.4, 22.1, 22.5, 22.6, 25.3, 25.6 and 26.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 8.5, 9.3, 9.8, 11.3, 12.1, 15.1,

15.2, 16.7, 17.0, 17.2, 17.5, 17.7, 18.7, 20.4, 22.1, 22.5, 22.6, 25.3, 25.6 and 26.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 2C.

[0150] One solid form is the mesylate salt form of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 2C.

[0151] One solid form is the mesylate salt form of Compound 1 and may be characterized by an ^1H NMR spectrum substantially as depicted in FIGURE 2A.

[0152] One solid form is the mesylate salt form of Compound 1 and may be characterized by a DSC curve substantially in accordance with FIGURE 2D.

[0153] One solid form is the mesylate salt form of Compound 1 and may be characterized by a TGA curve substantially in accordance with FIGURE 2E.

[0154] One solid form is the mesylate salt form of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 2F.

Maleate cocrystal form of Compound 1 or cocrystal form I

[0155] One solid form is the maleate cocrystal form of Compound 1.

[0156] A particular form of this solid form may be characterized by a ^1H -NMR spectrum substantially in accordance with FIGURE 3A.

[0157] A particular form of this solid form may be characterized by a DSC curve substantially in accordance with FIGURE 3C.

Phosphate cocrystal form A of Compound 1 or cocrystal form IIA

[0158] One solid form is the phosphate cocrystal form A of Compound 1. A particular form of this solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 4.2, 4.6, 6.4, 7.7, 8.4, 10.2, 12.5, 12.8, 13.9, 15.6, 16.8, 17.5, 18.6, 19.3, 20.4, 22.1, 22.9, 24.1, 24.8 or 25.1 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 4E. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 4.2, 4.6, 6.4, 7.7, 8.4, 10.2, 12.5, 12.8, 13.9, 15.6, 16.8, 17.5, 18.6, 19.3, 20.4, 22.1, 22.9, 24.1, 24.8 or 25.1 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 4E.

[0159] A particular form of this solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 4.2, 4.6, 6.4, 7.7, 8.4, 10.2, 12.5, 12.8, 13.9, 15.6, 16.8, 17.5, 18.6, 19.3, 20.4, 22.1, 22.9, 24.1, 24.8 or 25.1 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15 or more peaks at the following positions: 4.2, 4.6, 6.4, 7.7, 8.4, 10.2, 12.5, 12.8, 13.9, 15.6, 16.8, 17.5, 18.6, 19.3, 20.4, 22.1, 22.9, 24.1, 24.8 or 25.1 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 4E.

[0160] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 4.2, 7.7, 8.4, 12.8, 17.5 and 18.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0161] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 4.2, 7.7, 8.4, 12.8, 17.5 and 18.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0162] A particular form of this solid form is phosphate cocrystal form A of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 4.2, 4.6, 6.4, 7.7, 8.4, 10.2, 12.5, 12.8, 13.9, 15.6, 16.8, 17.5, 18.6, 19.3, 20.4, 22.1, 22.9, 24.1, 24.8 and 25.1 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 4.2, 4.6, 6.4, 7.7, 8.4, 10.2, 12.5, 12.8, 13.9, 15.6, 16.8, 17.5, 18.6, 19.3, 20.4, 22.1, 22.9, 24.1, 24.8 and 25.1 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 4E.

[0163] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 4E.

[0164] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by a ^1H -NMR spectrum substantially in accordance with FIGURE 4A.

[0165] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by a DSC curve substantially in accordance with FIGURE 4B.

[0166] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by a TGA curve substantially in accordance with FIGURE 4C.

[0167] One solid form is the phosphate cocrystal form A of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 4D.

Phosphate cocrystal form B of Compound 1 or cocrystal form IIB

[0168] One solid form is the phosphate cocrystal form B of Compound 1.

[0169] One solid form is the phosphate cocrystal form B of Compound 1 and may be characterized by a ^1H -NMR spectrum substantially in accordance with FIGURE 5A.

[0170] One solid form is the phosphate cocrystal form B of Compound 1 and may be characterized by a DSC curve substantially in accordance with FIGURE 5B.

[0171] One solid form is the phosphate cocrystal form B of Compound 1 and may be characterized by a TGA curve substantially in accordance with FIGURE 5C.

Fumarate cocrystal form of Compound 1 or cocrystal form III

[0172] In one embodiment, a solid form of the invention is fumarate cocrystal of Compound 1. In a particular embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta. In a more particular embodiment, a solid form of the invention

may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C. In a most particular embodiment, a solid form of the invention may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

[0173] In a particular embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta. In a most particular embodiment, a solid form of the invention may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

[0174] In one embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0175] In another embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta. In a particular embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 and 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta. In a most particular embodiment, a solid form of the invention may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 and 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

[0176] In one embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

[0177] In one embodiment, a solid form of the invention is fumarate cocrystal form of Compound 1 and may be characterized by a ¹H-NMR spectrum substantially in accordance with FIGURE 6A.

[0178] In one embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by a DSC curve substantially in accordance with FIGURE 6D.

[0179] In one embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by a TGA curve substantially in accordance with FIGURE 6E.

[0180] In one embodiment, a solid form of the invention is fumarate cocrystal of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 6F.

L-tartrate cocrystal form of Compound 1 or cocrystal form IV

[0181] One solid form is the L-tartrate cocrystal form of Compound 1. A particular form of this solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 3.7, 7.5, 7.8, 8.2, 10.2, 10.6, 13.2, 14.2, 15.0, 15.3, 15.6, 16.6, 17.4, 17.7, 19.0, 19.1, 20.4, 20.8, 22.7, 23.4, 23.7, 24.4, 26.2, 27.2, 29.3 or 32.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 7C. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 3.7, 7.5, 7.8, 8.2, 10.2, 10.6, 13.2, 14.2, 15.0, 15.3, 15.6, 16.6, 17.4, 17.7, 19.0, 19.1, 20.4, 20.8, 22.7, 23.4, 23.7, 24.4, 26.2, 27.2, 29.3 or 32.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 7C.

[0182] A particular form of this solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 3.7, 7.5, 7.8, 8.2, 10.2, 10.6, 13.2, 14.2, 15.0, 15.3, 15.6, 16.6, 17.4, 17.7, 19.0, 19.1, 20.4, 20.8, 22.7, 23.4, 23.7, 24.4, 26.2, 27.2, 29.3 or 32.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15 or more peaks at the following positions: 3.7, 7.5, 7.8, 8.2, 10.2, 10.6, 13.2, 14.2, 15.0, 15.3, 15.6, 16.6, 17.4, 17.7, 19.0, 19.1, 20.4, 20.8, 22.7, 23.4, 23.7, 24.4, 26.2, 27.2, 29.3 or 32.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 7C.

[0183] One solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 3.7, 7.5, 7.8, 13.2, 15.5 and 16.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0184] One solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 3.7, 7.5, 7.8, 13.2, 15.5 and 16.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0185] A particular form of this solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 3.7, 7.5, 7.8, 8.2, 10.2, 10.6, 13.2, 14.2, 15.0, 15.3, 15.6, 16.6, 17.4, 17.7, 19.0, 19.1, 20.4, 20.8, 22.7, 23.4, 23.7, 24.4, 26.2, 27.2, 29.3 and 32.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 3.7, 7.5, 7.8, 8.2, 10.2, 10.6, 13.2, 14.2, 15.0, 15.3, 15.6, 16.6, 17.4, 17.7, 19.0, 19.1, 20.4, 20.8, 22.7, 23.4, 23.7, 24.4, 26.2, 27.2, 29.3 and 32.6 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 7C.

[0186] One solid form is the L-tartrate cocrystal of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 7C.

[0187] One solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by a ¹H-NMR spectrum substantially in accordance with FIGURE 7D.

[0188] One solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by a DSC-TGA curve substantially in accordance with FIGURE 7A.

[0189] One solid form is the L-tartrate cocrystal form of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 7B.

L-malate cocrystal form of Compound 1 or cocrystal form V

[0190] One solid form is the L-malate cocrystal form of Compound 1. A particular form of this solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 6.3, 9.0, 10.6, 11.1, 12.6, 12.9, 13.9, 14.0, 15.0, 15.9, 16.2, 16.6, 16.8, 17.0, 17.9, 18.3, 18.7, 19.4, 20.4, 20.7, 21.1, 21.2, 21.6, 22.2, 22.3, 22.6, 23.3, 24.0, 24.8, 25.4, 25.9, 26.4, 26.6, 27.3, 28.0, 28.3, 29.7, 30.2, 30.8, 31.2, 31.6, 32.1, 33.8, 34.5, 35.1, 37.1, 38.4, 39.9, 41.5 or 43.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 8C. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 6.3, 9.0, 10.6, 11.1, 12.6, 12.9, 13.9, 14.0, 15.0, 15.9, 16.2, 16.6, 16.8, 17.0, 17.9, 18.3, 18.7, 19.4, 20.4, 20.7, 21.1, 21.2, 21.6, 22.2, 22.3, 22.6, 23.3, 24.0, 24.8, 25.4, 25.9, 26.4, 26.6, 27.3, 28.0, 28.3, 29.7, 30.2, 30.8, 31.2, 31.6, 32.1, 33.8, 34.5, 35.1, 37.1, 38.4, 39.9, 41.5 or 43.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 8C.

[0191] A particular form of this solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15, 20, 25 or more peaks at the following positions: 6.3, 9.0, 10.6, 11.1, 12.6, 12.9, 13.9, 14.0, 15.0, 15.9, 16.2, 16.6, 16.8, 17.0, 17.9, 18.3, 18.7, 19.4, 20.4, 20.7, 21.1, 21.2, 21.6, 22.2, 22.3, 22.6, 23.3, 24.0, 24.8, 25.4, 25.9, 26.4, 26.6, 27.3, 28.0, 28.3, 29.7, 30.2, 30.8, 31.2, 31.6, 32.1, 33.8, 34.5, 35.1, 37.1, 38.4, 39.9, 41.5 or 43.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15 or more peaks at the following positions: 6.3, 9.0, 10.6, 11.1, 12.6, 12.9, 13.9, 14.0, 15.0, 15.9, 16.2, 16.6, 16.8, 17.0, 17.9, 18.3, 18.7, 19.4, 20.4, 20.7, 21.1, 21.2, 21.6, 22.2, 22.3, 22.6, 23.3, 24.0, 24.8, 25.4, 25.9, 26.4, 26.6, 27.3, 28.0, 28.3, 29.7, 30.2, 30.8, 31.2, 31.6, 32.1, 33.8, 34.5, 35.1, 37.1, 38.4, 39.9, 41.5 or 43.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 8C.

[0192] One solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 6.3, 10.6, 15.0, 16.2 and 17.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0193] A particular form of this solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 6.3, 10.6, 15.0, 16.2 and 17.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0194] A particular form of this solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 6.3, 9.0, 10.6, 11.1, 12.6, 12.9, 13.9, 14.0, 15.0, 15.9, 16.2, 16.6, 16.8, 17.0, 17.9, 18.3, 18.7, 19.4, 20.4, 20.7, 21.1, 21.2, 21.6, 22.2, 22.3, 22.6, 23.3, 24.0, 24.8, 25.4, 25.9, 26.4, 26.6, 27.3, 28.0, 28.3, 29.7, 30.2, 30.8, 31.2, 31.6, 32.1, 33.8, 34.5, 35.1, 37.1, 38.4, 39.9, 41.5 and 43.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 6.3, 9.0, 10.6, 11.1, 12.6, 12.9, 13.9, 14.0, 15.0, 15.9, 16.2, 16.6, 16.8, 17.0, 17.9, 18.3, 18.7, 19.4, 20.4, 20.7, 21.1, 21.2, 21.6, 22.2, 22.3, 22.6, 23.3, 24.0, 24.8, 25.4, 25.9, 26.4, 26.6, 27.3, 28.0, 28.3, 29.7, 30.2, 30.8, 31.2, 31.6, 32.1, 33.8, 34.5, 35.1, 37.1, 38.4, 39.9, 41.5 and 43.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 8C.

[0195] One solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 8C.

[0196] One solid form is the L-malate cocrystal form of Compound 1 and may be characterized by an ^1H NMR spectrum substantially as depicted in FIGURE 8D.

[0197] One solid form is the L-malate cocrystal form of Compound 1 and may be characterized by a DSC-TGA curve substantially in accordance with FIGURE 8A.

[0198] One solid form is the L-malate cocrystal form of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 8B.

Saccharinate cocrystal form of Compound 1 or cocrystal form VI

[0199] One solid form is the saccharinate cocrystal form of Compound 1. A particular form of this solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 5.6, 6.5, 9.0, 9.8, 11.1, 11.3, 12.4, 13.0, 13.9, 14.7, 15.0, 15.6, 15.8, 16.4, 16.7, 17.0, 17.9, 18.5, 19.2, 19.4, 19.7, 20.0, 20.5, 20.8, 21.3, 21.6, 22.4, 23.9, 24.8, 25.5, 26.1, 27.0, 27.4, 27.9, 29.5, 30.3, 31.3, 32.0, 32.7, 33.6, 36.3, 36.9, 38.2 or 42.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 9C. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 5.6, 6.5, 9.0, 9.8, 11.1, 11.3, 12.4, 13.0, 13.9, 14.7, 15.0, 15.6, 15.8, 16.4, 16.7, 17.0, 17.9, 18.5, 19.2, 19.4, 19.7, 20.0, 20.5, 20.8, 21.3, 21.6, 22.4, 23.9, 24.8, 25.5, 26.1, 27.0, 27.4, 27.9, 29.5, 30.3, 31.3, 32.0, 32.7, 33.6, 36.3, 36.9, 38.2 or 42.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 9C.

[0200] A particular form of this solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15 or more peaks at the following positions: 5.6, 6.5, 9.0, 9.8, 11.1, 11.3, 12.4, 13.0, 13.9, 14.7, 15.0, 15.6, 15.8, 16.4, 16.7, 17.0, 17.9, 18.5, 19.2, 19.4, 19.7, 20.0, 20.5, 20.8, 21.3, 21.6, 22.4, 23.9, 24.8, 25.5, 26.1, 27.0, 27.4, 27.9, 29.5, 30.3, 31.3, 32.0, 32.7, 33.6, 36.3, 36.9, 38.2 or 42.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having at least 1, 5, 10, 15

or more peaks at the following positions: 5.6, 6.5, 9.0, 9.8, 11.1, 11.3, 12.4, 13.0, 13.9, 14.7, 15.0, 15.6, 15.8, 16.4, 16.7, 17.0, 17.9, 18.5, 19.2, 19.4, 19.7, 20.0, 20.5, 20.8, 21.3, 21.6, 22.4, 23.9, 24.8, 25.5, 26.1, 27.0, 27.4, 27.9, 29.5, 30.3, 31.3, 32.0, 32.7, 33.6, 36.3, 36.9, 38.2 or 42.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 9C.

[0201] One solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 5.6, 6.5, 11.3, 13.0, and 15.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0202] A particular form of this solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern comprising peaks at 5.6, 6.5, 11.3, 13.0, and 15.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0203] A particular form of this solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 5.6, 6.5, 9.0, 9.8, 11.1, 11.3, 12.4, 13.0, 13.9, 14.7, 15.0, 15.6, 15.8, 16.4, 16.7, 17.0, 17.9, 18.5, 19.2, 19.4, 19.7, 20.0, 20.5, 20.8, 21.3, 21.6, 22.4, 23.9, 24.8, 25.5, 26.1, 27.0, 27.4, 27.9, 29.5, 30.3, 31.3, 32.0, 32.7, 33.6, 36.3, 36.9, 38.2 and 42.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta. A particular form of this solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 5.6, 6.5, 9.0, 9.8, 11.1, 11.3, 12.4, 13.0, 13.9, 14.7, 15.0, 15.6, 15.8, 16.4, 16.7, 17.0, 17.9, 18.5, 19.2, 19.4, 19.7, 20.0, 20.5, 20.8, 21.3, 21.6, 22.4, 23.9, 24.8, 25.5, 26.1, 27.0, 27.4, 27.9, 29.5, 30.3, 31.3, 32.0, 32.7, 33.6, 36.3, 36.9, 38.2 and 42.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 9C.

[0204] One solid form is the saccharinate form of Compound 1 and may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 9C.

[0205] One solid form is the saccharinate form of Compound 1 and may be characterized by an ^1H NMR spectrum substantially as depicted in FIGURE 9D.

[0206] One solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by a DSC-TGA curve substantially in accordance with FIGURE 9A.

[0207] One solid form is the saccharinate cocrystal form of Compound 1 and may be characterized by a DVS curve substantially in accordance with FIGURE 9B.

PHARMACEUTICAL COMPOSITIONS

[0208] When employed as a pharmaceutical, the solid forms of the invention comprising Compound 1 are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise solid forms comprising Compound 1. Generally, solid forms comprising Compound 1 are administered in a pharmaceutically effective amount. The amount of compound 1 actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0209] The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, solid forms comprising Compound 1 are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[0210] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term 'unit dosage forms' refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, compound 1 is usually a minor component (from about 0.1 to about 70% by weight or preferably from about 1 to about 60% by weight, and even more preferably from about 1 to about 40%) with the remainder being various vehicles, excipients or carriers and processing aids helpful for forming the desired dosing form.

[0211] Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint or orange flavoring.

[0212] The above-described components for orally administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[0213] The pharmaceutical composition or solid form of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[0214] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

[0215] Solid forms comprising Compound 1 may be admixed as a dry powder with a dry gelatin binder, such that an approximate 1:2 weight ratio results. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 270 mg tablets (90 mg of compound 1 per tablet) in a tablet press.

Formulation 2 - Capsules

[0216] Solid forms comprising Compound 1 may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of compound 1 per capsule).

Formulation 3 - Liquid

[0217] Solid forms comprising Compound 1 (125 mg), may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color may be diluted with water and added with stirring. Sufficient water may then be added with stirring. Further sufficient water may be then added to produce a total volume of 5 mL.

Formulation 4 - Tablets

[0218] Solid forms comprising Compound 1 may be admixed as a dry powder with a dry gelatin binder, such that an approximate 1:2 weight ratio results. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 450 mg tablets (150 mg of compound 1) in a tablet press.

PHARMACEUTICAL UNIT DOSAGE COMPOSITIONS

[0219] The present invention further provides pharmaceutical unit dosage compositions.

[0220] In one embodiment, the present invention provides a pharmaceutical unit dosage composition comprising 70 mg to 300 mg of Compound 1.

[0221] In a particular embodiment, the unit dosage is in a form selected from a liquid, a tablet, a capsule, or a gelcap. In a most particular embodiment, the unit dosage is in the form of a tablet. In another most particular embodiment, the unit dosage is in the form of a capsule.

COMPOUNDS FOR USE IN AND/OR METHODS OF TREATMENT

[0222] In one embodiment, herein are provided inter alia, solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention, for use in medicine. In a particular embodiment, herein are provided inter alia, solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention, for use in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23.

[0223] In another embodiment, herein are provided inter alia, solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases,

metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23.

[0224] In additional method of treatment aspects, herein are provided inter alia methods of prophylaxis and/or treatment of a mammal afflicted with allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, multiple sclerosis, trisomy 21, psoriatic arthritis, ulcerative colitis and/or Crohn’s disease, which methods comprise the administration of an effective amount of Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition.

[0225] In one embodiment, herein are provided inter alia solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is an allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23 treatment agent.

[0226] In one embodiment, the present invention provides solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention, for use in the prophylaxis and/or treatment of allergic diseases. In a particular embodiment, the allergic disease is asthma.

[0227] In another embodiment, the present invention provides solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of allergic diseases. In a particular embodiment, the allergic disease is asthma.

[0228] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with allergic diseases, which methods comprise the administration of a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the allergic disease is asthma.

[0229] In one embodiment, the present invention provides solid forms of the invention or pharmaceutical compositions comprising a solid form of the invention, and another therapeutic agent. In a particular

embodiment, the other therapeutic agent is an allergic diseases treatment agent. In a particular embodiment, the allergic disease is asthma.

[0230] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in the prophylaxis and/or treatment of inflammatory diseases. In a particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and inflammatory bowel disease. In a more particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease.

[0231] In another embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of inflammatory disease. In a particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and inflammatory bowel disease. In a more particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease.

[0232] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with inflammatory diseases, which methods comprise the administration of an effective amount of a Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and inflammatory bowel disease. In a more particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease.

[0233] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is inflammatory diseases treatment agent. In a particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and inflammatory bowel disease. In a more particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease.

[0234] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in the prophylaxis and/or treatment of metabolic diseases. In a particular embodiment, the metabolic disease is type II diabetes and/or obesity.

[0235] In another embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of metabolic diseases. In a particular embodiment, the metabolic disease is type II diabetes and/or obesity.

[0236] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with metabolic diseases, which methods comprise the administration of an effective amount of Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the metabolic disease is type II diabetes and/or obesity.

[0237] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is a metabolic diseases treatment agent. In a particular embodiment, the metabolic disease is type II diabetes and/or obesity.

[0238] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in the prophylaxis and/or treatment of autoimmune diseases. In a particular embodiment, the autoimmune disease is COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus, interferonopathy, and inflammatory bowel disease.

[0239] In another embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of autoimmune diseases. In a particular embodiment, the autoimmune disease is COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus, interferonopathy, and inflammatory bowel disease.

[0240] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with autoimmune diseases, which methods comprise the administration of an effective amount of a Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the autoimmune disease is COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus, interferonopathy, and inflammatory bowel disease.

[0241] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is an autoimmune diseases treatment agent. In a particular embodiment, the autoimmune disease is COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus, interferonopathy, and inflammatory bowel disease.

[0242] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition

comprising a solid form of the invention, for use in the prophylaxis and/or treatment of autoinflammatory diseases. In a particular embodiment, the autoimmune disease is Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçets, Systemic-Onset Juvenile Idiopathic Arthritis (SJIA) or Still's disease.

[0243] In another embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of autoinflammatory diseases. In a particular embodiment, the autoimmune disease is Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçets, Systemic-Onset Juvenile Idiopathic Arthritis (SJIA) or Still's disease.

[0244] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with autoinflammatory diseases, which methods comprise the administration of an effective amount of a Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the autoimmune disease is Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçets, Systemic-Onset Juvenile Idiopathic Arthritis (SJIA) or Still's disease.

[0245] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is an autoinflammatory diseases treatment agent. In a particular embodiment, the autoimmune disease is Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçets, Systemic-Onset Juvenile Idiopathic Arthritis (SJIA) or Still's disease.

[0246] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in the prophylaxis and/or treatment of proliferative diseases. In a particular embodiment, the proliferative disease is cancer, leukemia, multiple myeloma and psoriasis.

[0247] In another embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of proliferative diseases. In a particular embodiment, the proliferative disease is cancer, leukemia, multiple myeloma and psoriasis.

[0248] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with proliferative diseases, which methods comprise the administration of an effective amount of Compound 1 in a solid form of the invention or a pharmaceutical composition

comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the proliferative disease is cancer, leukemia, multiple myeloma and psoriasis.

[0249] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is a proliferative diseases treatment agent. In a particular embodiment, the proliferative disease is cancer, leukemia, multiple myeloma and psoriasis.

[0250] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in the prophylaxis and/or treatment of diseases involving impairment of cartilage turnover. In a particular embodiment, the disease involving impairment of cartilage turnover is ankylosing spondylitis.

[0251] In another embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of diseases involving impairment of cartilage turnover. In a particular embodiment, the disease involving impairment of cartilage turnover is ankylosing spondylitis.

[0252] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with a disease involving impairment of cartilage turnover, which methods comprise the administration of an effective amount of Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the disease involving impairment of cartilage turnover is ankylosing spondylitis.

[0253] In one embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in medicine. In a particular embodiment, the present invention provides a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention, for use in the prophylaxis and/or treatment of diseases associated with hypersecretion of IFN α , IL-12 and/or IL-23. In a particular embodiment, the disease associated with hypersecretion of IFN α , IL-12 and/or IL-23 is a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, multiple sclerosis, trisomy 21, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.

[0254] In another embodiment, the present invention provides compounds a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of diseases associated with hypersecretion of IFN α , IL-12 and/or IL-23. In a particular embodiment, the disease associated with hypersecretion of IFN α , IL-12 and/or IL-23 is a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus,

lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, multiple sclerosis, trisomy 21, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.

[0255] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with diseases associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, which methods comprise the administration of an effective amount of Compound 1 in a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention for the treatment or prophylaxis of said condition. In a particular embodiment, the disease associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23 is a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, multiple sclerosis, trisomy 21, psoriatic arthritis, ulcerative colitis and/or Crohn's disease.

[0256] Injection dose levels can in some embodiments range from about 0.1 mg/kg/h to at least 10 mg/kg/h, all for from about 1 to about 120 h and especially 24 to 96 h. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 1 g/day for a 40 to 80 kg human patient.

[0257] For the prophylaxis and/or treatment of long-term conditions, such as degenerative conditions, the regimen for treatment can in some embodiments stretch over many months or years. In such embodiments, oral dosing may be preferred for patient convenience and tolerance. With oral dosing, one to four (1-4) regular doses daily, such as one to three (1-3) regular doses daily, typically one to two (1-2) regular doses daily, and most typically one (1) regular dose daily are representative regimens. Alternatively for long lasting effect drugs, with oral dosing, once every other week, once weekly, and once a day are representative regimens. In particular, dosage regimen can be every 1-14 days, more particularly 1-10 days, even more particularly 1-7 days, and most particularly 1-3 days.

[0258] Using these dosing patterns, in some embodiments each dose can provide from 70 to 300 mg of a solid form of the invention, with particular doses each providing from 75 to 300 mg, more particularly from 90 to 300 mg, further particularly from 90 to 225 mg, even more particularly from 90 to 225 mg, and most particularly from 90 to 150 mg.

[0259] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[0260] When used to prevent the onset of a condition, a solid form of the invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0261] A solid form of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other solid forms of the invention that demonstrate the same or a similar therapeutic activity and that are determined to be safe and efficacious for such

combined administration. In a specific embodiment, co-administration of two (or more) agents allows for significantly lower doses of each to be used, thereby reducing the side effects seen.

[0262] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is administered as a medicament. In a specific embodiment, said pharmaceutical composition additionally comprises a further active ingredient.

[0263] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of a disease involving inflammation, particular agents include, but are not limited to, immunoregulatory agents e.g. azathioprine, corticosteroids (e.g. prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, mycophenolate, mofetil, muromonab-CD3 (OKT3, e.g. Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

[0264] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of arthritis (e.g. rheumatoid arthritis), particular agents include but are not limited to analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, synthetic DMARDS (for example but without limitation methotrexate, leflunomide, sulfasalazine, auranofin, sodium aurothiomalate, penicillamine, chloroquine, hydroxychloroquine, azathioprine, tofacitinib, baricitinib, fostamatinib, and cyclosporin), and biological DMARDS (for example but without limitation infliximab, etanercept, adalimumab, rituximab, and abatacept).

[0265] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of proliferative disorders, particular agents include but are not limited to: methotrexate, leukovorin, adriamycin, prednisone, bleomycin, cyclophosphamide, 5-fluorouracil, paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, tamoxifen, toremifene, megestrol acetate, anastrozole, goserelin, anti-HER2 monoclonal antibody (e.g. Herceptin™), capecitabine, raloxifene hydrochloride, EGFR inhibitors (e.g. Iressa®, Tarceva™, Erbitux™), VEGF inhibitors (e.g. Avastin™), proteasome inhibitors (e.g. Velcade™), Glivec® and hsp90 inhibitors (e.g. 17-AAG). Additionally, the pharmaceutical composition or solid form of the invention may be administered in combination with other therapies including, but not limited to, radiotherapy or surgery. In a specific embodiment the proliferative disorder is selected from cancer, myeloproliferative disease or leukemia.

[0266] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of autoimmune diseases, particular agents include but are not limited to: glucocorticoids, cytostatic agents (e.g. purine analogs), alkylating agents (e.g. nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds, and others), antimetabolites (e.g. methotrexate, azathioprine and mercaptopurine), cytotoxic antibiotics (e.g. dactinomycin anthracyclines, mitomycin C, bleomycin, and mithramycin), antibodies (e.g. anti-CD20, anti-CD25 or anti-CD3 (OTK3) monoclonal antibodies, Atgam® and Thymoglobuline®), cyclosporin, tacrolimus, rapamycin (sirolimus), interferons (e.g. IFN-β),

TNF binding proteins (e.g. infliximab, etanercept, or adalimumab), mycophenolate, fingolimod and myriocin.

[0267] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of asthma and/or rhinitis and/or COPD, particular agents include but are not limited to: beta2-adrenoceptor agonists (e.g. salbutamol, levalbuterol, terbutaline and bitolterol), epinephrine (inhaled or tablets), anticholinergics (e.g. ipratropium bromide), glucocorticoids (oral or inhaled). Long-acting β 2-agonists (e.g. salmeterol, formoterol, bambuterol, and sustained-release oral albuterol), combinations of inhaled steroids and long-acting bronchodilators (e.g. fluticasone/salmeterol, budesonide/formoterol), leukotriene antagonists and synthesis inhibitors (e.g. montelukast, zafirlukast and zileuton), inhibitors of mediator release (e.g. cromoglycate and ketotifen), biological regulators of IgE response (e.g. omalizumab), antihistamines (e.g. cetirizine, cinnarizine, fexofenadine) and vasoconstrictors (e.g. oxymethazoline, xylomethazoline, nafazoline and tramazoline).

[0268] Additionally, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention may be administered in combination with emergency therapies for asthma and/or COPD, such therapies include oxygen or heliox administration, nebulized salbutamol or terbutaline optionally combined with an anticholinergic (e.g. ipratropium), systemic steroids (oral or intravenous, e.g. prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone), intravenous salbutamol, non-specific beta-agonists, injected or inhaled (e.g. epinephrine, isoetharine, isoproterenol, metaproterenol), anticholinergics (IV or nebulized, e.g. glycopyrrolate, atropine, ipratropium), methylxanthines (theophylline, aminophylline, bamiphylline), inhalation anesthetics that have a bronchodilatory effect (e.g. isoflurane, halothane, enflurane), ketamine and intravenous magnesium sulfate.

[0269] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of inflammatory bowel disease (IBD), particular agents include but are not limited to: glucocorticoids (e.g. prednisone, budesonide) synthetic disease modifying, immunomodulatory agents (e.g. methotrexate, leflunomide, sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and cyclosporin) and biological disease modifying, immunomodulatory agents (infliximab, adalimumab, rituximab, and abatacept).

[0270] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of systemic lupus erythematosus (SLE), particular agents include but are not limited to: human monoclonal antibodies (belimumab (Benlysta)), Disease-modifying antirheumatic drugs (DMARDs) such as antimalarials (e.g. plaquenil, hydroxychloroquine), immunosuppressants (e.g. methotrexate and azathioprine), cyclophosphamide and mycophenolic acid, immunosuppressive drugs and analgesics, such as nonsteroidal anti-inflammatory drugs, opiates (e.g. dextropropoxyphene and co-codamol), opioids (e.g.

hydrocodone, oxycodone, MS Contin, or methadone) and the fentanyl duragesic transdermal patch, and S1P receptor modulators (e.g. fingolimod, siponimod, ozanimod, cenerimod and ponesimod).

[0271] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of psoriasis, particular agents include but are not limited to: topical treatments such as bath solutions, moisturizers, medicated creams and ointments containing coal tar, dithranol (anthralin), corticosteroids like desoximetasone (Topicort™), fluocinonide, vitamin D3 analogues (for example, calcipotriol), argan oil and retinoids (etretinate, acitretin, tazarotene), systemic treatments such as methotrexate, cyclosporine, retinoids, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, fumaric acid esters or biologics such as Amevive™, Enbrel™, Humira™, Remicade™, Raptiva™ and ustekinumab (an IL-12 and IL-23 blocker). Additionally, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention may be administered in combination with other therapies including, but not limited to phototherapy, or photochemotherapy (e.g. psoralen and ultraviolet A phototherapy (PUVA)).

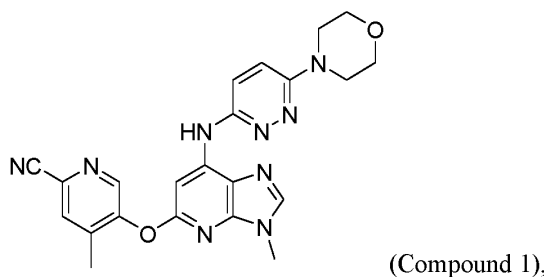
[0272] In one embodiment, a solid form of the invention or a pharmaceutical composition comprising a solid form of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of allergic reaction, particular agents include but are not limited to: antihistamines (e.g. cetirizine, diphenhydramine, fexofenadine, levocetirizine), glucocorticoids (e.g. prednisone, betamethasone, beclomethasone, dexamethasone), epinephrine, theophylline or anti-leukotrienes (e.g. montelukast or zafirlukast), anti-cholinergics and decongestants.

[0273] By co-administration is included any means of delivering two or more therapeutic agents to the patient as part of the same treatment regime, as will be apparent to the skilled person. Whilst the two or more agents may be administered simultaneously in a single formulation, *i.e.* as a single pharmaceutical composition, this is not essential. The agents may be administered in different formulations and at different times.

EMBODIMENTS OF THE INVENTION ACCORDING TO THE FIRST, SECOND & THIRD ASPECTS

[0274] The embodiments described below relate to the first, second and third aspects of the invention:

Embodiment A1 provides a pharmaceutical composition comprising Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl]amino]imidazo[4,5-b]pyridin-5-yl]oxy pyridine-2-carbonitrile)



or a pharmaceutically acceptable solvate thereof, and fumaric acid.

Embodiment A2 provides a composition according to the embodiment A1, wherein Compound 1 and fumaric acid are present in a 2:1 to 1:2 ratio, preferably in a 1.5:1 to 1:1.5 ratio, more preferably in a 1.2:1 to 1:1.2 ratio, even more preferably in a 1.1:1 to 1:1.1 ratio, yet more preferably in an approximately 1:1 ratio, most preferably in a 1:1 ratio.

Embodiment A3 provides a composition according to the embodiment A1 or A2, wherein Compound 1 and fumaric acid together form a solid form.

Embodiment A4 provides a composition according to the embodiment A1, A2 or A3, wherein Compound 1 and fumaric acid form a salt or a cocrystal.

Embodiment A5 provides a composition according to any of the embodiments A1, A2, A3 or A4, wherein Compound 1 and fumaric acid form a cocrystal.

Embodiment A6 provides a composition according to any of the embodiments A1, A2, A3, A4 or A5, wherein Compound 1 and fumaric acid together form a solid form and wherein the solid form is an unsolvated form.

Embodiment A7 provides a solid form according to any of the embodiments A1, A2, A3, A4 or A5, wherein Compound 1 and fumaric acid together form a solid form and wherein the solid form is a solvate.

Embodiment A8 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6 or A7, wherein Compound 1 and fumaric acid together form a solid form and wherein the solid form exhibits peaks on a XRPD spectrum.

Embodiment A9 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7 or A8, wherein Compound 1 and fumaric acid together form a solid form and wherein the solid form is fumarate cocrystal form of Compound 1.

Embodiment A10 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8 or A9, wherein the solid form may be characterized by an X-ray powder diffraction pattern having

one or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

Embodiment A11 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9 or A10, wherein the solid form may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A12 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10 or A11, wherein the solid form may be characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A13 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11 or A12, wherein the solid form may be characterized by an X-ray powder diffraction pattern comprising peaks at least at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

Embodiment A14 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12 or A13, wherein the solid form may be characterized by an X-ray powder diffraction pattern comprising peaks at 3.4, 7.1, 8.6, 12.4 and 13.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A15 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12 or A13, wherein the solid form may be characterized by an X-ray powder diffraction pattern comprising peaks at 7.1, 8.6, 12.4, 13.8 and 14.3 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A16 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12 or A13, wherein the solid form may be characterized by an X-ray powder diffraction pattern comprising peaks at 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A17 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12 or A13, wherein the solid form may be characterized by an X-ray powder diffraction pattern comprising peaks at 3.4 and/or 7.1 and/or 8.6 and/or 12.4 and/or 13.8 and/or 14.3 and/or 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A18 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16 or A17, wherein the solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 and 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

Embodiment A19 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17 or A18, wherein the solid form may be characterized by an X-ray powder diffraction pattern having peaks at all of the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6 and 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta; and an X-ray powder diffraction pattern substantially as depicted in FIGURE 6C.

Embodiment A20 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18 or A19, wherein the solid form may be characterized by a ^1H -NMR spectrum substantially in accordance with FIGURE 6A.

Embodiment A21 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19 or A20, wherein the solid form may be characterized by a DSC curve substantially in accordance with FIGURE 6D.

Embodiment A22 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19, A20 or A21, wherein the solid form may be characterized by a TGA curve substantially in accordance with FIGURE 6E.

Embodiment A23 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19, A20, A21 or A22, wherein the solid form may be characterized by a DVS curve substantially in accordance with FIGURE 6F.

Embodiment A24 provides a pharmaceutical composition comprising a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19, A20, A21, A22 or A23, and a pharmaceutical carrier, excipient or diluent.

Embodiment A25 provides a pharmaceutical composition according to embodiment A24, comprising a further therapeutically active ingredient.

Embodiment A26 provides a pharmaceutical composition according to embodiment A25, wherein the further therapeutically active ingredient is an agent for the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage

malformations, and/or diseases associated with hypersecretion of IFN α , interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease.

Embodiment A27 provides a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19, A20, A21, A22 or A23, or a pharmaceutical composition according to embodiment A24, A25 or A26, for use in the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease.

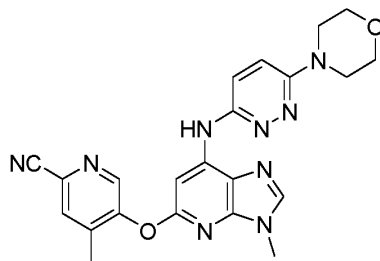
Embodiment A28 provides the use of a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19, A20, A21, A22 or A23, or a pharmaceutical composition according to embodiment A24, A25 or A26, in the manufacture of a medicament for the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease.

Embodiment A29 provides a method of treating an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease, comprising administering to a patient an effective amount of a solid form according to any of the embodiments A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, A19, A20, A21, A22 or A23, or a pharmaceutical composition according to embodiment A24, A25 or A26.

EMBODIMENTS OF THE INVENTION ACCORDING TO THE FOURTH ASPECT

[0275] The embodiments described below relate to the fourth aspect of the invention:

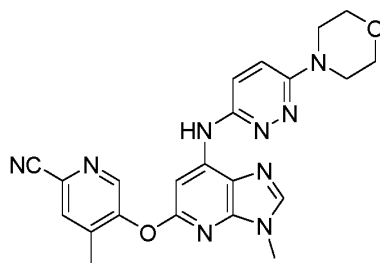
Embodiment B1 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl]amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile)



(Compound 1),

or a pharmaceutically acceptable solvate thereof, for use in the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease, wherein compound 1 is administered at a total daily dosage of at least 70 mg per day to 300 mg per day.

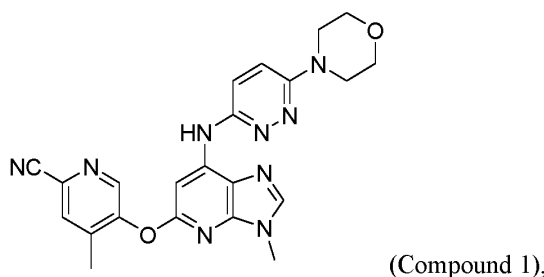
Embodiment B2 provides the use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl]amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile)



(Compound 1),

or a pharmaceutically acceptable solvate thereof, in the manufacture of a medicament for the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease, wherein compound 1 is administered at a total daily dosage of at least 70 mg per day to 300 mg per day.

Embodiment B3 provides a method of treating an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren’s syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn’s disease, comprising administering to a patient a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl]amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile)



or a pharmaceutically acceptable solvate thereof, wherein compound 1 is administered at a total daily dosage of at least 70 mg per day to 300 mg per day.

Embodiment B4 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the total daily dosage of compound 1 is administered as a once per day dosage (q.d.).

Embodiment B5 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein compound 1 is administered at a total daily dosage of at least 75 mg per day to 300 mg per day, preferably 75 mg per day to 250 mg per day.

Embodiment B6 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein compound 1 is administered at a total daily dosage of 75 mg per day, 90 mg per day, 100 mg per day, 110 mg per day, 120 mg per day, 125 mg per day, 130 mg per day, 140 mg per day, 150 mg per day, 160 mg per day, 170 mg per day, 175 mg per day, 180 mg per day, 190 mg per day, 200 mg per day, 225 mg per day or 250 mg per day.

Embodiment B7 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein compound 1 is administered at a total daily dosage

of 75 mg per day or 90 mg per day or 150 mg per day or 200 mg per day or 225 mg per day or 250 mg per day.

Embodiment B8 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein compound 1 is administered at a total daily dosage of 150 mg or 225 mg per day.

Embodiment B9 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein compound 1 is administered at a total daily dosage of 150 mg per day.

Embodiment B10 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for psoriasis.

Embodiment B11 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of compound 1 or method according to any of the preceding embodiments wherein the treatment is for psoriatic arthritis.

Embodiment B12 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for Crohn's disease.

Embodiment B13 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for ulcerative colitis.

Embodiment B14 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for systemic lupus erythematosus.

Embodiment B15 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for cutaneous lupus erythematosus.

Embodiment B16 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for lupus nephritis.

Embodiment B17 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for dermatomyositis.

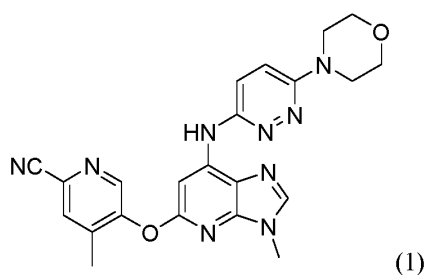
Embodiment B18 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the treatment is for polymyositis.

Embodiment B19 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the pharmaceutical composition comprising a fumarate cocrystal of Compound 1 is administered orally.

Embodiment B20 provides a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any of the preceding embodiments wherein the pharmaceutical composition comprising a fumarate cocrystal of Compound 1 is administered orally to a patient in a fed state.

Embodiment B21 provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a fumarate cocrystal of Compound 1 for use, use of a pharmaceutical composition comprising a fumarate cocrystal of Compound 1 or method according to any one of embodiments B01 to B20.

Embodiment B22 provides a pharmaceutical unit dosage composition comprising 70 mg to 300 mg of compound 1 as a fumarate cocrystal:



or a pharmaceutically acceptable solvate thereof, wherein the unit dosage form is suitable for oral administration up to a maximum total dosage of 300 mg of compound 1 per day.

Embodiment B23 provides the dosage form of embodiment B22 comprising from 75 mg to 300 mg of compound 1 in unit dosage form.

Embodiment B24 provides the dosage form of embodiment B22 or B23 comprising from 75 mg, 90 mg, 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 225 mg, 250 mg or 300 mg of compound 1 in unit dosage form.

Embodiment B25 provides the dosage form of embodiment B22 or B23 comprising 75 mg to 225 mg of compound 1 in unit dosage form.

Embodiment B26 provides the dosage form of embodiment B22, B23, B24 or B25 comprising 150 mg of compound 1 in unit dosage form.

Embodiment B27 provides the dosage form according to any one of embodiments B22, B23, B24, B25 or B26, wherein the unit dosage is in a form selected from a liquid, a tablet, a capsule, or a gelcap.

Embodiment B28 provides the dosage form according to any one of embodiments B22, B23, B24, B25, B26 or B27, wherein the unit dosage is in the form of a tablet or capsule.

Embodiment B29 provides the dosage form according to any one of embodiments B22, B23, B24, B25, B26, B27 or B28, wherein the unit dosage is in the form of a tablet.

Embodiment B30 provides the dosage form according to any one of embodiments B22, B23, B24, B25, B26, B27, B28 or B29 for use in the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease.

Embodiment B31 provides the use of the dosage form according to any one of B22, B23, B24, B25, B26, B27, B28 or B29, in the manufacture of a medicament for the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease.

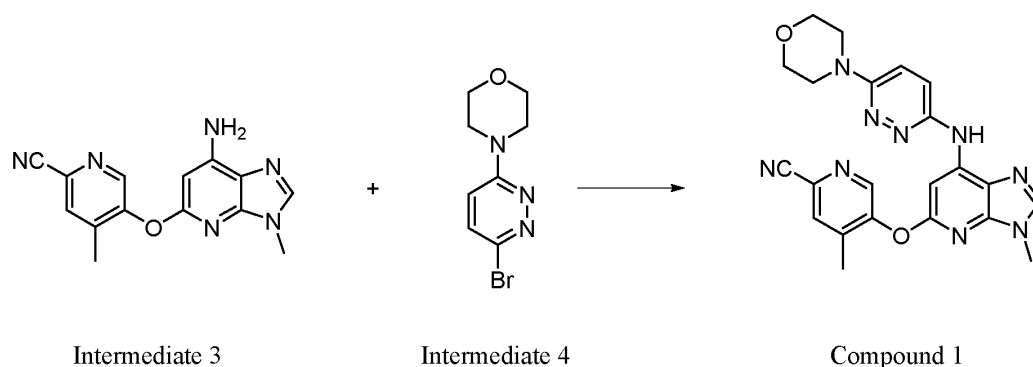
Embodiment B32 provides a method of treating an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III

interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease, comprising administering to a patient a dosage form according to any one of embodiments B22, B23, B24, B25, B26, B27, B28 or B29.

EMBODIMENTS OF THE INVENTION ACCORDING TO THE FIFTH & SIXTH ASPECTS

[0276] The embodiments described directly below relate to the fifth and sixth aspects of the invention, i.e. processes for the manufacture of Compound 1 and processes for the manufacture of compositions comprising Compound 1 according to the invention.

Embodiment C1 provides a process for the manufacture of Compound 1 or a pharmaceutically acceptable salt thereof, comprising the step of reacting intermediate 3 with intermediate 4 in the presence of a base, a palladium precursor and 1-[(S_P)-2-(dicyclohexylphosphino) ferrocenyl]ethyldi-tert-butylphosphine:



Embodiment C2 provides a process according to embodiment C1, wherein the molar ratio between Intermediate 3 and Intermediate 4 is from about 1.5:1 to about 1:1.5, preferably from about 1.1:1 to 1:1.1.

Embodiment C3 provides a process according to embodiment C1 or C2, wherein the molar ratio between Intermediate 3 and 1-[(S_P)-2-(dicyclohexylphosphino) ferrocenyl]ethyldi-tert-butylphosphine is from about 1:0.01 to about 1:0.1, preferably from about 1:0.02 to about 1:0.05, more preferably about 1:0.024.

Embodiment C4 provides a process according to any of the embodiments C1, C2 or C3, wherein the palladium precursor is selected from Pd(π -cinnamyl)Cl dimer, Pd(OAc)₂, Pd(Cl)₂, Pd₂(dba)₃, Pd(dba)₂, Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd(acac)₂ and Pd(PhCN)₂Cl₂, more preferably from Pd(π -cinnamyl)Cl dimer, Pd₂(dba)₃, Pd(dba)₂ and Pd(PPh₃)₄, the most preferably is Pd(π -cinnamyl)Cl dimer.

Embodiment C5 provides a process according to any of the embodiments C1, C2, C3 or C4 wherein the molar ratio between intermediate 3 and the palladium precursor is from about 1:0.001 to about 1:0.05, preferably from about 1:0.05 to about 1:0.02, more preferably about 1:0.01.

Embodiment C6 provides a process according to any of the embodiments C1, C2, C3, C4 or C5, wherein the base is selected from K_2CO_3 , DABCO, DBU, NaOtBu, Cs_2CO_3 , Li_2CO_3 , Na_2CO_3 , DMAP, NaHMDS and NEt_3 , more preferably from K_2CO_3 , DBU, and Cs_2CO_3 , the most preferably is Cs_2CO_3 .

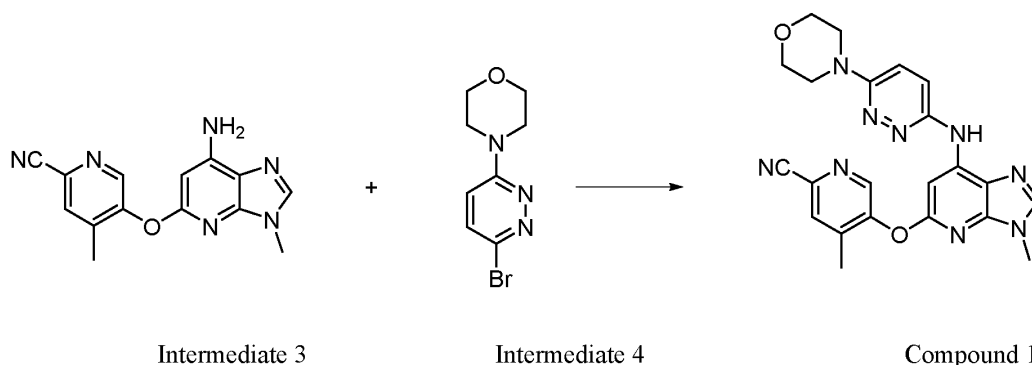
Embodiment C7 provides a process according to any of the embodiments C1, C2, C3, C4, C5 or C6, wherein the process being carried out in the presence of at least one solvent.

Embodiment C8 provides a process according to the embodiment C7, wherein the solvent is selected from acetonitrile, xylene, DMF or tert-amyl alcohol, preferably acetonitrile, DMF or tert-amyl alcohol.

Embodiment C9 provides a process according to any of the embodiments C1, C2, C3, C4, C5, C6, C7 or C8, wherein the process further comprises the steps of isolating Compound 1 from the reaction mixture by the addition of acetonitrile and/or water, optionally followed by filtering the solid.

Embodiment C10 provides a process according to any of the embodiments C1, C2, C3, C4, C5, C6, C7, C8 or C9, wherein the process comprises the following steps:

- mixing in degassed tert-amyl alcohol or DMF, and stirring under inert atmosphere, preferably under nitrogen or argon atmosphere, Intermediate 3, Intermediate 4 and a base,



- adding to the reaction mixture under an inert atmosphere, preferably under a nitrogen or argon atmosphere, as solids or as a premixed solution in acetonitrile, a palladium precursor and 1-[(S_P)-2-(dicyclohexylphosphino)ferrocenyl] ethyldi-tert-butylphosphine,
- stirring the reaction mixture at about 100 °C for at least 2 hours,
- cooling the reaction mixture to room temperature and adding acetonitrile,
- filtering the reaction mixture and wash it with water and then with acetonitrile,
- drying the solid filtrate.

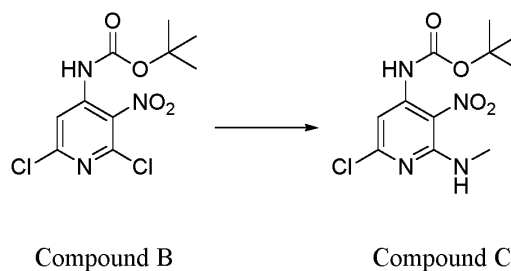
Intermediate 3

The reaction scheme shows the conversion of a pyridine derivative to a pyrimidine derivative. The starting material on the left is a 4-cyano-2-(4-cyano-2-methoxyphenyl)pyridine derivative. It features a pyridine ring with a cyano group (NC) at position 4 and a 4-cyano-2-methoxyphenyl group at position 2. The pyridine ring is substituted with a tert-butyl carbamate group (HN-C(=O)-O-C(CH₃)₃) at position 3 and a dimethylamino group (N(CH₃)₂) at position 6. A nitro group (NO₂) is attached to the pyridine ring at position 5. The reaction arrow points to the product on the right, which is a pyrimidine derivative. The product has a pyrimidine ring system with a cyano group (NC) at position 4 and a 4-cyano-2-methoxyphenyl group at position 2. The pyrimidine ring is substituted with a tert-butyl carbamate group (HN-C(=O)-O-C(CH₃)₃) at position 3 and a dimethylamino group (N(CH₃)₂) at position 6. The nitro group (NO₂) is attached to the pyrimidine ring at position 5.

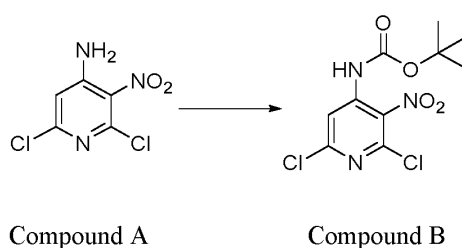
Compound E

Compound D

49



Embodiment C15 provides a process according to embodiment C14, wherein Compound B in said process is prepared following the step of reacting Compound A with a suitable base, preferably K_3PO_4 ; and di-tert-butyl dicarbonate, to yield Compound B:



Embodiment C16 provides a process according to any of the embodiments C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14 or C15, wherein the process further comprises the following steps:

- suspending Compound 1 in a suitable solvent, preferably acetic acid, acetone, ethanol or THF, more preferably acetic acid,
- adding to the suspension, at least one equivalent of fumaric acid, preferably in a C_{1-4} alcohol or water solution.
- aging the reaction mixture, and
- filtering and drying the reaction mixture.

Embodiment C17 provides a process for the manufacture of fumarate cocrystal form of Compound 1, comprising the following steps:

- suspending Compound 1 in a suitable solvent, preferably acetic acid, acetone, ethanol or THF, more preferably acetic acid,
- adding to the suspension, at least one equivalent of fumaric acid, preferably in a C_{1-4} alcohol or water solution.
- aging the reaction mixture, and
- filtering and drying the reaction mixture.

Embodiment C18 provides a process according to embodiment C16 or C17, wherein between 1 to 5 equivalents of fumaric acid are added to the suspension.

Embodiment C19 provides a process according to any of the embodiments C16, C17 or C18, wherein the aging step is carried out between about 20 °C to about 80 °C, preferably about 25 °C to 60 °C, for at least 72 hours.

Embodiment C20 provides a process according to any of the embodiments C16, C17, C18 or C19, further comprising the step of centrifugating or filtrating the reaction mixture after the aging step.

Embodiment C21 provides a process according to any of the embodiments C16, C17, C18, C19 or C20, wherein the drying step is performed under vacuum for at least 12 hours at a temperature between about 20 °C to about 60 °C, preferably about 30 °C.

CHEMICAL SYNTHETIC PROCEDURES

General

[0277] The methods for the preparation of Compound 1 have been described in WO2019076716 (Compound 1 is referred to as “compound 38” in WO2019076716) and a summary is provided below.

[0278] A solid form of the invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.* reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0279] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art (Greene, T W; Wuts, P G M., 1991).

[0280] The following methods are presented with details as to the preparation of a solid form of the invention as defined hereinabove and the comparative examples. A solid form of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[0281] All reagents were of commercial grade and were used as received without further purification, unless otherwise stated. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Column chromatography is performed on silica gel 60 (35-70 µm). Thin layer chromatography is carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). ¹H NMR spectra were recorded on Bruker Advance NMR spectrometers (300, 400 or 500 MHz) or alternatively, or on a Varian INOVA 400 MHz

NMR Spectrometer equipped with a Varian ATB probe. Chemical shifts (δ) for ^1H NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or the appropriate residual solvent peak, *i.e.* CHCl_3 (δ 7.27), as internal reference. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quin), multiplet (m) and broad (br). Electrospray MS spectra were obtained on a Waters platform LC/MS spectrometer or with Waters Acquity H-Class UPLC coupled to a Waters Mass detector 3100 spectrometer. Columns used: Waters Acquity UPLC BEH C18 1.7 μm , 2.1mm ID x 50mm L, Waters Acquity UPLC BEH C18 1.7 μm , 2.1mm ID x 30 mm L, or Waters Xterra MS 5 μm C18, 100 x 4.6mm. The methods are using either ACN/ H_2O gradients (H_2O contains either 0.1% TFA or 0.1% NH_3) or MeOH / H_2O gradients (H_2O contains 0.05% TFA).

Table I. List of abbreviations used in the experimental section:

Abbreviation	Definition	Abbreviation	Definition
$^{\circ}\text{C}$	degrees Celsius	EtOH	Ethanol
μg	microgram	g	gram
μL	microliter	h	hour
μm	micrometer	HPLC	High pressure liquid chromatography
ACN	acetonitrile	IPA	isopropyl alcohol
AUC	area under the curve	<i>i</i> PrOH	<i>iso</i> -Propanol
Boc_2O	di-tert-butyl dicarbonate	kg	kilogram
CI	counter ion	KOtBu	potassium tert-butoxide
D	gravimetric vapor sorption	L	liter
d	doublet	LCMS	Liquid Chromatography-Mass Spectrometry
dba	tris(dibenzylideneacetone)	MEK	methyl ethyl ketone
DABCO	1,4-diazabicyclo[2.2.2]octane	MeOH	Methanol
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene	mg	milligram
DCM	dichloromethane	MiBK	methyl isobutyl ketone
DMA	dimethylacetamide	min	minute
DMF	N,N-dimethylformamide	mL	milliliter
DMAP	4-dimethylaminopyridine	mmol	millimoles
DMSO	dimethylsulfoxide	MTBE	methyl tert-Butyl Ether
DSC	differential scanning calorimetry	NIS	N-iodosuccinimide
DVS	dynamic vapor sorption	NaHMDS	sodium bis(trimethylsilyl) amide
eq.	Equivalent	NaOtBu	sodium tert-butoxide
EtOAc	ethyl acetate	NEt_3	triethylamine

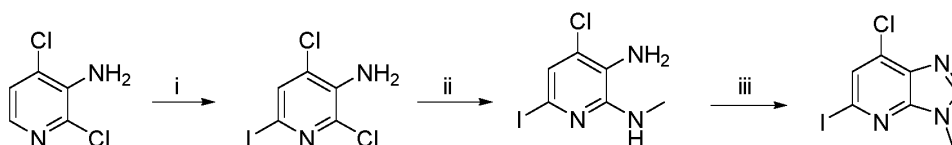
Abbreviation	Definition
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Pd(acac) ₂	palladium(II) bis(acetylacetonate)
[PdCl(allyl)] ₂	allylpalladium(II) chloride dimer
Pd(dppf)Cl ₂ . DCM	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(I), complex with dichloromethane
Pd(OAc) ₂	palladium(II) acetate
Pd(PhCN) ₂ Cl ₂	bis(benzonitrile)palladium dichloride
PET	positron emission topography
ppm	part-per-million
RH	Relative humidity

Abbreviation	Definition
Rt	retention time
r.t.	room temperature
SDTA	Simultaneous Difference Thermal Analysis
TFA	trifluoroacetic acid
TGA	thermogravimetric analysis
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMHD	2,2,6,6-tetramethyl heptanedione
UPLC	ultra performance liquid chromatography
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XRPD	X-Ray Powder Diffraction

SYNTHETIC PREPARATION OF THE COMPOUND 1

Example 1. Synthetic preparation of Compound 1

1.1. Synthesis of intermediate 1: 7-Chloro-5-iodo-3-methyl-3H-imidazo[4,5-b]pyridine



1.1.1. Step i: synthesis of 2,4-dichloro-6-iodo-pyridin-3-ylamine:

[0282] To a solution of 2,4-dichloro-3-aminopyridine (250 g, 1.54 mmol, 1 eq.) in dry ACN (1.2 L) under N₂ atmosphere at r.t. was added NIS (382 g, 1.70 mmol, 1.1 eq.) and TFA (35.45 mL, 0.46 mmol, 0.3 eq.). The mixture was stirred at 40 °C for 18 hours in 3 L round-bottom flask. Reaction mixture was then quenched with saturated Na₂S₂O₃ (500 mL) and NaHCO₃ (700 mL). Organic layer was washed with saturated NaHCO₃ and aqueous layers were washed twice with EtOAc (2 x 700 mL). Combined organic layers were dried over MgSO₄, filtered and concentrated to dryness to obtain crude product. It was purified by column chromatography using cyclohexane and EtOAc (10%) to give the desired product LCMS: m/z = 289 [M+H].

1.1.2. Step ii: synthesis of 4-Chloro-6-iodo-N2-methyl-pyridine-2,3-diamine:

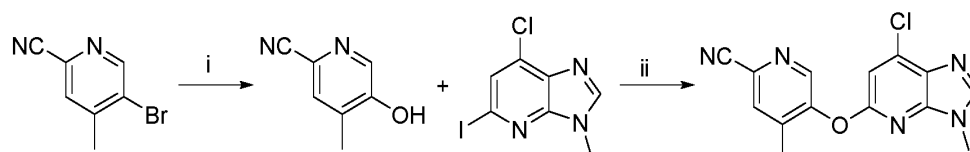
[0283] 2,4-dichloro-6-iodo-pyridin-3-amine (20 g, 0.07 mmol, 1 eq.) was dissolved in n-butanol (300 mL) at an autoclave (600 mL). Methylamine (33% in EtOH, 28.72 mL, 0.28 mmol, 4 eq.) was added under N₂

at r.t. The mixture was stirred at 180 °C for 18 hours and then cooled to r.t. This step was repeated twice and then, the reaction mixtures were combined and concentrated to give the desired compound that was used in next step as such. LCMS: $m/z = 284$ [M+H].

1.1.3. Step iii: synthesis of 7-Chloro-5-iodo-3-methyl-3H-imidazo[4,5-b]pyridine:

[0284] To a solution of 4-chloro-6-iodo-N-2-methyl-pyridine-2,3-diamine (60 g, 0.21 mmol, 1 eq.) in formic acid (30 mL) was added trimethyl orthoformate (69.5 mL, 0.64 mmol, 3 eq.). The mixture was stirred at 60 °C for 1 h. Reaction was concentrated to dryness after which the residue was diluted with DCM and quenched with saturated aqueous NaHCO_3 solution. After extraction with DCM, organic layer was dried over Na_2SO_4 , filtered and concentrated to dryness to afford crude material. It was purified by column chromatography using eluent cyclohexane/EtOAc from 10 to 60% of EtOAc to give the desired product. LCMS: $m/z = 294$ [M+H]. ^1H NMR (300MHz, DMSO-d_6) δ ppm: 8.46 (s, 1H), 7.83 (s, 1H), 3.81 (s, 3H).

1.2. Synthesis of intermediate 2: 5-(7-Chloro-3-methyl-3H-imidazo[4,5-b]pyridin-5-yloxy)-4-methylpyridine-2-carbonitrile



1.2.1. Step i: synthesis of 5-hydroxy-4-methylpyridine-2-carbonitrile:

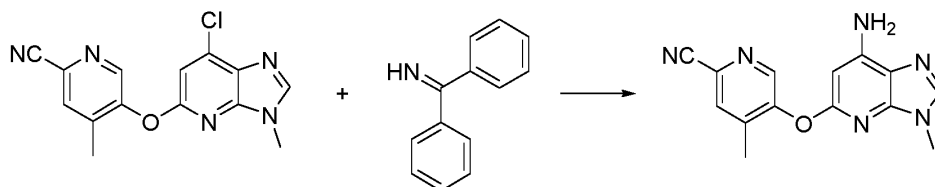
[0285] A mixture of 5-bromo-2-cyano-4-methylpyridine (CAS# 886364-86-9, 26.8 g, 136 mmol, 1 eq.), 4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (CAS# 73183-34-3, 48.4 g, 190 mmol, 1.4 eq.), $\text{Pd(dppf)Cl}_2 \cdot \text{DCM}$ (5.55 g, 6.80 mmol, 0.05 eq.), potassium acetate (40 g, 408 mmol, 3 eq.) were stirred under N_2 in 1,4-dioxane (500 mL) for 2 hours at 110 °C. Then, the reaction mixture was cooled to 0 °C prior to the addition dropwise of H_2O_2 (30% water solution, 83 mL, 816 mmol, 6.0 eq.). After 2 hours, the reaction mixture was diluted with DCM and washed with water. The aqueous phase was acidified to pH 4-5 and extracted 3 times with DCM. Combined organic extracts were dried and evaporated *in vacuo*. The resulting crude was purified by column chromatography (petroleum ether/EtOAc gradient elution 30% till 50% EtOAc). Obtained material was triturated with pentane and diethyl ether to afford the desired product.

1.2.2. Step ii: synthesis of 5-(7-Chloro-3-methyl-3H-imidazo[4,5-b]pyridin-5-yloxy)-4-methylpyridine-2-carbonitrile:

[0286] Intermediate 1 (68.51 g, 233.83 mmol, 1.0 eq.), 7-chloro-5-iodo-3-methyl-3H-imidazo[4,5-b]pyridine (47.0 g, 350.75 mmol, 1.5 eq.), CuI (8.89 g, 46.77 mmol, 0.2 eq.), TMHD (97.45 mL, 467.66 mmol, 2 eq.) and Cs_2CO_3 (152 g, 467.66 mmol, 2 eq.) were mixed together under air, DMF (234 mL) was added and the mixture was stirred at 85 °C for 2 nights. If full conversion was not reached, additional CuI (0.1 eq.) and TMHD (1 eq.) were added after which the mixture was stirred further at 85 °C for another night. Next, the mixture was cooled to 0 °C. The resulting thick paste was then filtered and the cake was washed with ice cooled DMF (2 x 20 mL). It was then washed with ice cooled MTBE (3 x 150 mL). After

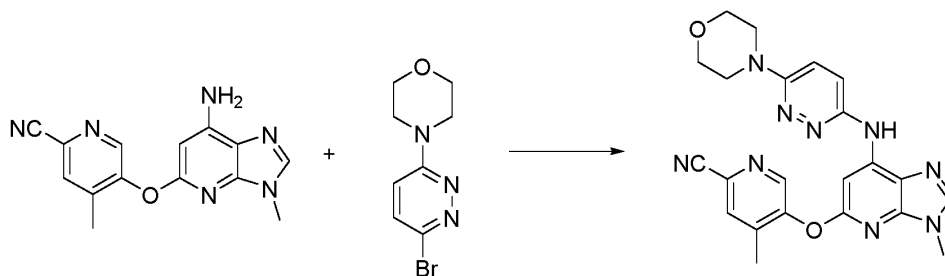
drying the cake, it was suspended in 500 mL of 10% aqueous TMEDA solution. It was stirred for 2 hours, filtered and the cake was washed with H₂O to afford the desired product. LCMS: $m/z = 300$ $[M+H]^+$.

1.3. Synthesis of intermediate 3: 5-(7-Amino-3-methyl-3H-imidazo[4,5-b]pyridin-5-yloxy)-4-methylpyridine-2-carbonitrile



[0287] To a mixture of intermediate 2 (5.0 g, 16.72 mmol, 1.0 eq.), benzophenone imine (CAS# 1013-88-3, 2.81 mL, 16.72 mmol, 1.0 eq.), Pd₂Cl₂(allyl)₂ (CAS# 12012-95-2, 122 mg, 0.33 mmol, 0.02 eq.), XantPhos (CAS# 161265-03-8, 387 mg, 0.67 mmol, 0.04 eq.) and Cs₂CO₃ (6.54 g, 20.07 mmol, 1.2 eq.) under N₂ atmosphere, 1,4-dioxane (100 mL) was added and the mixture was stirred at 110 °C for 24 h. After letting it cool down to r.t., the mixture was diluted with EtOAc and filtered over celite. The cake was washed with EtOAc (100 mL) and the filtrate was poured in 2N aqueous HCl solution (200 mL), stirring it for 10 min. After extraction with EtOAc, the aqueous phase was neutralized to pH = 7 using NaHCO₃. This was followed by an extraction with EtOAc (5 x 100 mL) after which the combined organic layers were dried over MgSO₄, filtered and concentrated to dryness to afford the crude material which was triturated with DCM to afford the desired product. LCMS: $m/z = 281$ $[M+H]^+$.

1.4. Synthesis of Compound 1: 4-Methyl-5-[3-methyl-7-(6-morpholin-4-yl-pyridazin-3-ylamino)-3H-imidazo[4,5-b]pyridin-5-yloxy]-pyridine-2-carbonitrile

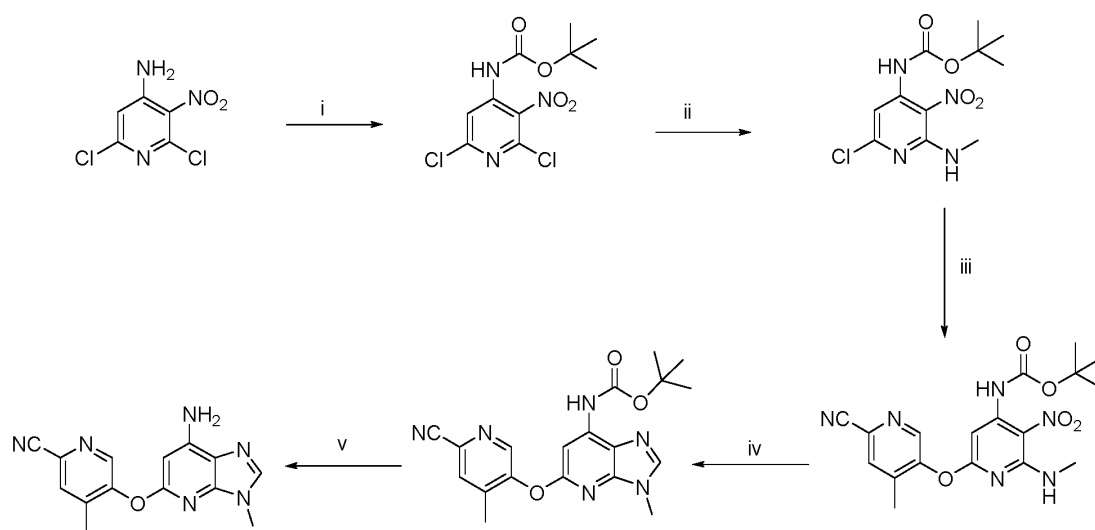


[0288] Intermediate 3 (409 g, 1.459 moles, 1.0 eq.) and Intermediate 4 (4-(6-bromopyridazin-3-yl)morpholine, CAS# 927673-86-7, 392 g, 1.1 eq.) were added to xylene mix of isomers (8 L) at r.t. To the mixture was added, under stirring at r.t., potassium phosphate tribasic (929.0 g, 3.0 eq.). The reaction mixture was heated from r.t. to 135 °C in 2 h and 30 min. Then a suspension of Pd(OAc)₂ (2 mol%, 6.6 g) and XantPhos (CAS# 161265-03-8, 4 mol%, 33.8 g) in xylenes (50 mL) was added to the hot mixture. The reaction was heated at reflux for 1 h and 30 min. Then a suspension of Pd(OAc)₂ (2 mol%, 6.6 g) and XantPhos (4 mol%, 33.8 g) in xylenes (50 mL) was added and the reaction was heated at reflux for an additional 1 h and 30 min. Then a suspension of Pd(OAc)₂ (2 mol%, 6.6 g) and XantPhos (4 mol%, 33.8 g) in xylenes (50 mL) was added one last time. The reaction was refluxed for an additional 1 h and 30 min. The reaction mixture was cooled down to r.t. and stirred overnight. The suspension was filtered, washed

with ACN (5 L). The solid was washed with water (15 L) until obtaining a neutral pH, dried under suction, then suspended in ACN (6.5 L) and stirred at r.t. for 1 h. The suspension was filtered, washed with ACN (2 L) and dried. Chromatography on SiO₂ (1 g of SiO₂ for 1 g of crude) using eluent CHCl₃/acetone (70/30) and then CHCl₃/MeOH (96/4) afforded the desired product (Compound 1).

Example 2. Alternative synthetic preparation of Compound 1

2.1. Alternative synthesis of Intermediate 3: 5-(7-Amino-3-methyl-3H-imidazo[4,5-b]pyridin-5-yloxy)-4-methyl-pyridine-2-carbonitrile



2.1.1. Step i: synthesis of tert-butyl (2,6-dichloro-3-nitropyridin-4-yl)carbamate

[0289] 4-amino-2,6-dichloro-3-nitropyridine (CAS# 2897-43-0, 520 g, 2.5 mol, 1.0 eq.), was added to ACN (5.2 L) at r.t. To the mixture were added, under stirring at r.t., Boc₂O (710 g, 3.25 mol, 1.3 eq.) and K₃PO₄ (1000 g, 4.71 mol, 1.9 eq.). The reaction mixture was heated at reflux for 1-2 hours. Then a solution of Boc₂O (110 g, 0.5 mol, 0.2 eq.) in ACN (100mL) was added and the reaction mixture was heated at reflux for one additional hour. The reaction mixture was cooled down to r.t. and filtered on a pad of Na₂SO₄. The Na₂SO₄ was washed with ACN (2 L). The filtrate was evaporated under reduced pressure and redissolved in DCM (5 L). The DCM layer was washed with water. The organic layer was extracted with DCM (5 L) and the combined organic layers were dried over Na₂SO₄, filtered and evaporated to afford the desired product. LCMS: m/z = 306/308 [M+H].

2.1.2. Step ii: synthesis of tert-butyl N-[6-chloro-2-(methylamino)-3-nitropyridin-4-yl]carbamate

[0290] tert-butyl-(2,6-dichloro-3-nitropyridin-4-yl)carbamate (770 g, 2.5 mol, 1.0 eq.) was added to isopropanol (11 L) at r.t. To the mixture were added, under stirring at r.t., methylamine 33% in EtOH (800 mL, 3.0 eq.) over 1 hour and 30 minutes. The reaction mixture was stirred at r.t. for 1 h and 30 min. The

suspension was filtered, washed with iPrOH (1 L) then water (4 L). Following drying the desired product was obtained. LCMS: $m/z = 302.9/304.8$ [M+H].

2.1.3. Step iii: tert-butyl N-[6-[(6-cyano-4-methylpyridin-3-yl)oxy]-2-(methylamino)-3-nitropyridin-4-yl]carbamate

[0291] Tert-butyl N-[6-chloro-2-(methylamino)-3-nitropyridin-4-yl]carbamate (788 g, 2.6 mol, 1.0 eq.), was added to ACN (5.5 L) at r.t. To the mixture were added, under stirring at r.t., 5-hydroxy-4-methylpyridine-2-carbonitrile (384 g, 2.86 mol, 1.1 eq.) and Na_2CO_3 (414 g, 3.9 mol, 1.5 eq.). The reaction mixture was heated at reflux for 48 h. The reaction mixture was cooled down to r.t. and the insoluble were filtered and washed with ACN (2 L). The combined organic layers were evaporated. The crude was washed with water (5 L), collected and dried to afford the desired product. LCMS: $m/z = 401.1$ [M+H] ; $m/z = 399.2$ [M-H]. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 10.70 (s, 1H), 9.05 (q, 1H), 8.62 (s, 1H), 8.13 (s, 1H), 7.23 (s, 1H), 2.59 (d, 3H), 2.24 (s, 3H), 1.50 (s, 9H).

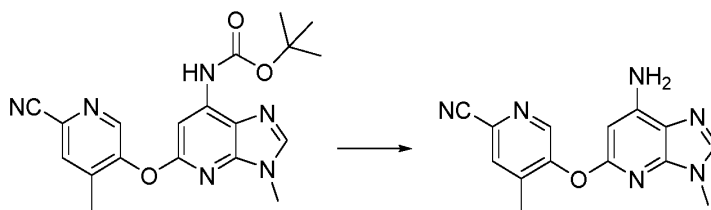
2.1.4. Step iv: tert-butyl N-(5-[(6-cyano-4-methylpyridin-3-yl)oxy]-3-methyl-3H-imidazo[4,5-b]pyridin-7-yl)carbamate

[0292] Tert-butyl N-[6-[(6-cyano-4-methylpyridin-3-yl)oxy]-2-(methylamino)-3-nitropyridin-4-yl]carbamate (150 g, 375 mmol, 1.0 eq.) was added to a mixture of acetic acid (750 mL, 35 eq.) and trimethyl orthoformate (750 mL, 18 eq.) at r.t. To the mixture were added by portions, under vigorous stirring at 20-21 °C, Zn dust < 10 μm (total of 120 g, 4.9 eq., added by portions of 15 g). Each addition was performed after the reaction mixture had cooled down to 20-21 °C. The reaction mixture was stirred during one hour after the last addition. The suspension was filtered on Dicalite 4158 (Carlo Erba, ref P8880014), washed with THF (1 L) and the combined organic layers were concentrated under vacuum. The residue was slowly poured into a cold mixture of 20% ammoniac solution (100 mL) and water (2 L). The resulting solid was filtered, washed with water (2 L) and dried to afford the desired product. LCMS: $m/z = 381.0$ [M+H]; $m/z = 379.2$ [M-H]. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 9.32 (bs, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 8.10 (s, 1H), 7.54 (s, 1H), 3.60 (s, 3H), 2.27 (s, 3H), 1.49 (s, 9H).

2.1.5. Step v: 5-[(7-Amino-3-methyl-3H-imidazo[4,5-b]pyridin-5-yl)oxy]-4-methylpyridine-2-carbonitrile

[0293] Tert-butyl N-(5-[(6-cyano-4-methylpyridin-3-yl)oxy]-3-methyl-3H-imidazo[4,5-b]pyridin-7-yl)carbamate (197 g, 0.518 mol, 1.0 eq.) was suspended in a mixture of HCl, 4 N solution in water (1 L) and THF (1 L). The reaction mixture was heated at 60 °C for 5 h. The reaction mixture was cooled down to r.t. and the solid was filtered, washed with THF (1 L) and dried to afford the desired product as hydrochloric salt. LCMS: $m/z = 281.4$ [M+H]. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ ppm: 9.28 (s, 1H), 8.54 (s, 1H), 8.12 (s, 1H), 7.57 (bs, 2H), 6.33 (s, 1H), 3.67 (s, 3H), 2.25 (s, 3H).

2.2. Alternative synthesis of intermediate 3: 5-(7-Amino-3-methyl-3H-imidazo[4,5-b]pyridin-5-yloxy)-4-methyl-pyridine-2-carbonitrile



[0294] In a reaction vessel were charged tert-butyl N-(5-((6-cyano-4-methylpyridin-3-yl)oxy)-3-methyl-3H-imidazo[4,5-b]pyridin-7-yl)carbamate (17.85 kg, 46.92 mol, 1.0 eq.), water (80.5 L, 4.5 Vol), glacial acetic acid (26.1 L, 1.5 Vol) and 1-butanol (13.7 L, 0.8 Vol) at r.t. The reaction mixture was heated to 60°C, and an aqueous solution of hydrochloric acid (9.06 kg, 91.94 mol, 2.0 eq.) in water (17.8 L, 1 Vol) was slowly added. The reaction mixture was stirred at 60 °C for at least 5 hours and upon complete conversion, it was cooled to r.t. and aged for at least 1 h. The resulting suspension was filtered and isolated solids were washed with MeOH (52.4 L, 3 Vol) and then with MeOH (26.8 L, 1.5 Vol) before drying under vacuum and N₂ flow at up to 50°C, to afford 13.36 kg of the desired intermediate.

2.3. Alternative synthesis of Compound 1: 4-Methyl-5-[3-methyl-7-(((6-morpholin-4-yl-pyridazin-3-yl)amino)-3H-imidazo[4,5-b]pyridin-5-yl)oxy]-pyridine-2-carbonitrile

[0295] Intermediate 3 (280 mg, 1 mmol, 1.0 eq.), Intermediate 4 (4-(6-bromopyridazin-3-yl)morpholine, CAS# 927673-86-7, 268 mg, 1.1 mmol, 1.1 eq.) and Cs₂CO₃ (977 mg, 3 mmol, 3 eq.) are mixed under argon at r.t. and degassed tert-amyl alcohol or DMF (5.5 mL) is added. [Pd(cinnamyl)Cl]₂ (5.18 mg, 0.010 mmol, 0.01 eq.) and JosiPhos (CAS# 158923-11-6, 13 mg, 0.024 mmol, 0.024 eq.) are added under argon either as solid or as pre-mixed solution in 1 mL degassed ACN. The mixture is heated to 100 °C for at least 2 h. The reaction mixture is then cooled to r.t. and ACN is added. The suspension is filtered, the solid is triturated first with water then ACN, and dried to afford the desired product.

Example 3. Ligand screening for the Palladium-catalyzed coupling reaction

3.1. Aim of the study

[0296] Evaluate the performance of the different catalytic systems for the reaction described in the Example 2.2, between Intermediate 3 and Intermediate 4 towards the formation of Compound 1 via palladium-catalyzed coupling reaction.

[0297] A palladium (II) or palladium (0) precursor known in the art to be compatible with cross-coupling reactions is a suitable palladium precursor for this transformation. Preferably, the palladium precursor is selected from Pd(π -cinnamyl)Cl dimer, Pd(OAc)₂, Pd(Cl)₂, Pd₂(dba)₃, Pd(dba)₂, Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd(acac)₂ and Pd(PhCN)₂Cl₂. More preferably, the palladium precursor is selected from Pd(π -cinnamyl)Cl dimer, Pd₂(dba)₃, Pd(dba)₂ and Pd(PPh₃)₄. Even more preferably, the palladium precursor is Pd(π -cinnamyl)Cl dimer.

[0298] A base known in the art to be compatible with cross-coupling reactions is a suitable base for this transformation. Preferably, the base is selected from K_2CO_3 , DABCO, DBU, NaOtBu, Cs_2CO_3 , Li_2CO_3 , Na_2CO_3 , DMAP, NaHMDS and NEt_3 . More preferably, the base is selected from K_2CO_3 , DABCO, DBU, and Cs_2CO_3 . Even more preferably, the base is Cs_2CO_3 .

3.2. Standard reaction conditions

[0299] Intermediate 3 (140 mg, 0.5 mmol, 1.0 eq.), Intermediate 4 (4-(6-bromopyridazin-3-yl)morpholine, CAS# 927673-86-7, 134 mg, 0.55 mmol, 1.1 eq.), and the corresponding base (3.0 eq.) were dissolved in DMF (2.8 mL). Later on, the corresponding palladium precursor (0.01 eq.) and ligand (0.024 eq.) were added. The reaction mixture was stirred at 100 °C for 3 hours.

[0300] The reaction was cooled to r.t., filtered over Celite and washed with acetonitrile. The volatiles were evaporated under reduced pressure. The crude residue was purified under column chromatography on SiO_2 using eluent $CHCl_3$ /acetone (70/30) and then $CHCl_3$ /MeOH (96/4) to yield Compound 1.

3.3. Palladium precursor screening

[0301] Different Palladium (Pd) precursors were tested under the reaction conditions describe above (Section 3.2) using Cs_2CO_3 as a base and JosiPhos as a ligand, and the results are presented in the following Table II.

Table II. Pd precursor screening

#	Pd precursor	Conversion of Int 3	Selectivity towards Compound 1	Yield %
1	Pd(π -cinnamyl)Cl dimer	100.0	92.4	92.1
2	Pd(π -cinnamyl)Cl dimer	100.0	93.2	92.4
3	Pd(OAc) ₂	100.0	62.6	57.6
4	Pd(Cl) ₂	90.1	79.3	62.5
5	Pd ₂ (dba) ₃	100.0	91.5	91.0
6	Pd ₂ (dba) ₃	74.8	55.8	55.8
7	Pd(dba) ₂	98.5	91.0	89.9
8	Pd(PPh ₃) ₄	99.5	96.2	93.7
9	Pd(PPh ₃) ₂ Cl ₂	83.0	95.4	80.0
10	Pd(acac) ₂	85.6	97.3	84.7
11	Pd(PhCN) ₂ Cl ₂	85.6	98.2	89.1
12	[Pd(allyl)Cl] ₂	99.0	78.3	78.3
13	Pd[P(o-tolyl) ₃] ₂ Cl ₂	80.9	96.6	80.7
14	Pd[P(o-tolyl) ₃] ₂	93.8	70.7	70.7

3.4. Base screening

[0302] Different bases were tested under the reaction conditions describe above (Section 2.2.) using Pd(π -cinnamyl) chloride dimer as a Pd precursor and JosiPhos as a ligand, and the results are presented in the following Table III.

Table III. Base screening

#	Base	Conversion of Int 3	Selectivity towards Cpd 1	Yield %
1	KOtBu	60.4	6.5	4.0
2	K ₂ CO ₃	40.7	96.3	39.2
3	KOH	100.0	0.0	0.0
4	DABCO	28.5	95.4	27.2
5	DBU	47.4	99.4	47.2
6	NaOtBu	90.5	40.3	36.5
7	CS ₂ CO ₃	94.1	92.8	87.3
8	Li ₂ CO ₃	23.8	92.2	22.0
9	Na ₂ CO ₃	27.4	86.5	23.7
10	DMAP	34.1	70.8	24.1
11	NaHMDS	99.8	9.3	9.2
12	NEt ₃	32.7	96.2	31.4

3.5. Ligand screening

[0303] Different ligands were tested under the standard reaction conditions and the results were summarized in the Table V.

[0304] All the ligands used in this study are commercially available and the following abbreviations were used to identify them.

Table IV. Ligand identification

Code	CAS#	Name
JosiPhos	158923-11-6	(R)-1-[(Sp)-2-(dicyclohexylphosphino)ferrocenyl] ethyldi-tert-butylphosphine
L1	224311-51-7	(2-biphenyl)di-tert-butylphosphine
L2	98327-87-8	($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
L3	97239-80-0	1,1'-bis-(diisopropylphosphino)ferrocene
L4	312959-24-3	1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)ferrocene
L5	4731-65-1	tris(o-methoxyphenyl)phosphine
L6	870703-48-3	dicyclohexyl(2,4,6-trimethylphenyl)phosphine
L7	857356-94-6	di-tert-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphine
L8	932710-63-9	4-(N,N-dimethylamino)phenyl)di-tert-butyl phosphine

L9	1160861-53-9	2-(di-tert-butylphosphino)-2',4',6'- triisopropyl-3,6-dimethoxy-1,1'-biphenyl
L10	1160556-64-8	2-Dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl
L11	185449-80-3	(S)-N,N-dimethyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine
L12	247940-06-3	2-(dicyclohexylphosphino)biphenyl
L13	657408-07-6	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
L14	213697-53-1	2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
L15	564483-18-7	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
L16	31570-04-4	tris(2,4-di-tert-butylphenyl)phosphite
L17	116-17-6	tri(isopropyl)phosphite
L18	1237588-12-3	Di(1-adamantyl)-2-morpholinophenylphosphine
L19	6737-42-4	1,3-bis(diphenylphosphino)propane
L20	121954-50-5	1,2-bis[(di-tert-butylphosphino)methyl]benzene
L21	76189-56-5	(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene
L22	672937-61-0	2-(di-tert-butylphosphino)-1-phenyl-1H-pyrrole
L23	1053658-91-5	2-(di-tert-butylphosphino)-1-(2-methoxyphenyl)-1H-pyrrole

[0305] The results of the screening study are summarized in the following:

Table V. Ligand screening

#	Ligand	Yield %
1	JosiPhos	85.4
2	JosiPhos	85.8
3	L1	9.3
4	L2	3.0
5	L3	8.7
6	L4	0.6
7	L5	0
8	L6	0.4
9	L7	0.8
10	L8	0
11	L9	2.1
12	L10	10.6
13	L11	0.3
14	L12	0.9
15	L13	5.1

#	Ligand	Yield %
16	L14	1.3
17	L15	0.2
18	L16	0.3
19	L17	3.5
20	L18	28.4
21	L19	0.0
22	L20	0.8
23	L21	9.2
24	L22	2.1
25	L23	4.4

[0306] As shown in the Table V, the ligand JosiPhos (row # 1 and 2) revealed the highest yield.

Example 4. Preparation of the salts of Compound 1.

4.1. Aim of the study

[0307] This study evaluates the formation of pharmaceutically acceptable salts comprising Compound 1 and an acid. Salt formation was evaluated using 3 different solvents and 21 different acids.

[0308] The acids tested in this study are selected from hydrochloric acid, sulfuric acid, ethane-1,2-disulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, benzenesulfonic acid, maleic acid, phosphoric acid, ethanesulfonic acid, L-glutamic acid, malonic acid, gentisic acid, fumaric acid, D-glucuronic acid, L-malic acid, gluconic acid, benzoic acid, succinic acid, glutaric acid and acetic acid.

4.2. General information

[0309] The selection of acids was based on the ΔpK_a between Compound 1 and the corresponding acid or counter ion. Preferable, the ΔpK_a between Compound 1 and the acid is more than 1 pKa unit.

[0310] Compound 1 has three potential ionization centers, therefore the three different pKa values for Compound 1 were determined as 6.0, 4.3 and -1.0.

[0311] The solvents used for the evaluation for salt formation were acetone, ethanol and THF.

[0312] Different stoichiometric ratios between Compound 1 and the corresponding acid were tested. Preferably the stoichiometric ratios used in this experiment were 2:1, 1:1, 1:2 and 1:3 (Compound 1:acid ratio).

4.3. General protocol for the salt formation.

[0313] A stoichiometric amount of the corresponding acid was added to a suspension of Compound 1 (approximately 17 mg) in the selected solvents targeting concentrations from about 17 mg/mL to about 34 mg/mL. The suspensions were subjected to a thermo-cycling profile.

[0314] In all the experiments, solids were isolated from the solution by centrifugation and dried under vacuum (10 millibar). The mother liquors were also evaporated under vacuum. All the obtained dried solids were analyzed by High Throughput XRPD. Subsequently, the solids were exposed to accelerated aging conditions (AAC) at 40 °C and 75% relative humidity for 2 days and re-analyzed by HT-XRPD to verify their physical stability.

4.4. Results

[0315] Under the conditions described above, several pharmaceutically acceptable salts were isolated with 5 of the acids previously listed. The results are summarized in following Table VI:

Table VI. Isolated stable salts of Compound 1

Salt form #	Acid	Solvent	Cpd 1:acid ratio
1	HCl	acetone, EtOH, THF	1:2, 1:3
2	1,2-ethane disulfonic acid	acetone, THF	1:1
3	1,2-ethane disulfonic acid	ethanol	2:1
4	1,2-ethane disulfonic acid	acetone	1:2
5	methane sulfonic acid	acetone, EtOH, THF	1:1
6	benzene sulfonic acid	acetone, THF, EtOH	1:1
7	ethanesulfonic acid	acetone, EtOH	1:1

4.4.1. HCl salt of Compound 1

[0316] HCl salt was obtained from the salt formation experiments described above with two molar equivalents of hydrochloric acid in EtOH as a solvent.

[0317] The ¹H-NMR spectrum of the HCl salt showed changes in the chemical shifts compared to Compound 1 as free base form. The chemical shift observed in FIGURE 1B at 9.8 ppm corresponding to the N-H bond suggests the salt formation.

[0318] The ¹H-NMR spectrum of the HCl salt of Compound 1 is shown in FIGURE 1A.

[0319] The DSC curve of the HCl salt of Compound 1 is shown in FIGURE 1D.

[0320] The TGA curve of the HCl salt of Compound 1 is shown in FIGURE 1E.

[0321] The DVS curve of the HCl salt of Compound 1 is shown in FIGURE 1F.

[0322] The HCl salt of Compound 1 XRPD pattern is shown in FIGURE 1C.

Table VII. HCl salt of Compound 1 peak table

Position [°2θ]	Rel. Int. [%]
4.8	87
6.0	87
7.6	100
8.7	16
9.2	13
9.7	69
11.7	46
11.9	28
12.3	20
14.2	32
14.5	18
15.0	37
16.4	11
18.0	37
19.2	16
21.4	12
22.5	30
23.6	38
24.1	52
25.8	64

4.4.2. Mesylate salt of Compound 1 or methanesulfonic acid derivative of Compound 1

[0323] Mesylate salt was obtained from the salt formation experiments described above with 1 molar equivalent of methanesulfonic acid in acetone as a solvent.

[0324] The ¹H-NMR spectrum of the mesylate salt of Compound 1 is shown in FIGURE 2A.

[0325] The ¹H-NMR spectrum of the mesylate salt showed changes in the chemical shifts compared to Compound 1 as free base form. The chemical shift observed in FIGURE 2B suggests the formation of the salt.

[0326] Mesylate salt of Compound 1 HR-XRPD pattern is shown in FIGURE 2C.

[0327] The DSC curve of the mesylate salt of Compound 1 is shown in FIGURE 2D.

[0328] The TGA curve of the mesylate salt of Compound 1 is shown in FIGURE 2E.

[0329] The DVS curve of the mesylate salt of Compound 1 is shown in FIGURE 2F.

Table VIII. Mesylate salt of Compound 1 peak table

Position [°2θ]	Rel. Int. [%]
8.5	28
9.3	12
9.8	12
11.3	12
12.1	12
15.1	13
15.2	41
16.7	39
17.0	10
17.2	10
17.5	11
17.7	11
18.7	12
20.4	30
22.1	9
22.5	10
22.6	15
25.3	100

Position [°2 θ]	Rel. Int. [%]
25.6	8
26.2	8

Example 5. Preparation of cocrystal forms of Compound 1.

5.1. Aim of the study

[0330] This study evaluates the formation of cocrystal forms comprising Compound 1 and a co-former. Cocrystal formation was evaluated in 3 solvents using 14 different co-formers. The co-formers tested in this study were selected from maleic acid, phosphoric acid, fumaric acid, salicylic acid, L-tartaric acid, citric acid, L-malic acid, L-ascorbic acid, succinic acid, nicotinic acid, caffeine, saccharine, meglumine and sorbitol.

5.2. General information

[0331] The solvents used for the evaluation for cocrystal formation were DCM, methyl ethyl ketone, MeOH, THF, isopropyl acetate.

[0332] Different stoichiometric ratios between Compound 1 and the corresponding co-former were tested. Preferably the stoichiometric ratios used in this experiment were 2:1, 1:1 and 1:2 (Compound 1:co-former).

5.3. Experimental protocol for the cocrystal formation.

[0001] Different types of experiments were conducted for the cocrystal formation, including:

- Solvent equilibration (i.e. slurries)
- Grinding or solvent drop grinding
- Evaporation
- Temperature cycling

5.3.1. Solvent equilibration technique

[0333] Compound 1 as free base (0.1 mmol, 46.0±1.0 mg, corrected for TGA weight loss) was suspended at 20/40 °C for 10-15 min in the corresponding solvent selected from DCM (1 mL), THF (1 mL), methyl ethyl ketone (3 mL) and methanol (3 mL). Then, the corresponding coformer (0.1 mmol) was added as solid. The suspension was stirred at 20/40 °C for 2 days. The resulting solids were isolated by filtration or centrifugation then dried under vacuum at r.t. for almost 2 h.

5.3.2. Drop grinding technique

[0002] Compound 1 as free base and the corresponding coformer were ground in a mortar with a pestle by adding methyl ethyl ketone (100-200 μ L) as a solvent.

5.3.3. Evaporation technique

[0334] Compound 1 as free base was dissolved in 10 mL of DCM or THF and stirred for 30 min. The corresponding coformer was also dissolved in DCM or THF (2.0 - 2.5 mL) or water (60 - 120 μ L), stirred

for 10 mins and then the resulting solution was added to the solution containing Compound 1. Then, the samples were evaporated under low nitrogen flow.

5.3.4. Temperature cycling technique

[0335] The amorphous samples obtained from the evaporation technique (described in the section 5.3.3) were submitted to the following temperature cycling: 4 cycles 20 – 40 °C, with 2 h of stirring at each temperature.

5.3.5. Results

[0336] Following the different techniques described above, the following cocrystal forms were isolated.

Table IX. Isolated stable cocrystal forms of Compound 1

Cocrystal form #	Acid	Cpd 1:acid ratio
I	maleic acid	NA
IIA	phosphoric acid	1:1
IIB	phosphoric acid	1:2
III	fumaric acid	1:1
IV	L-tartaric acid	1:1
V	L-malic acid	2:1
VI	saccharine	1:1

5.3.6. Maleate cocrystal form of Compound 1 or cocrystal form I

[0337] The cocrystal form I was obtained from the formation experiments described above with two molar equivalents of maleic acid in THF as a solvent.

[0338] The ¹H-NMR spectrum of the maleate cocrystal form of Compound 1 is shown in FIGURE 3A.

[0339] The ¹H-NMR spectrum of the maleate cocrystal form of Compound 1 (red in FIGURE 3B) showed no changes in the chemical shifts compared to Compound 1 free base (green in FIGURE 3B).

[0340] The DSC curve of the maleate cocrystal form of Compound 1 is shown in FIGURE 3C.

5.3.7. Phosphate cocrystal forms of Compound 1 or cocrystal forms II

[0341] Two different phosphate cocrystal forms of Compound 1 with different stoichiometries were identified. A mono-phosphate cocrystal form (phosphate cocrystal form A of Compound 1) was obtained using equimolar amount of phosphoric acid, and a di-phosphate cocrystal form (phosphate cocrystal form B of Compound 1) was obtained using two molar equivalents of phosphoric acid.

5.3.7.1. *Phosphate cocrystal form A of Compound 1 or cocrystal form IIA*

[0342] The ^1H -NMR spectrum of phosphate cocrystal form A showed no changes in the chemical shifts compared to Compound 1 free base.

[0343] The stoichiometry of the phosphoric acid and Compound 1 was analyzed by HPLC.

[0344] The ^1H -NMR spectrum of the phosphate cocrystal form A of Compound 1 is shown in FIGURE 4A.

[0345] The DSC curve of the phosphate cocrystal form A form of Compound 1 is shown in FIGURE 4B.

[0346] The TGA curve of the phosphate cocrystal form A form of Compound 1 is shown in FIGURE 4C.

[0347] The DVS curve of the phosphate cocrystal form A form of Compound 1 is shown in FIGURE 4D.

[0348] Phosphate cocrystal form A of Compound 1 XRPD pattern is shown in FIGURE 4E.

[0349] Phosphate cocrystal form A of Compound 1 XRPD show the following peak pattern:

Table X. Phosphate cocrystal form A form of Compound 1 peak table

Position [2θ]	Rel. Int. [%]
4.2	83
4.6	11
6.4	11
7.7	31
8.4	46
10.2	25
12.5	28
12.8	100
13.9	28
15.6	38
16.8	25
17.5	44
18.6	43
19.3	19
20.4	20
22.1	29
22.9	43
24.1	42

Position [°2θ]	Rel. Int. [%]
24.8	76
25.1	66

5.3.7.2. Phosphate cocrystal form B of Compound 1 or cocrystal form IIB

[0350] Phosphate cocrystal form B of Compound 1 was obtained as pure crystalline phase in a single salt formation experiment performed with two-molar equivalent of phosphoric acid in acetone.

[0351] The ¹H-NMR spectrum of phosphate cocrystal form B of Compound 1 showed no changes in the chemical shifts compared to Compound 1 free base.

[0352] The ¹H-NMR spectrum of the phosphate cocrystal form B of Compound 1 is shown in FIGURE 5A.

[0353] The DSC curve of the phosphate cocrystal form B form of Compound 1 is shown in FIGURE 5B.

[0354] The TGA curve of the phosphate cocrystal form B form of Compound 1 is shown in FIGURE 5C.

5.3.8. Fumarate cocrystal form of Compound 1 or cocrystal form III

[0355] Fumarate cocrystal form of Compound 1 was obtained from the formation experiments described above with one molar equivalents of fumaric acid using acetone, ethanol or THF as a solvent.

[0356] The ¹H-NMR spectrum of the fumarate cocrystal form of Compound 1 is shown in FIGURE 6A.

[0357] The ¹H-NMR spectrum of the fumarate cocrystal form of Compound 1 (red in FIGURE 6B) showed no changes in the chemical shifts compared to Compound 1 free base (green in FIGURE 6B).

[0358] The fumarate cocrystal form of Compound 1 XRPD pattern is shown in FIGURE 6C.

[0359] The DSC curve of the fumarate cocrystal form of Compound 1 is shown in FIGURE 6D.

[0360] The TGA curve of the fumarate cocrystal form of Compound 1 is shown in FIGURE 6E.

[0361] The DVS curve of the fumarate cocrystal form of Compound 1 is shown in FIGURE 6F.

Table XI. Fumarate cocrystal form of Compound 1 peak table

Position [°2θ]	Rel. Int. [%]
3.4	19
6.8	23
7.1	79
8.6	51
11.0	16
12.4	64
13.8	100
14.3	53

Position [°2θ]	Rel. Int. [%]
14.8	45
15.5	10
17.1	8
18.3	28
20.5	21
20.8	15
21.2	10
22.4	10
22.9	14
23.9	18
24.9	64
25.6	46
26.5	14

5.3.1. L-tartrate cocrystal form of Compound 1 or cocrystal form IV

[0362] L-tartrate cocrystal form of Compound 1 was obtained from the formation experiments described above with one molar equivalent of the corresponding acid.

[0363] The ¹H-NMR spectrum of the L-tartrate cocrystal form of Compound 1 showed no changes in the chemical shifts compared to Compound 1 free base. The ¹H-NMR spectrum of the L-tartrate cocrystal form of Compound 1 is shown in FIGURE 7D.

[0364] The DSC-TGA curve of the L-tartrate cocrystal form of Compound 1 is shown in FIGURE 7A.

[0365] The DVS curve of the L-tartrate cocrystal form of Compound 1 is shown in FIGURE 7B.

[0366] L-tartrate cocrystal form of Compound 1 XRPD show the following peak pattern:

Table XII. L-tartrate cocrystal form of Compound 1 peak table

Position [°2θ]	Rel. Int. [%]
3.7	60
7.5	100
7.8	33
8.2	3

Position [°2θ]	Rel. Int. [%]
10.2	7
10.6	1
13.2	39
14.2	22
15.0	6
15.3	1
15.6	21
16.6	27
17.4	8
17.7	14
19.0	18
19.1	14
20.4	11
20.8	4
22.7	16
23.4	13
23.7	13
24.4	15
26.2	10
27.2	8
29.3	4
32.6	4

5.3.2. *L-malate cocrystal form of Compound 1 or cocrystal form V*

[0367] L-malate cocrystal form of Compound 1 was obtained from the formation experiments described above with 0.5 molar equivalents of L-malic acid using THF as a solvent.

[0368] The ¹H-NMR spectrum of L-malate cocrystal form of Compound 1 showed no changes in the chemical shifts compared to the free base of Compound 1. The ¹H-NMR spectrum of L-malate cocrystal form of Compound 1 is shown in FIGURE 8D.

[0369] The DSC-TGA curve of L-malate cocrystal form of Compound 1 is shown in FIGURE 8A.

[0370] The DVS curve of L-malate cocrystal form of Compound 1 is shown in FIGURE 8B.

[0371] L-malate cocrystal form of Compound 1 XRPD show the following peak pattern:

Table XIII. L-malate cocrystal form of Compound 1 peak table

Position [°2θ]	Rel. Int. [%]
6.3	100
9.0	1
10.6	46
11.1	5
12.6	10
12.9	4
13.9	2
14.0	4
15.0	15
15.9	11
16.2	26
16.6	7
16.8	5
17.0	12
17.9	7
18.3	4
18.7	1
19.4	3
20.4	8
20.7	10
21.1	8
21.2	6
21.6	11
22.2	7
22.3	9

Position [°2 θ]	Rel. Int. [%]
22.6	5
23.3	7
24.0	6
24.8	3
25.4	2
25.9	29
26.4	28
26.6	8
27.3	4
28.0	2
28.3	2
29.7	12
30.2	1
30.8	1
31.2	1
31.6	1
32.1	2
33.8	1
34.5	2
35.1	1
37.1	1
38.4	1
39.9	1
41.5	1
43.2	1

5.3.3. Saccharinate cocrystal form of Compound 1 or cocrystal form VI

[0372] Saccharinate cocrystal form was obtained from the formation experiments described above with 1 molar equivalent of saccharine.

[0373] The ^1H -NMR spectrum of saccharinate cocrystal form of Compound 1 showed no changes in the chemical shifts compared to the free base of Compound 1. The ^1H -NMR spectrum of saccharinate cocrystal form of Compound 1 is shown in FIGURE 9D.

[0374] The DSC-TGA curve of saccharinate cocrystal form of Compound 1 is shown in FIGURE 9A.

[0375] The DVS curve of saccharinate cocrystal form of Compound 1 is shown in FIGURE 9B.

[0376] Saccharinate cocrystal form of Compound 1 XRPD shows the following peak pattern:

Table XIV. Saccharinate cocrystal form of Compound 1 peak table

Position [$^{\circ}2\theta$]	Rel. Int. [%]
5.6	60
6.5	100
9.0	2
9.8	7
11.1	15
11.3	42
12.4	9
13.0	59
13.9	4
14.7	6
15.0	27
15.6	16
15.8	24
16.4	12
16.7	13
17.0	6
17.9	14
18.5	15
19.2	6
19.4	7
19.7	10
20.0	15

Position [°2 θ]	Rel. Int. [%]
20.5	5
20.8	9
21.3	11
21.6	3
22.4	14
23.9	4
24.8	7
25.5	7
26.1	41
27.0	7
27.4	69
27.9	8
29.5	1
30.3	2
31.3	2
32.0	2
32.7	2
33.6	3
36.3	1
36.9	1
38.2	1
42.2	1

[0377] Study apparatus

high resolution, high throughput x-ray powder diffraction (HR-XRPD)	Data were collected in transmission mode on a Panalytical X'pert Pro instrument (PANalytical B.V., Almelo, Netherlands) with X'celerator detector. Detector scan was performed using 0.017° per step with 60.7 sec/step scan speed. The generator was operated at a voltage of 40 kV and amperage of 40 mA. The data were evaluated using the HighScore Plus software. Data collection was carried out at room temperature and ambient humidity using Cu Kα1 radiation (1.54056 Å) between 2° and 45° 2θ. Alternatively, data were collected on a D8 Advance diffractometer using Cu Kα1 radiation (1.54056 Å) with germanium monochromator at room temperature. The data were collected from 3° to 41.5° 2θ. Detector scan on solid state LynxEye detector was performed using 0.014° per step with 10 sec/step scan speed. The sample was measured in 8 mm long glass capillary with 0.3 mm outer diameter Alternatively, XRPD patterns were obtained using a SSR T2 high-throughput XRPD equipment. The plates were mounted on a Bruker General Area Detector Diffraction System (GADDS) equipped with a VÅNTEC-500 gas area detector corrected for intensity and geometric variations. The calibration of the measurement accuracy (peaks position) was performed using NIST SRM1976 standard (Corundum). Data collection was carried out at room temperature using monochromatic CuKα radiation in the 2Å region between 1.5° and 41.5° 2θ. The diffraction pattern of each well was collected in two 2θ ranges (1.5° ≤ 2θ ≤ 21.5° for the first frame, and 19.5° ≤ 2θ ≤ 41.5° for the second) with an exposure time of 90s for each frame.
TGA	Thermal analyses were recorded on a TGA/SDTA 851e instrument (Mettler-Toledo GmbH, Switzerland), which resulted in a weight versus temperature curve. The TGA/SDTA 851e was calibrated with samples of indium and aluminum. Samples were weighed into 100 µL aluminum crucibles and sealed. The seals were pin-holed, and the crucibles heated in the TGA from 25 to 300°C at a heating rate of 10°C/min. Dry N₂ gas was used for purging. The gases coming from the TGA samples were analyzed by a mass spectrometer Omnistar GSD 301 T2 (Pfeiffer Vacuum GmbH, Germany). The latter is a quadrupole mass spectrometer, which analyzes masses in the range of 0-200 amu. Alternatively, TGA analyses were run on a TA Instruments' Q5000 equipment. 2mg to 20mg samples were weighed into aluminum crucibles and sealed before heating them in the TGA from room temperature to 350°C at a heating rate of 10°C/min. Dry N₂ gas was used for purging.
DVS	Moisture sorption isotherms were collected on a DVS-1 system from Surface Measurement Systems (London, United Kingdom). Sample size was circa 5 mg of solid material and maintained at 25 °C. After initial settling of the sample at 40% RH, a sorption and desorption isotherm were recorded by varying the relative humidity from 40 - 95 - 0 - 40 % (giving 1 complete cycle) in steps of 10 % at a constant temperature of 25 °C. Weight equilibration per step was set at 60 min. Alternatively, the DVS analyses were run on an IGA Sorp instrument (Hidden Isochema, United Kingdom). After initial settling of the sample at 50% RH, a sorption and desorption isotherm were recorded by varying the relative humidity from 50 - 90 - 0 - 90 % in steps of 10 % at a constant temperature of 25 °C.

Chemical Purity Determination by HPLC

Purity analysis was performed on an Agilent 1200 equipped with a diode array detector (DAD) set at 300 nm.

Sample preparation	0.2 mg/mL in Acetonitrile:Water:TFA (50:50:0.1 v/v/v)		
Column	Waters Sunfire C18 (100 x 4.6mm; 3.5µm)		
Column temperature (°C)	35		
Injection (µl)	5		
Flow rate (mL/min)	1.0		
Phase A	0.1% TFA in Water		
Phase B	0.1% TFA in Acetonitrile		
Gradient table	Time (min)	% Phase A	% Phase B
	0	90	10
	9	10	90
	10	90	10
	11	90	10

Alternatively, purity analysis was performed according to conditions presented in table below:

Column	Waters XBridge C18 (150 x 4.6mm; 3.5µm)		
Column temperature (°C)	55		
Injection (µl)	5		
Flow rate (mL/min)	1.5		
Phase A	0.1% TFA in Water		
Phase B	0.1% TFA in Acetonitrile		
Gradient table	Time (min)	% Phase A	% Phase B
	0	95	5
	2	95	5
	5	83	17
	6	83	17
	7	82	18
	8	82	18
	13	70	30
	18	70	30
	19	95	5
	22	95	5

Thermodynamic Aqueous Solubility by HPLC	The solubility was determined in water, SGF at pH 1.2 and SIF at pH 6.8. Suspensions prepared in the different media were incubated at 25°C for 2, 7 and 24 hours. The API concentration in solution was determined by HPLC using a calibration line made of G1256067 free base. Upon completion of the experiment, the final pH of each suspension was measured, and the residual solids were analyzed by HT-XRPD after drying under vacuum. Alternatively, the solubility profile in 4 bio-relevant media at 37°C was examined. pH solubility in H₂O, SGF, FeSSIF and FaSSIF was carried out at 2, 6 and 24 hrs at 37°C; the residues were isolated and checked by XRPD. Condition set-up: - H₂O - SGF at pH 1.6, - FeSSIF at pH 5.0, - FaSSIF at pH 6.5. - The saturated solutions were left under stirring at 37°C and tested after 2, 6 and 24 hours. The samples were prepared at a concentration of approx. 8 mg/mL. - pH of the solutions monitored at each time point for each condition. - At each test point 1 mL was taken and centrifuged at 14500 rpm for 10 minutes and an aliquot of supernatant was analyzed by HPLC method.
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Example 6. Preparation of solid forms of the fumarate cocrystal of Compound 1.

6.1. Aim of the study

[0378] The aim of this study was to investigate the existence of different solid forms of the fumarate cocrystal of Compound 1.

6.2. Solid forms of Compound 1

[0379] Compound 1 as a freebase exists in amorphous form and in two polymorphic forms: Form A, which is the polymorph of the hydrate of Compound 1, and Form C, which is the polymorph of anhydrous Compound 1.

[0380] The XRPD pattern of Form A (hydrate of Compound 1) is shown in FIGURE 10A.

[0381] Form A (hydrate of Compound 1) shows the following peak pattern:

Table XV. Form A (hydrate of Compound 1) peak table

Pos. [°2θ]	Rel. Int. [%]
5.4	36
5.9	22
7.4	21
9.1	100

Pos. [°2θ]	Rel. Int. [%]
9.9	20
10.8	2
11.8	21
12.7	31
14.0	12
14.9	69
15.4	19
16.3	42
17.7	4
18.3	23
19.2	6
19.9	6
20.3	9
21.2	3
22.6	8
23.7	23
24.7	20
25.7	22
26.5	18
27.7	8
29.0	5
29.7	4
31.0	3
34.7	1
37.1	1
38.7	1
40.1	1
43.3	3

[0382] The XRPD pattern of Form C (hydrate of Compound 1) is shown in FIGURE 10B.

[0383] Form C (anhydrous Compound 1) show the following peak pattern:

Table XVI. Form C (anhydrous Compound 1) peak table

Pos. [°2 θ]	Rel. Int. [%]
7.5	100
9.6	27
9.9	57
12.8	36
14.2	11
14.5	39
15.9	11
16.4	66
17.2	18
18.6	8
19.2	13
19.9	84
20.8	8
21.4	64
22.0	37
22.3	19
22.5	11
24.2	14
24.6	56
25.8	63
26.5	9
26.9	8
27.4	12
27.9	9
28.3	3
28.6	4
29.2	9
29.6	4
30.1	7
30.4	4
30.9	3
32.0	8
33.3	2
33.8	4
35.4	1
36.4	2

Pos. [°2 θ]	Rel. Int. [%]
37.1	2
38.1	3
38.7	4
39.5	2
42.3	2
42.9	2

6.3. Screen for different polymorphic forms of fumarate cocrystal of Compound 1

[0384] The solvents used for the evaluation of polymorphic forms of the fumarate cocrystal of Compound 1 are displayed in Table XVII below:

Table XVII. Solvents used in polymorph screen

Entry	Solvent	Bp (°C)	Temp range (°C)
1	NMP	202	5-70
2	DMSO	189	
3	DMSO/water aw 0.5	189	
4	DMA	165	
5	Anisole	153.8	
6	DMF	153	
7	xylenes	139	
8	Pyrimidine	123	
9	1-butanol	117	
10	MiBK	116	
11	pyridine	115	
12	Toluene	110.6	
13	Formic acid	100.8	
14	2-butanol	100	
15	Water	100	
16	Heptane	98.4	
17	IPA	82.5	
18	Acetonitrile	82	
19	Acetonitrile/water aw 0.8	82	
20	2-methyl THF	80.2	

Entry	Solvent	Bp (°C)	Temp range (°C)
21	MEK	79.6	
22	Ethanol	78.4	
23	Ethyl acetate	77.1	
24	THF	66	5-50
25	Methanol	64.7	
26	Methanol/water	64.7	
27	acetic acid	60.1	
28	Methyl acetate	57.1	
29	acetone	56	
30	Acetone/water	56	
31	MTBE	55.2	
32	DCM	39.6	5-30

6.4. Experimental protocols for investigation of polymorphic forms of fumarate cocrystal of Compound 1

[0385] Different types of techniques were conducted for the polymorph screen, including:

- Temperature cycle
- Solvent drop grinding
- Vapour diffusion (from amorphous material)
- Vapour diffusion (from mother liquors and anti-solvents)
- Anti-solvent additions
- Slow evaporation
- Crash cooling

6.4.1. Temperature cycle technique

[0386] The following steps were carried out for the polymorph screen on 32 selected solvents:

- Approximately 1920 mg of the fumarate cocrystal of Compound 1 (as Form III) was weighed out and dissolved in 384 mL of 1,4-dioxane:water (80:20 %v/v), with heating using a heat gun until a clear solution was obtained.
- The solution was pipetted into 20mL vials in 15.15 mL aliquots (5mg/mL).
- Every vial was placed in the freezer for 3 h and then the frozen samples were then placed into the freeze drier under vacuum for 72h.
- The solids from 1 representative vial were analyzed by XRPD and ¹H-NMR analysis to confirm amorphous form achieved.

- The appropriate volume of the appropriate solvent system was added to each of the freeze-dried samples to try and obtain slurries.
- For solvent systems which had boiling points $>70^{\circ}\text{C}$, the samples were then left to temperature cycle for 96h (2.5 cycles), between $5-70^{\circ}\text{C}$ at a ramp rate of $0.1^{\circ}\text{C}/\text{min}$ and a hold of 1h at both temperatures.
 - o The solids were then isolated from their slurries by centrifugation at 60°C and the solids were analyzed by XRPD.
 - o Some samples were clear solutions with solid crusts present, crusts were analyzed by XRPD.
 - o Some samples were dry solids due to evaporation of solvent and for these, an additional 2 mL solvent was added to each vial and left to stir at 40°C overnight before centrifugation and analysis by XRPD.
- For solvent systems which had boiling points $< 70^{\circ}\text{C}$, the samples were then left to temperature cycle for 96h (2.5 cycles), between $5-50^{\circ}\text{C}$ or $5-30^{\circ}\text{C}$ at a ramp rate of $0.1^{\circ}\text{C}/\text{min}$ and a hold of 1h at both temperatures.
 - o The solids were then isolated from their slurries by centrifugation at 50°C or 30°C and the solids were analyzed by XRPD.
 - o Some samples were clear solutions with solid crusts present, crusts were analyzed by XRPD.
 - o Some samples were dry solids due to evaporation of solvent and for these, an additional 2 mL solvent was added to each vial and left to stir at 40°C overnight before centrifugation and analysis by XRPD.
- All wet solids will be dried at 40°C under vacuum and will be reanalyzed by XRPD.
- The mother liquors were split up into 4×2 mL vials to be used for the mother liquor experiments: Vapour diffusion, slow evaporation, anti-solvent additions and crash cooling.

[0387] NB: isolation was performed at elevated temperature to maximize material recovery in saturated solutions.

6.4.2. Solvent drop technique

[0003] The following steps were carried out to explore a wider polymorphic landscape through the use of solvent drop grinding using amorphous material.

- 500mg of the fumarate cocrystal of Compound 1 (as Form III) was weighed out and transferred into a duran flask.
- 100mL of 1,4-dioxane:H₂O (80:20 % v/v) was added to the duran and dissolution was aided by using a heat gun.
 - o This solution was used for both the solvent drop grinding and vapour diffusion experiments.
- 2mL aliquots were pipetted into 2 mL bead mill vials.
- Samples were then placed into the freezer for 3h.

- The frozen samples were then placed into the freeze drier for 24h under vacuum.
 - o 1 representative vial was used for XRPD and ¹H NMR analysis of the freeze-dried material to confirm amorphous form achieved.
- 3 beads and 2 µL of the appropriate solvent system was then added to each vial containing 10mg of amorphous fumarate cocrystal of Compound 1.
- The samples were placed into the bead mill to mill for 1h.
- 10 × 90s with 10s intervals at speed of 5000rpm.
- Each sample was then analyzed by XRPD.
- All wet solids were dried at 40°C under vacuum and reanalyzed by XRPD.

6.4.3. *Vapour diffusion (from amorphous material) technique*

[0388] The following procedure was carried for the solvent vapour diffusion experiments from amorphous material:

- Using previously prepared amorphous material (according to temperature cycle or solvent drop techniques), 3 mL of the appropriate solvent systems were pipetted into 20 mL vials.
- Each sample of the amorphous material which were held in the 2 mL vials were uncapped and placed into the assigned 20 mL vial.
- The 20 mL vials were then capped, sealed with parafilm and will be left to diffuse at 20°C for 1 week, and then characterized.
- Any sample still containing amorphous material by XRPD, is placed into an oven at 40°C for 1 week to encourage diffusion
- All solids will be dried at 40°C under vacuum for 24h and will be re-analyzed by XRPD.

6.4.4. *Vapour diffusion (from mother liquors and anti-solvents) technique*

[0389] The following steps were carried out for the vapour diffusion of the mother liquors obtained from the above polymorph screen samples (temperature cycle or solvent drop technique) and their anti-solvents:

- 0.5 mL of filtered mother liquors were placed into 2 mL vials.
- 3 mL of appropriate anti-solvent was pipetted into 20 mL vials.
- The uncapped 2 mL vials were placed inside of the 20 mL vial which was capped and sealed with parafilm.
- These will be left for 1 week at 20 °C and then characterized.
- All wet solids will be dried at 40°C under vacuum for 24h and will be reanalyzed by XRPD.

6.4.5. *Anti-solvent additions technique*

[0390] The following steps were carried out for anti-solvent addition using the mother liquors obtained from the above polymorph screen samples (temperature cycle or solvent drop technique) and their anti-solvents:

- Approx. 0.5 mL of filtered mother liquors were placed into 2mL vials with stirrer bar, and vials were placed in a water bath at 40°C.

- 100 µL aliquots of the appropriate anti-solvent was added until either precipitation had taken place or until 1.5 mL had been added.
- The samples were then left to stir at 5°C for 72h.
- Samples which were found to be slurries were isolated by centrifuge and analyzed by XRPD.
- Samples which were clear solutions were placed into the freezer for 1 week.
- All wet solids will be dried at 40°C under vacuum for 24h and will be analyzed by XRPD.

6.4.6. *Slow evaporation technique*

[0391] The following steps were carried out to slowly evaporate the mother liquors obtained from the above polymorph screen samples (temperature cycle or solvent drop technique):

- 0.5 mL of filtered mother liquors were transferred into 2 mL vials.
- The vials were uncapped and left to evaporate for 1 week at 20 °C and then characterized.
- Any experiments which remain as clear solutions were allowed to evaporate at 40 °C for 1 week
- All wet solids were dried at 40°C under vacuum for 24h and reanalyzed by XRPD.

6.4.7. *Crash cooling technique*

[0392] The following steps were carried out to rapidly cool the mother liquors obtained from the above polymorph screen samples (temperature cycle or solvent drop technique) to encourage precipitation:

- 0.5 mL of filtered mother liquors were transferred into 2 mL vials.
- The vials were capped and placed into the freezer at -18 °C for 1 week, and then characterized.
- All wet solids will be dried at 40°C under vacuum for 24h and will be reanalyzed by XRPD.

6.4.8. *Results*

[0393] Following the different techniques described above, the solids forms were isolated and identified. In general, the solid form identified in the cocrystal screening with most solvents was the fumarate cocrystal form of Compound 1, i.e. the cocrystal form III (see 5.3.8 above), and possessing the XRPD pattern shown in FIGURE 6C and showing the peaks indicated in Table XI. However, in certain experiments with acetic acid a crystalline form of a solvate was observed, whilst in other experiments amorphous material was recovered, and in some other experiments using certain of the techniques a dissociation of the cocrystal occurred affording either polymorphic Form A or Form C of Compound 1 as free base or fumaric acid.

BIOLOGICAL EXAMPLES

Example 7. PK Dog study of fumarate cocrystal form of Compound 1

7.1.1. *Experimental set up*

[0394] The exposure of Compound 1 as free base was evaluated in beagle dogs in different pharmacokinetic studies (fasted and fed conditions).

[0395] Compound 1 as a free base form was administered orally as single dose up to 30 mg/kg as suspension in Solutol/MC 0.5% (2/98 v/v) and up to 100 mg/kg as an amorphous solid dispersion (ASD) powder dispersed in HPMC-acetate succinate as suspension in citrate buffer. Blood samples were collected over a 24-h period and plasma was analyzed.

[0396] Fumarate cocrystal form of Compound 1 was administered orally as single dose of 100 mg/kg as suspension in 5% HPMC in pharmacokinetic studies and at 12.5, 25 and 50 mg/kg in a chronic toxicity studies. Blood samples were collected over a 24-h period and plasma was analyzed.

7.1.2. Results

[0397] A higher rate of absorption (C_{max}) and extent of absorption (AUC) were observed with the fumarate co-crystal form compared with the free base form.

[0398] A summary of the pharmacokinetic parameters after single dose administration is provided in the following Table XVIII.

Table XVIII. Pharmacokinetic parameters after single oral administration to beagle dogs

Compound 1 / formulation	N	Sex	Dose (mg/kg)	Feeding condition	t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC _{0-t} ($\mu\text{g.h/mL}$)	C_{max}/Dose ($\mu\text{g/mL})/(\text{mg/kg})$	AUC _{0-t}/\text{Dose} ($\mu\text{g.h/mL})/(\text{mg/kg})$}
Free base / Solutol/MC0.5 %	3	M	5	Fasted	1	0.575	1.63	0.115	0.325
Free base / Solutol/MC0.5 %	3	M	30	Fasted	1	0.777	3.21	0.0259	0.107
Free base / Solutol/MC0.5 %	3	M	30	Fasted	1	0.814	5.56	0.0271	0.185
Free base / Solutol/MC0.5 %	3	M	30	Fed	3	1.12	8.76	0.0375	0.292
Free base / ASD in citrate buffer	3	M	10	Fasted	1	0.795	3.22	0.0795	0.322
Free base / ASD in citrate buffer	3	M	30	Fasted	2	1.45	7.28	0.0484	0.243
Free base / ASD in citrate buffer	3	M	100	Fasted	2	2.47	19.2	0.0247	0.192
Fumarate co-crystal/HPMC	3	M	100	Fed	2	7.46	103	0.746	1.03
Fumarate co-crystal/HPMC	3	M	12.5	Fed	1	1.32	5.71	0.106	0.457

Compound 1 / formulation	N	Sex	Dose (mg/kg)	Feeding condition	t _{max} (h)	C _{max} (µg/mL)	AUC _{0-t} (µg.h/mL)	C _{max} /Dose (µg/mL)/(mg/kg)	AUC _{0-t} /Dose (µg.h/mL) /(mg/kg)
Fumarate co-crystal/HPMC	3	F	12.5	Fed	1	1.22	5.64	0.0974	0.451
Fumarate co-crystal/HPMC	3	M	25	Fed	2	2.41	13.3	0.0963	0.532
Fumarate co-crystal/HPMC	3	F	25	Fed	2	1.98	11.7	0.0793	0.468
Fumarate co-crystal/HPMC	3	M	50	Fed	2	2.91	21.0	0.0582	0.420
Fumarate co-crystal/HPMC	3	F	50	Fed	2	2.91	18.0	0.0581	0.360
Fumarate co-crystal/HPMC	3	M	12.5	Fed	1	1.66	4.97	0.133	0.398
Fumarate co-crystal/HPMC	3	F	12.5	Fed	1	1.58	4.88	0.126	0.391
Fumarate co-crystal/HPMC	3	M	25	Fed	1	2.47	12.9	0.0988	0.514
Fumarate co-crystal/HPMC	3	F	25	Fed	1	3.34	10.8	0.134	0.434
Fumarate co-crystal/HPMC	3	M	50	Fed	1	3.93	19.9	0.0786	0.398
Fumarate co-crystal/HPMC	3	F	50	Fed	1	4.55	19.5	0.0910	0.391

AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max} = maximum plasma concentration; M = male; N = number of animals; t_{max} = time to maximum concentration.

Values are means, except median for t_{max}.

7.2. PK Dog study mesylate salt form of Compound 1 and HCl salt form of Compound 1

7.2.1. Experimental set up

[0399] The exposure of Compound 1 as free base was evaluated in beagle dogs in pharmacokinetic studies (fasted).

[0400] Compound 1 as a free base form was produced as a spray-dried powder following the protocol mentioned in the section 7.3.2.

[0401] Compound 1 free base as a spray-dried powder was administered orally as single dose of 30 or 100 mg/kg with a 20 wt% drug loading in cellulose acetate phthalate (CAP), and also with a 25 wt% drug loading in hydroxypropyl methylcellulose acetate succinate (HPMC-AS). Blood samples were collected over a 24-h period and plasma was analyzed.

[0402] Mesylate salt form of Compound 1 was administered orally as single dose of 30 or 100 mg/kg as suspension in 2% of HPMC and 0.5 % of Solutol in water. Blood samples were collected over a 24-h period and plasma was analyzed.

[0403] HCl salt form of Compound 1 was administered orally as single dose of 30 mg/kg as suspension in 2% of HPMC and 0.5 % of Solutol in water. Blood samples were collected over a 24-h period and plasma was analyzed.

7.2.2. Preparation of spray-dried powder of Compound 1

7.2.2.1. Spray dryer set up:

- Buchi B-290 mini-spray dryer with inert loop B-295 at -15 °C.
- Inlet temperature 110 °C.
- Aspirator rate: 100%.
- Nozzle type: twin fluid nozzle.
- Nozzle pressure: 50 psi.
- Feed rate: 10 mL/min.
- Spray solvent: DCM/ MeOH (3:1).
- Solution concentration: 10% w/w solids.
- Batch size: 52 g solids.

[0404] All formulations were dried in a vacuum oven for one night at 40 °C to minimize residual solvent content.

7.2.2.2. Protocol

[0405] The preparation of the Compound 1 free base as a spray dried powder was done by following this steps:

- Mixing and dissolving Compound 1 and cellulose acetate phthalate (CAP) (20% w/w of Compound 1 in CAP at 10% w/w solids concentration) in DCM/MeOH (3:1) to obtain a corresponding solution.
- Connecting the solution to the spray dryer and dry the particles using the appropriate settings.
- Transferring the spray-dried powder to a suitable dryer for post-drying in order to remove the remaining solvents, (e.g. overnight at 40 °C in a vacuum oven).
- Tightly packing the spray-dried powder to prevent exposure to moisture.
- Suspending the appropriate amount of spray dried powder in a citrate buffer to allow oral administration via gavage.

7.2.3. Results

[0406] A higher rate of absorption (C_{max}) and extent of absorption (AUC) were observed with the free base (as ASD) compared with the mesylate or HCl salt form of Compound 1.

[0407] A summary of the pharmacokinetic parameters after single dose administration is provided in the following Table XIX.

Table XIX. Pharmacokinetic parameters after single oral administration to beagle dogs

Compound 1 / formulation	N	Sex	Dose (mg/kg)	Feeding condition	t _{max} (h)	C _{max} (µg/mL)	AUC _{0-t} (µg.h/mL)	C _{max} /Dose (µg/mL)/(mg/kg)	AUC _{0-t} /Dose (µg.h/mL)/(mg/kg)
Free base / ASD "CAP"- in citrate buffer	3	M	30	Fasted	1	3.30	20.1	0.116	0.708
Free base / ASD "HPMC" in citrate buffer	3	M	30	Fasted	2	2.24	13.5	0.0774	0.466
Mesylate / HPMC/Solutol	3	M	30	Fasted	1	2.41	11.5	0.0806	0.384
HCl / HPMC/Solutol	3	M	30	Fasted	2	2.34	10.7	0.0779	0.356
Free base / ASD "CAP"- in citrate buffer	3	M	100	Fasted	2	8.15	65.3	0.0873	0.700
Mesylate / HPMC/Solutol	3	M	100	Fasted	1	4.70	18.2	0.0478	0.185

AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max} = maximum plasma concentration; M = male; N = number of animals; t_{max} = time to maximum concentration.

Values are means, except median for t_{max}.

FINAL REMARKS

[0408] It will be appreciated by those skilled in the art that the foregoing descriptions are exemplary and explanatory in nature and intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. All such modifications coming within the scope of the appended claims are intended to be included therein. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

[0409] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication is specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[0410] It should be understood that factors such as the differential cell penetration capacity of the various compounds can contribute to discrepancies between the activity of the compounds in the *in vitro* biochemical and cellular assays.

[0411] At least some of the chemical names of solid form of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing

this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

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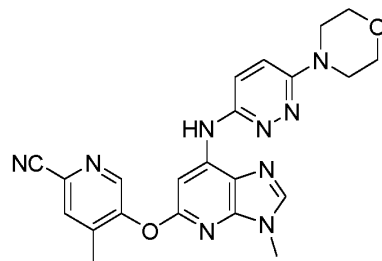
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CLAIMS

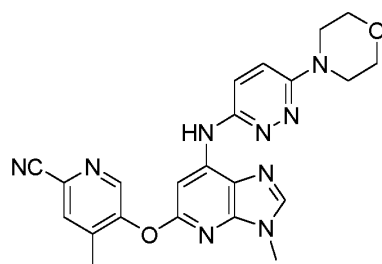
1. A pharmaceutical composition comprising Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl]amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile)



(Compound 1),

or a pharmaceutically acceptable solvate thereof, and fumaric acid.

2. A pharmaceutical composition according to claim 1, wherein Compound 1 and fumaric acid form a salt or a cocrystal, preferably a cocrystal.
3. A pharmaceutical composition according to claim 1 or 2, wherein Compound 1 and fumaric acid are present in an approximately 1:1 ratio.
4. A solid form of a fumarate cocrystal of Compound 1 (4-methyl-5-[3-methyl-7-[(6-morpholin-4-yl)pyridazin-3-yl]amino]imidazo[4,5-b]pyridin-5-yl]oxypyridine-2-carbonitrile):



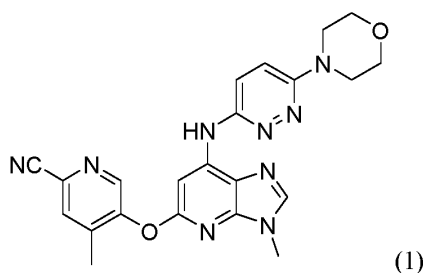
(Compound 1)

5. A solid form according to claim 4, characterized by an X-ray powder diffraction pattern having one or more peaks at the following positions: 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6, or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
6. A solid form according to claim 4 or 5, characterized by an X-ray powder diffraction pattern comprising at least three of the peaks at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
7. A solid form according to claim 4, 5 or 6, characterized by an X-ray powder diffraction pattern comprising at least four of the peaks at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
8. A solid form according to claim 4, 5, 6 or 7, characterized by an X-ray powder diffraction pattern comprising at least five of the peaks at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

9. A solid form according to claim 4, 5, 6, 7 or 8, characterized by an X-ray powder diffraction pattern comprising at least six of the peaks at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
10. A solid form according to claim 4, 5, 6, 7, 8 or 9, characterized by an X-ray powder diffraction pattern comprising peaks at 3.4, 7.1, 8.6, 12.4, 13.8, 14.3 and 14.8 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
11. A solid form according to claim 4, 5, 6, 7, 8, 9 or 10, which X-ray powder diffraction pattern is further comprising one or more peaks at the following positions: 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6, or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
12. A solid form according to claim 4, 5, 6, 7, 8, 9, 10 or 11, which X-ray powder diffraction pattern is further comprising at least three of the peaks at the following positions: 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6, or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
13. A solid form according to claim 4, 5, 6, 7, 8, 9, 10, 11 or 12, which X-ray powder diffraction pattern is further comprising at least five of the peaks at the following positions: 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6, or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
14. A solid form according to claim 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, which X-ray powder diffraction pattern is further comprising at least seven of the peaks at the following positions: 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6, or 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
15. A solid form according to claim 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14, characterized by an X-ray powder diffraction pattern comprising peaks at 3.4, 6.8, 7.1, 8.6, 11.0, 12.4, 13.8, 14.3, 14.8, 15.5, 17.1, 18.3, 20.5, 20.8, 21.2, 22.4, 22.9, 23.9, 24.9, 25.6, and 26.5 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
16. A solid form according to claim 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the solid form is a crystalline form.
17. A pharmaceutical composition comprising a solid form according to any of the claims 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, and a pharmaceutically acceptable carrier.
18. A pharmaceutical composition according to any one of claims 1, 2, 3 or 17, comprising a further therapeutic agent.
19. A pharmaceutical composition according to any one of claims 1, 2, 3, 17 or 18, or a solid form according to any of claims 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, for use in medicine.
20. A pharmaceutical composition according to any one of claims 1, 2, 3, 17 or 18, or a solid form according to any of claims 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, for use in the prophylaxis and/or treatment of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis,

Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease.

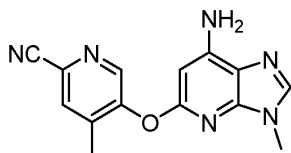
21. A method for the treatment and/or prophylaxis of allergic diseases, inflammatory diseases, metabolic diseases, autoinflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease, comprising administering to a patient a pharmaceutical composition according to any one of claims 1, 2, 3, 17 or 18, or a solid form according to any of claims 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16.
22. A pharmaceutical unit dosage composition comprising 70 mg to 300 mg of compound 1 as a fumarate cocrystal:



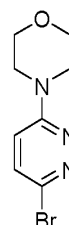
or a pharmaceutically acceptable solvate thereof, wherein the unit dosage form is suitable for oral administration up to a maximum total dosage of 300 mg of compound 1 per day.

23. The dosage form of claim 22 comprising from 75 mg to 300 mg of compound 1 in unit dosage form.
24. The dosage form according to claim 22 or 23 comprising from 75 mg, 90 mg, 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 225 mg, 250 mg or 300 mg of compound 1 in unit dosage form.
25. The dosage form according to claim 22 or 23 comprising 75 mg to 225 mg of compound 1 in unit dosage form.
26. The dosage form according to claim 22, 23, 24 or 25 comprising 150 mg of compound 1 in unit dosage form.
27. The dosage form according to claim 22, 23, 24, 25 or 26, wherein the unit dosage is in a form selected from a liquid, a tablet, a capsule, or a gelcap.
28. The dosage form according to claim 22, 23, 24, 25, 26 or 27, wherein the unit dosage is in the form of a tablet or capsule.
29. The dosage form according to claim 22, 23, 24, 25, 26, 27 or 28, wherein the unit dosage is in the form of a tablet.

30. The dosage form according to claim 22, 23, 24, 25, 26, 27, 28 or 29, for use in the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease.
31. The use of a dosage form according to claim 22, 23, 24, 25, 26, 27, 28 or 29, in the manufacture of a medicament for the treatment of an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease.
32. A method of treating an inflammatory disease and/or a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23, in particular a disease selected from systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, trisomy 21, ulcerative colitis and/or Crohn's disease, comprising administering to a patient a dosage form according to any one of claims 22, 23, 24, 25, 26, 27, 28 or 29.
33. A process for the manufacture of Compound 1 or a pharmaceutically acceptable salt thereof, comprising reacting Intermediate 3 and Intermediate 4, in the presence of a solvent, a base, a palladium precursor and a JosiPhos ligand:



Intermediate 3



Intermediate 4

34. A process according to claim 33, wherein the base is Cs₂CO₃.
35. A process according to claim 33 or 34, wherein the palladium precursor is Pd(π -cinnamyl)Cl dimer.
36. A process according to claim 33, 34 or 35, wherein the JosiPhos ligand is (R)-1-[(Sp)-2-(dicyclohexylphosphino)ferrocenyl]ethyl-di-tert-butylphosphine.
37. A process for the manufacture of a fumarate cocrystal form of Compound 1, comprising the following steps:
- suspending Compound 1 in a solvent, preferably at room temperature,

- ii. adding to the suspension at least one equivalent of fumaric acid,
 - iii. aging the reaction mixture, preferably at 25 °C for 72 hours,
 - iv. centrifugating the reaction mixture, and
 - v. drying the solid under vacuum, preferably for at least 12 hours at 30 °C.
38. A process for the manufacture of fumarate cocrystal form III, comprising the following steps:
- i) reacting Intermediate 3 and Intermediate 4, in the presence of a solvent, a base, a palladium precursor and JosiPhos as a ligand,
 - ii) isolating Compound 1 from the reaction mixture,
 - iii) suspending Compound 1 in a solvent, preferably at room temperature,
 - iv) adding to the suspension at least one equivalent of fumaric acid,
 - v) aging the reaction mixture, preferably at 25 °C for 72 hours,
 - vi) centrifugating the reaction mixture, and
 - vii) drying the solid under vacuum, preferably for at least 12 hours at 30 °C.
39. A process according to claim 38, wherein the base is Cs_2CO_3 .
40. A process according to claim 38 or 39, wherein palladium precursor is $\text{Pd}(\pi\text{-cinnamyl})\text{Cl}$ dimer.
41. A process according to claim 38, 39 or 40, wherein the JosiPhos ligand is (R)-1-[(Sp)-2-(dicyclohexylphosphino)ferrocenyl]ethyl-di-tert-butylphosphine.