

IMIDAZO[4,5-B]PYRIDINE DERIVATIVES USEFUL FOR THE TREATMENT OF ALLERGIC DISEASES, INFLAMMATORY DISEASES, METABOLIC DISEASES, AUTOINFLAMMATORY DISEASES, AUTOIMMUNE DISEASES AND PROLIFERATIVE DISEASES

FIELD OF THE INVENTION

[0001] The present invention relates to compounds which may be 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 compounds of the invention inhibit Janus kinases (JAKs), a family of tyrosine kinases, and more particularly TYK2. The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention, 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 the compounds of the invention.

BACKGROUND OF THE INVENTION

[0002] Janus kinases (JAKs) are cytoplasmic tyrosine kinases that transduce cytokine signalling 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 et al., 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 et al., 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, IL-12, IL-13, IL-19, IL-20, IL-22, IL-23, IL-27, IL-28, IL-29, IL-31, IL-35 and/or type 1 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).

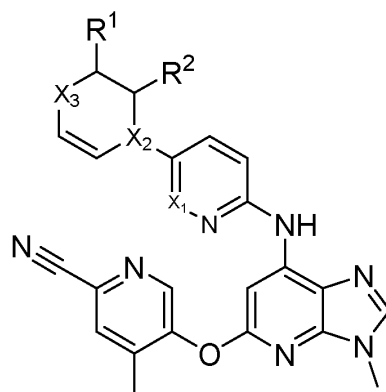
[0005] Furthermore, TYK2 has been reported as a target for multiple autoimmune disorders, providing protection against inflammatory diseases as well as type 2 diabetes with a limited impact on the immune system. (Dendrou et al., 2016)

[0006] Accordingly, there remains a need for new compounds which would effectively and selectively inhibit JAK enzymes, in particular TYK2, thus allowing the design of specific treatments and dosages tailored to the pathology.

SUMMARY OF THE INVENTION

[0007] The present invention relates to compounds 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 compounds of the invention inhibit JAKs, a family of tyrosine kinases, and more particularly TYK2. The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention, 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 the compounds of the invention.

[0008] Accordingly, in a first aspect of the invention, the compounds of the invention are provided having a Formula I:



I

wherein

X_1 and X_2 are independently N or CH;

X_3 is NR^3 , O, or $CR^{4a}R^{4b}$;

R^1 is H or $-CH_3$;

R^2 is H or $-CH_3$;

R^3 is H, or C_{1-2} alkyl unsubstituted or substituted with one or more halo; and

R^{4a} and R^{4b} are independently H, $-CN$, $-N(CH_3)_2$, or $-CH_2-OH$; or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof.

[0009] In a particular aspect, the compounds of the invention are provided 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 $IFN\alpha$, interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23.

[0010] Furthermore, it has also been unexpectedly demonstrated that the compounds of the invention exhibit improved selectivity towards TYK2 versus other JAK family members, which may be advantageous in the treatment of $IFN\alpha$, interferons (“interferonopathies”, especially type I or type III interferonopathies), IL-12 and/or IL-23 associated diseases, 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.

[0011] Moreover, the compounds of the invention and their TYK2 selectivity may be advantageous for the design of patient specific treatments and patient tailored dosages.

[0012] In a further aspect, the present invention provides pharmaceutical compositions comprising a compound 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 compounds 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, 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.

[0013] Moreover, the compounds of the invention, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0014] In a further aspect of the invention, this invention provides 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, , 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, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the invention as described herein.

[0015] The present invention also provides pharmaceutical compositions comprising a compound 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, 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.

[0016] In additional aspects, this invention provides methods for synthesizing the compounds of the invention, with representative synthetic protocols and pathways disclosed later on herein.

[0017] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0018] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0019] 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.

[0020] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. 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.

[0021] 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.

[0022] ‘Alkyl’ means straight or branched aliphatic hydrocarbon having the specified number of carbon atoms. Particular alkyl groups have 1 to 6 carbon atoms or 1 to 4 carbon atoms. Branched means that one or more alkyl groups such as methyl, ethyl or propyl is attached to a linear alkyl chain. Particular alkyl groups are methyl ($-\text{CH}_3$), ethyl ($-\text{CH}_2\text{CH}_3$), n-propyl ($-\text{CH}_2\text{CH}_2\text{CH}_3$), isopropyl ($-\text{CH}(\text{CH}_3)_2$), n-butyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), tert-butyl ($-\text{CH}_2\text{C}(\text{CH}_3)_3$), sec-butyl ($-\text{CH}_2\text{CH}(\text{CH}_3)_2$), n-pentyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), n-hexyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), and 1,2-dimethylbutyl ($-\text{CHCH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$). Particular alkyl groups have between 1 and 4 carbon atoms.

[0023] ‘Alkenyl’ refers to monovalent olefinically (unsaturated) hydrocarbon groups with the number of carbon atoms specified. Particular alkenyl has 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups include ethenyl ($-\text{CH}=\text{CH}_2$), n-propenyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), isopropenyl ($-\text{C}(\text{CH}_3)=\text{CH}_2$) and the like.

[0024] ‘Alkoxy’ refers to the group O-alkyl, where the alkyl group has the number of carbon atoms specified. In particular the term refers to the group $-\text{O}-\text{C}_{1-6}$ alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0025] ‘Aryl’ refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, monocyclic or fused polycyclic, with the number of ring atoms specified. Specifically, the term includes groups that include from 6 to 10 ring members. Particular aryl groups include phenyl, and naphthyl.

[0026] 'Halo' or 'halogen' refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

[0027] 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

[0028] As used herein, term 'substituted with one or more' refers to one to four substituents. In one embodiment it refers to one to three substituents. In further embodiments it refers to one or two substituents. In a yet further embodiment it refers to one substituent.

[0029] '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.

[0030] 'Pharmaceutically acceptable salt' refers to a salt of a compound 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.

[0031] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0032] 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention, which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the

invention which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0033] ‘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, EtOH, acetic acid and the like. The compounds 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.

[0034] ‘Subject’ includes humans. The terms ‘human’, ‘patient’ and ‘subject’ are used interchangeably herein.

[0035] ‘Effective amount’ means the amount of a compound 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.

[0036] ‘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).

[0037] 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.

[0038] ‘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.

[0039] 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.

[0040] 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.

[0041] 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 disease (*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 disease. More particularly the term refers to rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and inflammatory bowel disease. Most particularly the term refers to rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), and inflammatory bowel disease.

[0042] 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.

[0043] As used herein the term ‘autoinflammatory diseases(s)’ refers to the group of diseases including cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçet’s disease, systemic-onset juvenile idiopathic arthritis (SJIA), and Still’s disease.

[0044] 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 (CLE), lupus nephritis, dermatomyositis, Sjögren’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.

[0045] 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 thrombocythosis and myelofibrosis), leukemia (*e.g.* acute myeloid leukaemia, acute and chronic lymphoblastic leukemia), multiple myeloma, psoriasis, restenosis, scleroderma or fibrosis. In particular the term refers to cancer, leukemia, multiple myeloma and psoriasis.

[0046] 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 (metastasise) 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, leukaemia, 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, ependymoblastoma, 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.

[0047] 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 leukaemia (AML), and acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukaemia (CLL).

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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 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.

[0052] 'Compound(s) of the invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as herein described, which expression includes the pharmaceutically acceptable salts, and the solvates, *e.g.* hydrates, and the solvates of the pharmaceutically acceptable salts 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.

[0053] When ranges are referred to herein, for example but without limitation, C₁₋₈ alkyl, the citation of a range should be considered a representation of each member of said range.

[0054] Other derivatives of the compounds of this 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 compounds of this 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 compounds of the invention.

[0055] The present disclosure includes all isotopic forms of the compounds of the invention provided herein, 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.

[0056] 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.

[0057] 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 ¹¹C, ¹⁸F, ¹⁵O and ¹³N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0058] 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’.

[0059] 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'.

[0060] '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.

[0061] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0062] The compounds 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.

[0063] Unless indicated otherwise, the description or naming of a particular 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.

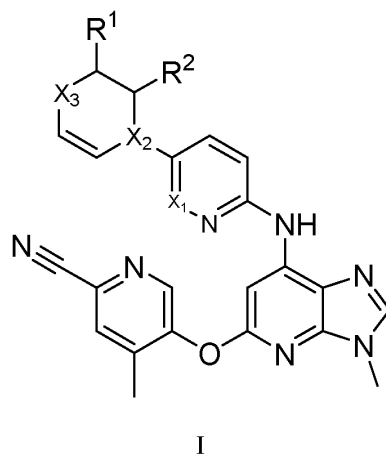
[0064] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

THE INVENTION

[0065] The present invention relates to compounds which may be 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, 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. In particular, the compounds of the invention inhibit JAKs, a family of tyrosine kinases, and more particularly TYK2. The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention, 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, 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, by administering the compounds of the invention.

[0066] Accordingly, in a first aspect of the invention, the compounds of the invention are provided having a Formula I:



wherein

X₁ and X₂ are independently N or CH;

X₃ is NR³, O, or CR^{4a}R^{4b};

R¹ is H or -CH₃;

R² is H or -CH₃;

R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more halogen atoms; and

R^{4a} and R^{4b} are independently H, -CN, -N(CH₃)₂, or -CH₂-OH; or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof.

[0067] Preferred values of R¹, R², R³, R^{4a}, R^{4b}, X₁, X₂, and X₃ are, in any combination thereof, as set out below.

[0068] Preferably X₁ is N.

[0069] Preferably X₂ is N.

[0070] Preferably X₃ is NR³ or O.

[0071] Most preferably X₃ is O.

[0072] Preferably R¹ is H.

[0073] Preferably R² is H.

[0074] Preferably R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more independently selected F, Cl, or Br.

[0075] More preferably R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more independently selected F or Cl.

[0076] Even more preferably R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more F.

- [0077] More preferably still R^3 is H, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CF_3$.
- [0078] Most preferably R^3 is H, $-CH_3$, or $-CH_2CF_3$.
- [0079] Preferably R^{4a} and R^{4b} are independently H, $-CN$, $-N(CH_3)_2$, or $-CH_2OH$.
- [0080] More preferably R^{4a} and R^{4b} are independently H, $-CN$, or $-N(CH_3)_2$.
- [0081] Even more preferably R^{4a} and R^{4b} are independently H or $-CN$.
- [0082] Most preferably R^{4a} is H and R^{4b} is $-CN$.
- [0083] Embodiments according to the invention are provided as set out below.
- [0084] Embodiment 1 provides compounds of Formula I, as defined above.
- [0085] Embodiment 2 provides compounds according to embodiment 1, wherein R^1 is H.
- [0086] Embodiment 3 provides compounds according to embodiment 1 or 2, wherein R^2 is H.
- [0087] Embodiment 4 provides compounds according to any one of embodiments 1 to 3, wherein X_1 is N.
- [0088] Embodiment 5 provides compounds according to any one of embodiments 1 to 4, wherein X_2 is N.
- [0089] Embodiment 6 provides compounds according to any one of embodiments 1 to 5, wherein R^{4a} and R^{4b} are independently H, $-CN$, $-N(CH_3)_2$, or $-CH_2OH$.
- [0090] Embodiment 7 provides compounds according to any one of embodiments 1 to 6, wherein R^{4a} and R^{4b} are independently H, $-CN$, or $-N(CH_3)_2$.
- [0091] Embodiment 8 provides compounds according to any one of embodiments 1 to 7, wherein R^{4a} and R^{4b} are independently H or $-CN$.
- [0092] Embodiment 9 provides compounds according to any one of embodiments 1 to 8, wherein R^{4a} is H and R^{4b} is $-CN$.
- [0093] Embodiment 10 provides compounds according to any one of embodiments 1 to 9, wherein X_3 is NR^3 or O.
- [0094] Embodiment 11 provides compounds according to any one of embodiments 1 to 10, wherein R^3 is H, or C_{1-2} alkyl unsubstituted or substituted with one or more independently selected F, Cl, or Br.
- [0095] Embodiment 12 provides compounds according to any one of embodiments 1 to 11, wherein R^3 is H, or C_{1-2} alkyl unsubstituted or substituted with one or more independently selected F or Cl.
- [0096] Embodiment 13 provides compounds according to any one of embodiments 1 to 12, wherein R^3 is H, or C_{1-2} alkyl unsubstituted or substituted with one or more F.
- [0097] Embodiment 14 provides compounds according to any one of embodiments 1 to 13, wherein R^3 is H, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CF_3$.
- [0098] Embodiment 15 provides compounds according to any one of embodiments 1 to 14, wherein R^3 is H, $-CH_3$, or $-CH_2CF_3$.
- [0099] Embodiment 16 provides compounds according to any one of embodiments 1 to 15, wherein X_3 is O.
- [0100] A preferred group of compounds according to the invention are those of formula I-1, which are compounds of formula I wherein X_1 is N or CH; X_2 is N; X_3 is NR^3 , O, or $CR^{4a}R^{4b}$; R^1 is H or $-CH_3$; R^2 is

H or -CH₃; R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more halo; and R^{4a} and R^{4b} are independently H, -CN, -N(CH₃)₂, or -CH₂-OH.

[0101] A further preferred group of compounds according to the invention are those of formula I-2, which are compounds of formula I wherein X₁ is N or CH; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H or -CH₃; R² is H; R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more halo; and R^{4a} and R^{4b} are independently H, -CN, -N(CH₃)₂, or -CH₂-OH.

[0102] A further preferred group of compounds according to the invention are those of formula I-3, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H or -CH₃; R² is H; R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more halo; and R^{4a} and R^{4b} are independently H, -CN, -N(CH₃)₂, or -CH₂-OH.

[0103] A further preferred group of compounds according to the invention are those of formula I-4, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H; R² is H; R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more halo; and R^{4a} and R^{4b} are independently H, -CN, -N(CH₃)₂, or -CH₂-OH.

[0104] A further preferred group of compounds according to the invention are those of formula I-5, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H; R² is H; R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more independently selected F, Cl, or Br; and R^{4a} and R^{4b} are independently H, -CN, -N(CH₃)₂, or -CH₂-OH.

[0105] A further preferred group of compounds according to the invention are those of formula I-6, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H; R² is H; R³ is H, or C₁₋₂ alkyl unsubstituted or substituted with one or more independently selected F or Cl; and R^{4a} and R^{4b} are independently H, -CN, or -N(CH₃)₂.

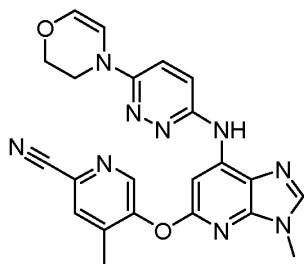
[0106] A further preferred group of compounds according to the invention are those of formula I-7, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H; R² is H; R³ is H, -CH₃, -CH₂CH₃, -CHF₂, -CF₃, -CH₂CHF₂, or -CH₂CF₃; and R^{4a} and R^{4b} are independently H or -CN.

[0107] A further preferred group of compounds according to the invention are those of formula I-8, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³, O, or CR^{4a}R^{4b}; R¹ is H; R² is H; R³ is H, -CH₃, or -CH₂CF₃; and R^{4a} is H and R^{4b} is -CN.

[0108] A further preferred group of compounds according to the invention are those of formula I-9, which are compounds of formula I wherein X₁ is N; X₂ is N; X₃ is NR³ or O; R¹ is H; R² is H; and R³ is H, -CH₃, or -CH₂CF₃.

[0109] In one embodiment, the compound of the invention is 5-(((7-((6-(2,3-dihydro-4H-1,4-oxazin-4-yl)pyridazin-3-yl)amino)-3-methyl-3H-imidazo[4,5-b]pyridin-5-yl)oxy)-4-methylpicolinonitrile.

[0110] In one embodiment, the compound of the invention is



[0111] In one embodiment, the compounds of the invention are provided in a natural isotopic form.

[0112] In one embodiment, the compounds of the invention are provided 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 of the invention. In one embodiment, the atoms of the compounds of the invention are in an isotopic form which is not radioactive. In one embodiment, one or more atoms of the compounds of the invention 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.

[0113] In one embodiment, a compound of the invention is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, a compound of the invention is provided whereby two or more atoms exist in an unnatural variant isotopic form.

[0114] 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.

[0115] In one embodiment a compound of the invention is not an isotopic variant.

[0116] In one aspect a compound of the invention according to any one of the embodiments herein described is present as the free base.

[0117] In one aspect a compound of the invention according to any one of the embodiments herein described is a pharmaceutically acceptable salt.

[0118] In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of the compound.

[0119] In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of a pharmaceutically acceptable salt of a compound.

[0120] While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

[0121] While specified groups for each embodiment have generally been listed above separately, a compound of the invention may be one for which one or more variables (for example, R groups) is selected

from one or more embodiments according to any of the Formula(e) listed above. Therefore, the present invention is intended to include all combinations of variables from any of the disclosed embodiments within its scope.

[0122] Alternatively, the exclusion of one or more of the specified variables from a group or an embodiment, or combinations thereof is also contemplated by the present invention.

[0123] In certain aspects, the present invention provides prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0124] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but 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 compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly useful are the C₁ to C₈ alkyl, C₂-C₈ alkenyl, aryl, C₇-C₁₂ substituted aryl, and C₇-C₁₂ arylalkyl esters of the compounds of the invention.

PHARMACEUTICAL COMPOSITIONS

Formulation 1 - Tablets

[0125] A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 240-270 mg tablets (80-90 mg of active compound of the invention according to Formula I per tablet) in a tablet press.

Formulation 2 - Capsules

[0126] A compound of the invention according to Formula I 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 active compound of the invention according to Formula I per capsule).

Formulation 3 - Liquid

[0127] A compound of the invention according to Formula I (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

[0128] A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 450-900 mg tablets (150-300 mg of active compound of the invention according to Formula I) in a tablet press.

Formulation 5 - Injection

[0129] A compound of the invention according to Formula I may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[0130] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of A compound of the invention according to Formula I (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) may be added and the resulting mixture may be stirred until it congeals.

[0131] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent.

[0132] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein 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. In a more particular embodiment, the other therapeutic agent is an inflammatory diseases, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, 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.

[0133] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is an allergic diseases treatment agent. In a particular embodiment, the other therapeutic agent is an asthma treatment agent.

[0134] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is inflammatory diseases treatment agent. In a particular embodiment, the other therapeutic agent is a rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and/or inflammatory bowel disease treatment agent. In a more particular embodiment, the other therapeutic agent is a rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), and/or inflammatory bowel disease treatment agent.

[0135] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is metabolic

diseases treatment agent. In a particular embodiment, the other therapeutic agent is a type II diabetes and/or obesity treatment agent.

[0136] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is an autoinflammatory diseases treatment agent. In a particular embodiment, the other therapeutic agent is a cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçet's disease, systemic-onset juvenile idiopathic arthritis (SJIA), and/or Still's disease treatment agent.

[0137] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is an autoimmune diseases treatment agent. In a particular embodiment, the other therapeutic agent is a COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus, interferonopathy, and/or inflammatory bowel disease treatment agent.

[0138] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is a proliferative diseases treatment agent. In a particular embodiment, the other therapeutic agent is a cancer, leukemia, multiple myeloma, and/or psoriasis treatment agent.

[0139] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is a transplantation rejection treatment agent. In a particular embodiment, the other therapeutic agent is a graft versus host disease treatment agent.

[0140] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is a disease involving impairment of cartilage turnover treatment agent. In a particular embodiment, the other therapeutic agent is an ankylosing spondylitis treatment agent.

[0141] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is a congenital cartilage malformations treatment agent. In a particular embodiment, the other therapeutic agent is a microtia, anotia, and/or metaphyseal chondrodysplasia treatment agent.

[0142] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention and another therapeutic agent, wherein the other therapeutic agent is a diseases associated with hypersecretion of IFN α , interferons ("interferonopathies", especially type I or type III interferonopathies), IL-12 and/or IL-23 treatment agent. In a particular embodiment, the other therapeutic agent is a 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 treatment agent.

COMPOUNDS FOR USE IN AND METHODS OF TREATMENT

[0143] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in medicine. In a particular embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound 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, 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. In a more particular embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of inflammatory diseases, psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, 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.

[0144] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament 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 a more particular embodiment, the present invention provides the use of compounds of the invention or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of inflammatory diseases, psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, 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.

[0145] In another embodiment, this invention provides 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, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a more particular embodiment, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with prophylaxis and/or treatment of inflammatory diseases, psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, 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, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition.

[0146] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of allergic diseases. In a particular embodiment, the allergic disease is asthma.

[0147] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of allergic diseases. In a particular embodiment, the allergic disease is asthma.

[0148] In another embodiment, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with allergic diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the allergic disease is asthma.

[0149] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound 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.

[0150] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for 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.

[0151] In another embodiment, 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 of the invention or one or more of the pharmaceutical compositions herein described 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/or inflammatory bowel disease. In a more particular embodiment, the inflammatory disease is rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease.

[0152] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound 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.

[0153] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of metabolic diseases. In a particular embodiment, the metabolic disease is type II diabetes and/or obesity.

[0154] In another embodiment, 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 a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the metabolic disease is type II diabetes and/or obesity.

[0155] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound 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.

[0156] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for 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.

[0157] In another embodiment, 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 of the invention or one or more of the pharmaceutical compositions herein described 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.

[0158] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of autoinflammatory diseases. In a particular embodiment, the autoinflammatory disease is cryopyrin-

associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçet's disease, systemic-onset juvenile idiopathic arthritis (SJIA), or Still's disease.

[0159] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of autoinflammatory diseases. In a particular embodiment, the autoinflammatory disease is cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçet's disease, systemic-onset juvenile idiopathic arthritis (SJIA), or Still's disease.

[0160] In another embodiment, 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 of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the autoinflammatory disease is cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Behçet's disease, systemic-onset juvenile idiopathic arthritis (SJIA), or Still's disease.

[0161] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound 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.

[0162] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of proliferative diseases. In a particular embodiment, the proliferative disease is cancer, leukemia, multiple myeloma and psoriasis.

[0163] In another embodiment, 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 a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the proliferative disease is cancer, leukemia, multiple myeloma and psoriasis.

[0164] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of transplantation rejection. In a particular embodiment, the transplantation rejection is graft versus host disease.

[0165] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of transplantation rejection. In a particular embodiment, the transplantation rejection is graft versus host disease.

[0166] In another embodiment, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with transplantation rejection, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the transplantation rejection is graft versus host disease.

[0167] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound 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.

[0168] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for 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.

[0169] In another embodiment, 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 a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the disease involving impairment of cartilage turnover is ankylosing spondylitis.

[0170] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of congenital cartilage malformations. In a particular embodiment, the congenital cartilage malformation is selected from microtia, anotia, and/or metaphyseal chondrodysplasia.

[0171] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of congenital cartilage malformations. In a particular embodiment, the congenital cartilage malformation is selected from microtia, anotia, and/or metaphyseal chondrodysplasia.

[0172] In another embodiment, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with congenital cartilage malformations, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the congenital cartilage malformation is selected from microtia, anotia, and/or metaphyseal chondrodysplasia.

[0173] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of 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 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 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.

[0174] In another embodiment, the present invention provides the use of compounds of the invention, or pharmaceutical compositions comprising a compound of the invention in the manufacture of a medicament for the prophylaxis and/or treatment of 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 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 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.

[0175] In another embodiment, 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 a compound of the invention or one or more of the pharmaceutical compositions herein described 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 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.

[0176] Injection dose levels 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.

[0177] For the prophylaxis and/or treatment of long-term conditions, such as degenerative conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to four (1-4) regular doses daily, especially 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.

[0178] Using these dosing patterns, each dose provides from about 1 to about 1000 mg of a compound of the invention, with particular doses each providing from about 10 to about 500 mg and especially about 30 to about 250 mg.

[0179] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[0180] When used to prevent the onset of a condition, a compound 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.

[0181] A compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compounds 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.

[0182] In one embodiment, a compound of the invention or a pharmaceutical composition comprising a compound of the invention is administered as a medicament. In a specific embodiment, said pharmaceutical composition additionally comprises a further active ingredient.

[0183] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of inflammatory diseases. 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.

[0184] In one embodiment, a compound 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, filgotinib, upadacitinib, fostamatinib, and cyclosporin), and biological DMARDS (for example but without limitation infliximab, etanercept, adalimumab, rituximab, and abatacept).

[0185] In one embodiment, a compound 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, a compound of the invention according to Formula I 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 leukaemia.

[0186] In one embodiment, a compound 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 compound of the inventions, 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.

[0187] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of transplant rejection. Particular agents include but are not limited to: calcineurin inhibitors (e.g. cyclosporin or tacrolimus (FK506)), mTOR inhibitors (e.g. sirolimus, everolimus), anti-proliferatives (e.g. azathioprine, mycophenolic acid), corticosteroids (e.g. prednisolone, hydrocortisone), antibodies (e.g. monoclonal anti-IL-2R α receptor antibodies, basiliximab, daclizumab), polyclonal anti-T-cell antibodies (e.g. anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG)).

[0188] In one embodiment, a compound 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. ceterizine, cinnarizine, fexofenadine) and vasoconstrictors (e.g. oxymethazoline, xylomethazoline, nafazoline and tramazoline).

[0189] Additionally, a compound 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.

[0190] In one embodiment, a compound 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).

[0191] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of 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.

[0192] In one embodiment, a compound 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 compound 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)).

[0193] In one embodiment, a compound 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.

[0194] 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.

CHEMICAL SYNTHETIC PROCEDURES

General

[0195] The compounds 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.

[0196] 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).

[0197] The following methods are presented with details as to the preparation of a compound of the invention as defined hereinabove and the comparative examples. A compound of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[0198] 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 a Bruker Avance II Ultrashield 400 NMR spectrometer (400 MHz). 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), multiplet (m), and broad (br). Electrospray MS spectra were obtained on an Agilent 1260 Infinity LC/MSD spectrometer or on an Agilent 1290 Infinity II LC/MSD spectrometer, both coupled to Agilent DAD, PDA and MSD (ESI pos/neg) detectors. Columns used: Waters XSelect CSH C18 3.5 μm , 2.1 mm ID $\times$ 30 mm L, Waters XSelect CSH XP C18 2.5 μm , 2.1 mm ID $\times$ 50 mm L. The methods are using MeCN/H₂O gradients (H₂O containing 10 mM $(\text{NH}_4)\text{HCO}_3$ or both MeCN and H₂O containing 0.1% formic acid).

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

Abbreviation	definition
μL	microliter
μm	micrometer
br	broad
CAS#	CAS Registry number
Cat#	catalog number
Cpd	compound
d	doublet
DCM	dichloromethane
dd	doublet of doublet
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMSO	dimethyl sulfoxide
DMF	<i>N,N</i> -dimethylformamide
EtOAc	ethyl acetate
g	gram
h	hour
HPLC	high-performance liquid chromatography

Abbreviation	definition
Int	intermediate
LCMS	liquid chromatography-mass spectrometry
m	multiplet
MeCN	acetonitrile
MeOH	methanol
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MS (mes)	measured mass
Mtd	method
MW (calc)	molecular weight calculated
NA	not available
NMR	nuclear magnetic resonance
ppm	parts-per-million
q	quartet

Abbreviation	definition
RT	room temperature
s	singlet
SM	starting material

Abbreviation	definition
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran

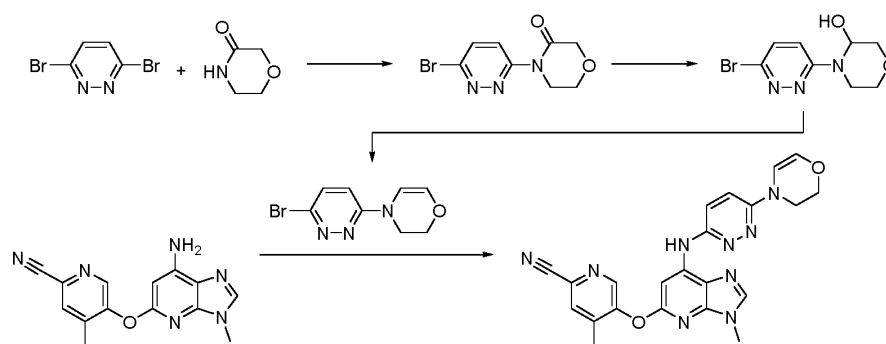
SYNTHETIC PREPARATION OF THE COMPOUNDS OF THE INVENTION

General synthetic methods

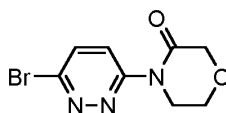
[0199] The compounds of the invention can be prepared from readily available starting materials according to the syntheses and procedures described below or described in pages 56-149 of WO2019/076716, or syntheses and procedures analogous thereto, whilst also taking account of procedures commonly known in the art (inc. those described in March's Advanced Organic Chemistry, 8th edition March 2020, ISBN: 978-1-119-37180-9, John Wiley & Sons).

[0200] Certain compounds of the invention can be produced according to the following schemes.

Scheme 1



1.1. Int 1

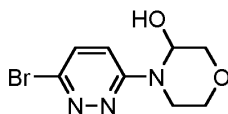


[0201] Morpholin-3-one (CAS# 109-11-5; 9.5 g, 1.0 eq.), 3,6-dibromopyridazine (CAS# 17973-86-3; 24.6 g, 1.1 eq.) and K_3PO_4 (39.9 g, 2.0 eq.) were mixed in dry 1,4-dioxane (190 mL) and purged with argon for 10 min. After the addition of DMEDA (0.8 g, 1.0 mL, 0.10 eq.) and copper(I) iodide (0.9 g, 0.05 eq.), the mixture was purged with argon for 15 min and stirred at 110 °C for 4.5 h. The mixture was cooled to 80 °C, the solids were filtered off and rinsed with THF. The filtrate was concentrated to afford **Int 1**.

LCMS: MW (calc): 258.1; m/z MS (mes): 257.9/259.9 $[M+H]^+$

1H NMR (400 MHz, $DMSO-d_6$) δ 8.25 (d, 1H), 8.02 (d, 1H), 4.33 (s, 2H), 4.10 – 4.00 (m, 4H)

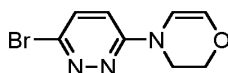
1.2. Int 2



[0202] To crude **Int 1** (24 g, 1.0 eq.), under argon atmosphere, in dry THF (1 L) was added diisobutylaluminum hydride, 1 M in hexanes (141 mL, 1.5 eq.) at -78 °C and the reaction mixture was stirred for 1.5 h. The reaction mixture was diluted with MeOH (100 mL) and concentrated *in vacuo* to afford **Int 2**.

LCMS: MW (calc): 260.1; m/z MS (mes): 260.0/262.0 [M+H]⁺

1.3. Int 3



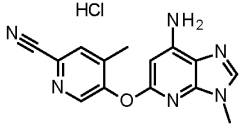
[0203] To a solution of crude **Int 2** (24.45 g, 1.0 eq.) in DCM (1 L) was added AlCl₃ (21.93 g, 1.75 eq.) at RT and the mixture was stirred for 20 h. Aqueous saturated Rochelle salt (200 mL) was added. Solids were filtered off, the layers were separated, and the aqueous layer was extracted with DCM (3 × 300 mL). The combined organic layers were concentrated *in vacuo*. The residue was purified by flash column chromatography (eluting with heptane/EtOAc 100/0 to 25/75) afforded **Int 3**.

LCMS: MW (calc): 242.1; m/z MS (mes): 242.0/244.0 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, 1H), 6.81 (d, 1H), 6.21 (d, 1H), 6.16 (d, 1H), 4.26 – 4.18 (m, 2H), 4.07 – 3.96 (m, 2H)

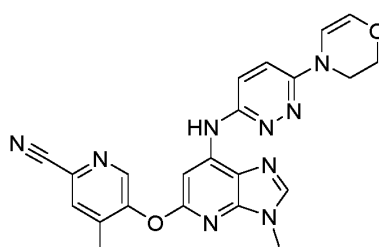
Table II. Intermediates towards illustrative compounds of the invention

Int	Structure	Name	SM	Mtd	MW (calc)	MS (mes)
1		4-(6-bromopyridazin-3-yl)morpholin-3-one	CAS# 109-11-5 + CAS# 17973-86-3	Ex. 1.1	258.1	257.9 259.9
2		4-(6-bromopyridazin-3-yl)morpholin-3-ol	Int 1	Ex. 1.2	260.1	260.0 262.0
3		4-(6-bromopyridazin-3-yl)-2,3-dihydro-1,4-oxazine	Int 2	Ex. 1.3	242.1	242.0 244.0

Int	Structure	Name	SM	Mtd	MW (calc)	MS (mes)
4		5-(7-amino-3-methylimidazo[4,5-b]pyridin-5-yl)oxy-4-methylpyridine-2-carbonitrile hydrochloride (CAS# 2308525-45-1)	Cf. WO2019/076716 page 66		280.1	NA

Illustrative examples

1.4. Cpd 1



[0204] **Int 4** (2.88 g, 1.1 eq.), **Int 3** (2.0 g, 1.0 eq.), Cs₂CO₃ (8.08 g, 3.0 eq.) and water (0.15 mL, 1.0 eq.) were mixed in dry DMF (80 mL) and purged with argon for 15 min. After addition of JosiPhos SL-J009-1 (CAS# 158923-11-6; 0.098 g, 0.022 eq.) and Pd(cinnamyl)Cl₂ (CAS# 12131-44-1; 0.043 g, 0.010 eq.), the mixture was purged with argon for 10 min and stirred at 110 °C for 16 h. Aqueous work-up, purification by flash column chromatography (eluent: DCM, from 0% to 8% MeOH), and freeze-drying afforded **Cpd 1**. LCMS: MW (calc): 441.5; m/z MS (mes): 442.2 [M+H]⁺

[0205] Further compounds of the invention can be made by similar processes and/or employing techniques known to the person skilled in the art.

Table III. Illustrative compounds of the invention

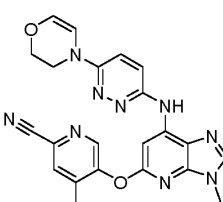
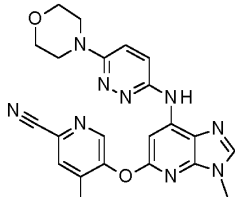
Cpd	Structure	Name	SM	Mtd	MW (calc)	MS (mes)
1		5-((7-((6-(2,3-dihydro-4H-1,4-oxazin-4-yl)pyridazin-3-yl)amino)-3-methyl-3H-imidazo[4,5-b]pyridin-5-yl)oxy)-4-methylpicolinonitrile	CAS# 2308525-45-1 + Int 3	Ex. 1.4	441.5	442.2

Table IV. ¹H NMR of final compounds

Cpd	¹ H NMR
1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.86 (s, 1H), 8.53 (s, 1H), 8.19 (s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.66 (d, 1H), 7.44 (d, 1H), 6.61 (d, 1H), 6.13 (d, 1H), 4.15 (t, 2H), 3.89 (t, 2H), 3.61 (s, 3H), 2.30 (s, 3H)

Table V. Comparative compounds

Cpd	Structure	Name	SM	Mtd	MW (calc)	MS (mes)
C1		4-methyl-5-[3-methyl-7-(6-morpholin-4-ylpyridazin-3-ylamino)-3H-imidazo[4,5-b]pyridin-5-yloxy]pyridine-2-carbonitrile (CAS# 2308520-97-8)	Cf. WO2019/076716 page 100		443.2	NA

BIOLOGICAL EXAMPLES**Example 2. In vitro assays****2.1. JAK1 inhibition assay**

[0206] Human JAK1 inhibition was tested in the JAK1 Human TK Kinase Enzymatic Radiometric Assay [Km ATP], KinaseProfiler assay at Eurofins Discovery (Eurofins Cerep SA, Celle-L'Evescault, France; Cat# 14-918KP).

2.1.1. Protocol

[0207] Recombinant human JAK1 (catalytic domain, amino acids 866-1154; UNIPROT number P23458) was incubated with 20 mM Tris/HCl pH 7.5, 0.2 mM EDTA, 500 μM GEEPLYWSFPAKKK, 10 mM magnesium acetate, and [γ-³³P]-ATP (specific activity and concentration as required). The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 min at RT, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 μL of the reaction was then spotted onto a P30 filtermat and washed four times for 4 min in 0.425% phosphoric acid and once in MeOH prior to drying and scintillation counting.

2.2. JAK2 inhibition assay

[0208] Human JAK2 inhibition was tested in the JAK2 Human TK Kinase Enzymatic Radiometric Assay [Km ATP], KinaseProfiler assay at Eurofins Discovery (Eurofins Cerep SA, Celle-L'Evescault, France; Cat# 14-640KP).

2.2.1. Protocol

[0209] Recombinant human JAK2 (catalytic domain, amino acids 808-1132; UNIPROT number O60674) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 100 μ M KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC, 10 mM magnesium acetate and [γ -³³P]-ATP (specific activity and concentration as required). The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 min at RT, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 μ L of the reaction was then spotted onto a P30 filtermat and washed four times for 4 min in 0.425% phosphoric acid and once in MeOH prior to drying and scintillation counting.

2.3. JAK3 inhibition assay

[0210] Human JAK3 inhibition was tested in the JAK3 Human TK Kinase Enzymatic Radiometric Assay [Km ATP], KinaseProfiler assay at Eurofins Discovery (Eurofins Cerep SA, Celle-L'Evescault, France; Cat# 14-629KP).

2.3.1. Protocol

[0211] Recombinant human JAK3 (catalytic domain, amino acids 781-1124; UNIPROT number P52333) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 500 μ M GEEEEYFELVKKKK, 10 mM magnesium acetate and [γ -³³P]-ATP (specific activity and concentration as required). The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 min at RT, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 μ L of the reaction was then spotted onto a P30 filtermat and washed four times for 4 min in 0.425% phosphoric acid and once in MeOH prior to drying and scintillation counting.

2.4. TYK2 inhibition assay

[0212] Human TYK2 inhibition was tested in the Tyk2 Human TK Kinase Enzymatic Radiometric Assay [Km ATP], KinaseProfiler assay at Eurofins Discovery (Eurofins Cerep SA, Celle-L'Evescault, France; Cat# 14-924KP).

2.4.1. Protocol

[0213] Recombinant human TYK2 (catalytic domain, amino acids 875-1187; UNIPROT number P29597) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μ M GGMEDIYFEFMGGKKK, 10 mM magnesium acetate and [γ -³³P]-ATP (specific activity and concentration as required). The reaction was initiated by the addition of the Mg/ATP mix. After incubation for 40 min at RT, the reaction was stopped by the addition of phosphoric acid to a concentration of 0.5%. 10 μ L of the reaction was then spotted onto a P30 filtermat and washed four times for 4 min in 0.425% phosphoric acid and once in MeOH prior to drying and scintillation counting.

Table VI. JAK kinases IC₅₀ values of illustrative compounds of the invention and comparative compounds

Cpd	JAK1 IC ₅₀ (nM)	JAK2 IC ₅₀ (nM)	JAK3 IC ₅₀ (nM)	TYK2 IC ₅₀ (nM)
1	197 (n= 2)	142 (n=2)	>1000 (n=2)	2.5 (n=2)
C1	NA	55 (n=1)	>1000 (n=3)	3 (n=1)

2.5. Conclusions

[0214] The *in vitro* assay data reported above show the selectivity of the illustrative compounds of the invention towards TYK2 over the other JAK family members (JAK1, JAK2, JAK3).

[0215] Moreover, the *in vitro* assay data reported above show that while maintaining TYK2 potency and selectivity versus JAK3, the illustrative compound of the invention provides additional selectivity versus JAK2, relative to the comparative compound.

Example 3. Selectivity assays

[0216] In order to determine the selectivity of the illustrative compounds of the invention, specific pathways inhibition is measured.

[0217] In particular, whereas both IFN α and IL-12 signalings are TYK2-dependent, IFN α can also be inhibited by a JAK1-selective inhibitor. However, the activation of STAT1 by IL-6 is strictly dependent on JAK1.

3.1. Cellular assays

3.1.1. IFN α activation of STAT1 in PBMC

3.1.1.1. Protocol

[0218] Peripheral blood mononuclear cells (PBMC) are isolated from buffy coats under sterile conditions by density gradient centrifugation using LymphoPrepTM medium (Axis-Shield, Cat# 1114545) followed by 2 subsequent wash steps in PBS (Sigma, Cat# P4417-100TAB). After these 2 wash steps the cell pellet is dissolved in ammonium chloride buffer (1.5 M NH₄Cl, 100 mM NaHCO₃ and 10 mM Na₂EDTA) for lysis of the red blood cells. Subsequently cells are centrifuged and the PBMC are resuspended in plain RPMI-1640 medium (Lonza, Cat# BE12-115F/U1) containing 10% (v/v) heat inactivated FBS (Sigma Aldrich, Cat# F7524).

[0219] Immediately after isolation, PBMC are seeded in 96 well plates at 1.0E06 cells/well in a volume of 180 μ L RPMI-1640 containing 10% (v/v) FBS.

[0220] PBMC are treated with test compound for 30 min at 37 °C 5% CO₂. 0.6 μ L of 333x concentrated compound dilution is added to the wells using the Mosquito. After 30 min of test compound / vehicle pre-treatment, PBMC are stimulated for 30 min at 37 °C 5% CO₂ with recombinant human IFN α (PeproTech,

Cat# 300-02A) at a final concentration of 5 ng/mL by addition of 20 µL (10x concentrated) cytokine trigger to obtain a final volume of 200 µL per well.

[0221] All compounds are tested in single starting from 30 µM followed by a 1/3 serial dilution, 10 doses in total (30 µM, 10 µM, 3.3 µM, 1.11 µM, 0.370 µM, 0.123 µM, 0.0412 µM, 0.0137 µM, 0.0046 µM and 0.0015 µM) in a final concentration of 0.3% DMSO.

[0222] After 30 min of cytokine stimulation, 200 µL of cell suspension is transferred to a 96-well V-bottom plate, centrifugated for 5 min at 1000 rpm to pellet cells, followed by removal of supernatant. The cell pellet is reconstituted in 100 µL 1x Lysis buffer supplemented with EDTA-free Protease Inhibitor Cocktail (Roche Applied Sciences, Product Number 11836170001) followed by sample freezing and storage at -80 °C. 1x Lysis buffer is provided with the Phospho-STAT1 Elisa Kit and contains phosphatase inhibitors. Endogenous levels of phosphorylated STAT1 are quantified using a 96-well PathScan® Phospho-STAT1 (Tyr701) Sandwich ELISA Kit (Cell Signaling, Product Number #7234) according to manufacturer's instructions.

[0223] HRP activity (HRP is conjugated to the secondary antibody) is measured by addition of 100 µL of freshly prepared luminol substrate (BM Chemiluminescence ELISA Substrate (POD), Roche, Product Number 11582950001), incubation for 5 min at RT in the dark and measured in an Envision (Perkin Elmer) (integration time of 100 msec).

3.1.1.2. Results

[0224] A positive control (CAS# 1187594-09-7, 10 µM in vehicle) and a negative control (vehicle, 0% inhibition) are used to calculate 'percent inhibition (PIN)' values.

[0225] The percentage inhibition is calculated as:

$$\text{PIN} = \left(1 - \left(\frac{\text{RCLU}(\text{test compound}) - \text{RCLU}(\text{positive control})}{\text{RCLU}(\text{vehicle control}) - \text{RCLU}(\text{positive control})} \right) \right) * 100$$

wherein

[0226] RCLU(vehicle control): Relative Chemiluminescent signal determined in presence of vehicle and trigger

[0227] RCLU(test compound): Relative Chemiluminescent signal determined in presence of test compounds and trigger

[0228] RCLU(positive control): Relative Chemiluminescent signal determined in presence of positive control and trigger

[0229] PIN values are plotted for compounds tested in dose-response and average IC₅₀ values are derived using GraphPad Prism Software applying non-linear regression (sigmoidal) curve fitting.

3.2. Human whole blood assay (hWBA)

3.2.1. Materials

[0230] Li-heparin Vacutainer® tubes (Becton Dickinson and Co., Cat# 367880)

[0231] RPMI-1640 medium (Capricorn Scientific GmbH, Cat# RPMI-HXA)

- [0232] Bovine serum albumin (Merck KGaA, Cat# A3059)
- [0233] DPBS, no calcium, no magnesium, 1X (Thermo Fisher Scientific Inc., Cat# 14190)
- [0234] Human Universal Type I IFN α (Pestka Biomedical Laboratories, Inc., Cat# 11200-1)
- [0235] Recombinant human IL-2 protein (R&D Systems Inc., Cat# 202-IL-010)
- [0236] Recombinant human IL-6 protein (R&D Systems Inc., Cat# 206-IL-010)
- [0237] Recombinant human GM-CSF protein (R&D Systems Inc., Cat# 215-GM-010)
- [0238] Lyse/Fix buffer, 5X (Becton Dickinson and Co., Cat# 558049)
- [0239] PE Mouse anti-STAT1 (pY701), clone 4a antibody (Becton Dickinson and Co., Cat# 562069)
- [0240] Alexa Fluor[®] 647 Mouse anti-STAT3 (pY705), clone 4/P-STAT3 antibody (Becton Dickinson and Co., Cat# 557815)
- [0241] PE Mouse anti-STAT5 (pY694), clone 47/Stat5(pY694) antibody (Becton Dickinson and Co., Cat# 612567)
- [0242] V500 Mouse anti-human CD4, clone RPA-T4 antibody (Becton Dickinson and Co., Cat# 560768)
- [0243] CD33 APC, clone P67.6 antibody (Becton Dickinson and Co., Cat# 345800)
- [0244] Falcon[®] 5 mL polypropylene round bottom tubes (Corning Inc., Cat# 352063)
- [0245] Falcon[®] 96-well polystyrene round bottom microplates (Corning Inc., Cat# 351177)
- [0246] SL40R centrifuge (Thermo Fisher Scientific Inc.)
- [0247] Attune NxT flow cytometer (Thermo Fisher Scientific Inc.)

3.2.2. Methods

[0248] Human whole blood was collected in lithium heparin tubes. Tubes were incubated for 30 min at 37 °C for stabilization before the beginning of the assay.

[0249] Compounds were thawed, and pre-dilutions in DMSO were prepared from the compound stock solution in 10 consecutive concentrations, by transferring 10 μ L of the highest concentration stock solution to 20 μ L of DMSO (3 fold-serial dilutions) Compound working solutions (10X concentrated) were then prepared in RPMI-1640 medium by transferring 20 μ L of prediluted compound in DMSO to 180 μ L of RPMI-1640 medium. 10 μ L of each diluted compound (10X concentrated) was added to 5 mL round bottom tubes, followed by addition of 100 μ L whole blood. The whole blood was incubated with the compounds for 30 min at 37 °C on an orbital rocker. DMSO was used as vehicle control.

[0250] IFN α trigger: recombinant human IFN α was thawed on ice and diluted in PBS + 0.1 % BSA in 1.5 mL Eppendorf tubes (polypropylene) to 5500 U/mL. 10 μ L of trigger or vehicle was added to the tubes with whole blood in order to obtain the final testing concentration (500 U/mL). Whole blood was incubated with trigger for 20 min at 37 °C on an orbital rocker.

[0251] IL-2 trigger: recombinant human IL-2 was thawed on ice and diluted in PBS + 0.1 % BSA in 1.5 mL Eppendorf tubes (polypropylene) to 330 ng/mL. 10 μ L of trigger or vehicle (PBS + 0.1 % BSA) was added to the tubes with whole blood in order to obtain the final testing concentration (30 ng/mL). Whole blood was gently mixed and incubated with trigger for 30 min at 37 °C on an orbital rocker.

[0252] IL-6 trigger: recombinant human IL-6 was thawed on ice and diluted in PBS + 0.1 % BSA in 1.5 mL Eppendorf tubes (polypropylene) to 8.8 ng/mL. 10 μ L of trigger or vehicle (PBS + 0.1 % BSA) was added to the tubes with whole blood in order to obtain the final testing concentration (0.8 ng/mL). Whole blood was gently mixed and incubated with trigger for 20 min at 37 °C on an orbital rocker.

[0253] GM-CSF trigger: recombinant human GM-CSF was thawed on ice and diluted in PBS + 0.1 % BSA in 1.5 mL Eppendorf tubes (polypropylene) to 220 pg/mL. 10 μ L of trigger or vehicle (PBS + 0.1 % BSA) was added to the tubes with whole blood in order to obtain the final testing concentration (20 pg/mL). Whole blood was gently mixed and incubated with trigger for 20 min at 37 °C on an orbital rocker.

[0254] Following trigger incubation, 1 mL of freshly prepared and pre-warmed 1X Lyse/Fix buffer was added to whole blood. Samples were vortexed, 1 mL of buffer was added, and samples were vortexed again in order to ensure complete RBC lysis. The tubes were incubated at 37 °C in a water bath for 10 min. Cells were pelleted by centrifugation at 500 $\times$ g for 8 min, at RT, and supernatant was discarded by inverting the tubes. Cell pellets were resuspended in 2 mL of DPBS and centrifuged at 500 $\times$ g for 8 min, at RT. Supernatants were discarded again by inverting the tubes and 900 μ L of ice-cold MeOH was added dropwise to cells under gentle agitation on a vortex. Tubes were locked and stored at -20 °C until further use for labeling and flow cytometry analysis.

[0255] After permeabilization (-20 °C in MeOH), cells were pelleted by centrifugation at 500 $\times$ g for 8 min, at RT and supernatants were removed by inverting the tubes. Cell pellets were washed by adding 2 mL of PBS + 3 % BSA, vortexed, and cells were pelleted by centrifugation at 500 $\times$ g for 8 min, at RT. Once again, supernatants were removed by inverting the tubes.

[0256] Cells were transferred to 96-well plate and antibody cocktails for staining were added:

- IFN α and IL-6 trigger groups: to each well 5 μ L of CD4-V500 and pSTAT1-PE antibodies and 20 μ L of pSTAT3-AF647 antibody were added
- IL-2 trigger group: to each well 5 μ L of CD4-V500 and 20 μ L of pSTAT5-PE antibodies were added
- GM-CSF trigger group: to each well 5 μ L of CD33-APC and 20 μ L of pSTAT5-PE antibodies were added

[0257] Samples were incubated at RT in the dark for 1 h. At the end of incubation, samples were washed with DPBS by adding 100 μ L of DPBS to each well, pelleted by centrifugation at 500 $\times$ g for 8 min, at RT and supernatant was removed by flicking the plates. Washing step was repeated by addition of 200 μ L of DPBS to each well and centrifuge at 500 $\times$ g for 8 min, at RT. After the last wash, cells were resuspended in 240 μ L of DPBS and half of the suspension, 120 μ L, from each well was transferred to a new plate as a technical duplicate. 120 μ L of DPBS was added to each well of both plates and samples were resuspended by pipetting. One plate was used immediately for analysis on the Attune flow cytometer, while second plate was stored at 4 °C until the analysis was finished and safely discarded.

3.2.3. Data analysis

[0258] On the Attune flow cytometer, cells were gated inside P1 gate (FSC-A vs SSC-A plot), and 13,000 events in this gate was set as stopping option for sample collection.

[0259] Data was further analyzed in FlowLogic software by gating CD4+/CD33+ cells inside P2 gate (SSC-A vs CD4/CD33). From P2, histogram plots for pSTAT proteins of interest (depending on trigger group) were created. Unstimulated vehicle sample of each donor was used for setting the gates for pSTATs in the manner that it contains less than 1 % of positive events. Percentages of pSTAT positive cells were exported to MS Excel and percentages of inhibition (PIN) values were calculated. For IC₅₀ determination, the PIN values were plotted against log compound concentrations in GraphPad Prism software.

3.2.4. Results

[0260] Using the above protocol, the following results were obtained.

Cpd	Pathway	Trigger	Readout	IC ₅₀ (μM)
1	JAK1/TYK2	IFNα	pSTAT1	3.1
1	JAK1/TYK2	IFNα	pSTAT3	0.3
1	JAK1/JAK2	IL-6	pSTAT1	24
1	JAK1/JAK2	IL-6	pSTAT3	> 33
1	JAK1/JAK3	IL-2	pSTAT5	> 100
1	JAK2/JAK2	GM-CSF	pSTAT5	> 100

3.3. Conclusions

[0261] Whereas JAK1 is a key driver in IFNα, IL-6, IL-10 and IL-22 signaling, TYK2 is involved in type I interferons (including IFNα, INFβ), IL-23 and IL-12 signaling (Gillooly et al., 2016; Sohn et al., 2013). The whole blood assay data reported above show a selective inhibition of TYK2-dependant pathways by the illustrative compounds of the invention. In particular, a potency at least 7.7 times higher against the IFNα-triggered pathways than on IL-6-triggered pathways is recorded for the illustrative compounds of the invention, thus confirming the TYK2-selectivity of the compounds of the invention over JAK2.

Example 4. In vivo assay

4.1. Murine model of psoriatic-like epidermal hyperplasia induced by intradermal injections of IL-22 or IL-23

4.1.1. Materials

[0262] Mouse recombinant IL-22 (582-ML-CF), carrier free is provided by R&D systems. Mouse recombinant IL-23, carrier free (14-8231, CF) is provided by e-Bioscience.

4.1.2. Animals

[0263] Balb/c mice (female, 18-20 g body weight) are obtained from CERJ (France). Mice are kept on a 12 h light/dark cycle (07:00 – 19:00). Temperature is maintained at 22 °C, food and water are provided *ad libitum*.

4.1.3. Study design

[0264] The design of the study is adapted from Rizzo et al, 2011.

[0265] On the first day (D1), the mice are shaved around the two ears.

[0266] For 4 consecutive days (D1 to D4), the mice received a daily intradermal dose of mouse recombinant IL-22 or IL-23 (1 µg/20 µL in PBS/0.1% BSA) in the right pinna ear and 20 µL of PBS/0.1% BSA in the left pinna ear under anesthesia induced by inhalation of isoflurane.

[0267] From D1 to D5, mice are dosed with test-compound (3, 10, 30, or 100 mg/kg, po, qd in MC 0.5%), 1 h prior IL-23/IL-22 injection or with vehicle.

4.1.4. Assessment of disease

[0268] The thickness of both ears is measured daily with an automatic caliper. Body weight is assessed at initiation and at sacrifice. On fifth day, 2 h after the last dosing, the mice are sacrificed. The pinnae of the ear are cut, excluding cartilage. The pinnae are weighed and then, placed in vial containing 1 mL of RNAlater solution or in formaldehyde.

[0269] At D4, blood samples are also collected from the retro-orbital sinus for PK profile just before dosing (T0) and 1 h, 3 h, 6 h post-dosing.

[0270] There are 10 mice per group. The results are expressed as mean ± sem and statistical analysis is performed using one-way Anova followed by Dunnett's post-hoc test versus IL-22 or IL-23 vehicle groups.

4.1.5. Histology

[0271] After sacrifice, ears are collected and fixed in 3.7% formaldehyde before embedding in paraffin. Two µm thick sections are done and stained with hematoxylin and eosin. Ear epidermis thickness is measured by image analysis (SisNcom software) with 6 images per ear captured at magnification x20. Data are expressed as mean ± sem and statistical analysis is performed using one-way Anova followed by Dunnett's post-hoc test versus IL-22 or IL-23 vehicle groups.

4.1.6. RNA extraction, RT-PCR and real-time PCR

[0272] IL-17a, IL-22, IL-1β, LCN2 and S100A9 transcript levels in ear tissue are determined using real-time quantitative PCR.

FINAL REMARKS

[0273] 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.

[0274] 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 was specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[0275] 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.

[0276] At least some of the chemical names of compound 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.

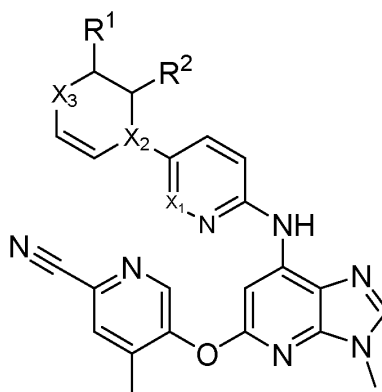
REFERENCES

- Babon, J.J., Lucet, I.S., Murphy, J.M., Nicola, N.A., Varghese, L.N., 2014. The molecular regulation of Janus kinase (JAK) activation. *Biochem. J.* 462, 1–13. <https://doi.org/10.1042/BJ20140712>
- Broekman, F., Giovannetti, E., Peters, G.J., 2011. Tyrosine kinase inhibitors: Multi-targeted or single-targeted? *World J. Clin. Oncol.* 2, 80–93. <https://doi.org/10.5306/wjco.v2.i2.80>
- Dendrou, C.A., Cortes, A., Shipman, L., Evans, H.G., Attfield, K.E., Jostins, L., Barber, T., Kaur, G., Kuttikkatte, S.B., Leach, O.A., Desel, C., Faergeman, S.L., Cheeseman, J., Neville, M.J., Sawcer, S., Compston, A., Johnson, A.R., Everett, C., Bell, J.I., Karpe, F., Ultsch, M., Eigenbrot, C., McVean, G., Fugger, L., 2016. Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity. *Sci. Transl. Med.* 8, 363ra149. <https://doi.org/10.1126/scitranslmed.aag1974>
- Fabian, M.A., Biggs, W.H., Treiber, D.K., Atteridge, C.E., Azimioara, M.D., Benedetti, M.G., Carter, T.A., Ciceri, P., Edeen, P.T., Floyd, M., Ford, J.M., Galvin, M., Gerlach, J.L., Grotzfeld, R.M., Herrgard, S., Insko, D.E., Insko, M.A., Lai, A.G., Lélias, J.-M., Mehta, S.A., Milanov, Z.V., Velasco, A.M., Wodicka, L.M., Patel, H.K., Zarrinkar, P.P., Lockhart, D.J., 2005. A small molecule–kinase interaction map for clinical kinase inhibitors. *Nat. Biotechnol.* 23, 329–336. <https://doi.org/10.1038/nbt1068>
- Gillooly, K., Zhang, Y., Yang, X., Zupa-Fernandez, A., Cheng, L., Strnad, J., Cunningham, M., Heimrich, E., Zhou, X., Chen, J., Chaudhry, C., Li, S., McIntyre, K., Carman, J., Moslin, R., Wroblewski, S., Weinstein, D., Burke, J., 2016. BMS-986165 Is a Highly Potent and Selective Allosteric Inhibitor of Tyk2, Blocks IL-12, IL-23 and Type I Interferon Signaling and Provides for Robust Efficacy in Preclinical Models of Systemic Lupus Erythematosus and Inflammatory Bowel Disease. *ACR Meet. Abstr.*
- Neubauer, H., Cumano, A., Müller, M., Wu, H., Huffstadt, U., Pfeffer, K., 1998. Jak2 Deficiency Defines an Essential Developmental Checkpoint in Definitive Hematopoiesis. *Cell* 93, 397–409. [https://doi.org/10.1016/S0092-8674\(00\)81168-X](https://doi.org/10.1016/S0092-8674(00)81168-X)
- O'Shea, J.J., Plenge, R., 2012. JAKs and STATs in Immunoregulation and Immune-Mediated Disease. *Immunity* 36, 542–550. <https://doi.org/10.1016/j.immuni.2012.03.014>
- Parganas, E., Wang, D., Stravopodis, D., Topham, D.J., Marine, J.-C., Teglund, S., Vanin, E.F., Bodner, S., Colamonici, O.R., van Deursen, J.M., Grosveld, G., Ihle, J.N., 1998. Jak2 Is Essential for Signaling through a Variety of Cytokine Receptors. *Cell* 93, 385–395. [https://doi.org/10.1016/S0092-8674\(00\)81167-8](https://doi.org/10.1016/S0092-8674(00)81167-8)
- Schwartz, D.M., Bonelli, M., Gadina, M., O'Shea, J.J., 2016. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat. Rev. Rheumatol.* 12, 25–36. <https://doi.org/10.1038/nrrheum.2015.167>
- Sohn, S.J., Barrett, K., Abbema, A.V., Chang, C., Kohli, P.B., Kanda, H., Smith, J., Lai, Y., Zhou, A., Zhang, B., Yang, W., Williams, K., Macleod, C., Hurley, C.A., Kulagowski, J.J., Lewin-Koh, N., Dengler, H.S., Johnson, A.R., Ghilardi, N., Zak, M., Liang, J., Blair, W.S., Magnuson, S., Wu,

- L.C., 2013. A Restricted Role for TYK2 Catalytic Activity in Human Cytokine Responses Revealed by Novel TYK2-Selective Inhibitors. *J. Immunol.* 191, 2205–2216. <https://doi.org/10.4049/jimmunol.1202859>
- Vainchenker, W., Dusa, A., Constantinescu, S.N., 2008. JAKs in pathology: Role of Janus kinases in hematopoietic malignancies and immunodeficiencies. *Semin. Cell Dev. Biol.* 19, 385–393. <https://doi.org/10.1016/j.semcdb.2008.07.002>

CLAIMS

1. A compound according to Formula I:



I

wherein

X_1 and X_2 are independently N or CH;

X_3 is NR^3 , O, or $CR^{4a}R^{4b}$;

R^1 is H or $-CH_3$;

R^2 is H or $-CH_3$;

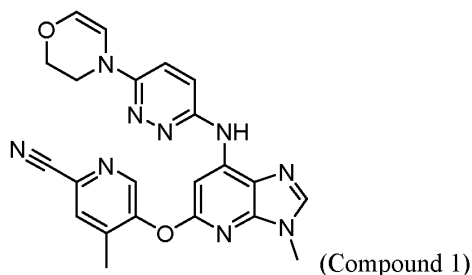
R^3 is H, or C_{1-2} alkyl unsubstituted or substituted with one or more halo; and

R^{4a} and R^{4b} are independently H, $-CN$, $-N(CH_3)_2$, or $-CH_2-OH$;

or a pharmaceutically acceptable salt/cocrystal thereof, or a solvate or the solvate of a salt/cocrystal thereof.

2. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein X_1 is N.
3. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein X_2 is N.
4. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein X_3 is NR^3 .
5. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein R^3 is H, $-CH_3$, or $-CH_2CF_3$.
6. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein X_3 is $CR^{4a}R^{4b}$.
7. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, and 6, wherein R^{4a} is H and R^{4b} is $-CN$.
8. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein X_3 is O.
9. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-8, wherein R^2 is H.
10. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1-8, wherein R^1 is H.

11. The compound, or salt/cocrystal or solvate or solvate of a salt/cocrystal thereof, according to claim 1, wherein the compound is 5-((7-((6-(2,3-dihydro-4H-1,4-oxazin-4-yl)pyridazin-3-yl)amino)-3-methyl-3H-imidazo[4,5-b]pyridin-5-yl)oxy)-4-methylpicolinonitrile (Compound 1).



12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to any one of claims 1-11.
13. The pharmaceutical composition according to claim 11 comprising a further therapeutic agent.
14. The compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-11, or the pharmaceutical composition according to any one of claims 12-13, for use in medicine.
15. A compound, or salt/cocrystal or a solvate or the solvate of a salt/cocrystal thereof, according to any one of claims 1-11, or the pharmaceutical composition according to any one of claims 12-13, for use in the treatment 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.
16. The use of a compound, or salt/cocrystal or solvate or solvate of a salt/cocrystal thereof, according to any one of claims 1-11, or the pharmaceutical composition according to any one of claims 12-13, in the manufacture of a medicament for the treatment of an inflammatory disease, a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I 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, ulcerative colitis and/or Crohn's disease.
17. A method of treating an inflammatory disease, a disease associated with hypersecretion of IFN α and/or interferons ("interferonopathies", especially type I 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, ulcerative colitis and/or Crohn's disease, comprising administering to a

patient a compound, or salt/cocrystal or solvate or solvate of a salt/cocrystal thereof, according to any one of claims 1-11, or the pharmaceutical composition according to any one of claims 12-13.

18. The compound for use according to claim 15, the use of the compound according to claim 16, or the method according to claim 17, wherein the disease to be treated is systemic lupus erythematosus, dermatomyositis, polymyositis, psoriasis, ulcerative colitis and/or Crohn's disease.