Title: NOVEL COMPOUNDS USEFUL FOR THE TREATMENT OF DEGENERATIVE AND INFLAMMATORY DISEASES

Abstract: [1,2,4]Triazolo[1,5-a]pyridine compounds are disclosed that have a formula represented by the following: (I)

These compounds may be prepared as a pharmaceutical composition, and may be used for the prevention and treatment of a variety of conditions in mammals including humans, including by way of non-limiting example, diseases involving cartilage degradation, bone or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection) and proliferative diseases.
NOVEL COMPOUNDS USEFUL FOR THE TREATMENT OF DEGENERATIVE AND INFLAMMATORY DISEASES

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that are inhibitors of JAK, a family of tyrosine kinases that are involved in the modulation of the degradation of cartilage, joint degeneration and diseases involving such degradation and/or inflammation. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds, methods for the prevention and/or treatment of diseases involving cartilage degradation, bone and/or joint degradation, conditions involving inflammation or immune responses, endotoxin-driven disease states, cancer, and organ transplant rejection; and/ or methods for the prevention and/or treatment of diseases involving cartilage degradation, joint degradation and/or inflammation by administering a compound of the invention.

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

[0003] The combination of genetic models and small molecule JAK inhibitor research revealed the therapeutic potential of several JAKs. JAK3 is validated by mouse and human genetics as an immune-suppression target (O’Shea J. et al. (2004)). JAK inhibitors were successfully taken into clinical development, initially for organ transplant rejection but later also in other immuno-inflammatory indications such as rheumatoid arthritis (RA), psoriasis and Crohn’s disease (http://clinicaltrials.gov/).

[0004] TYK2 is a potential target for immuno-inflammatory diseases, being validated by human genetics and mouse knock-out studies (Levy D. and Loomis C. (2007)).

[0005] JAK1 is a novel target in the immuno-inflammatory disease area. JAK1 heterodimerizes with the other JAKs to transduce cytokine-driven pro-inflammatory signaling. Therefore, inhibition of JAK1 and/or other JAKs is expected to be of therapeutic benefit for a range of inflammatory conditions as well as for other diseases driven by JAK-mediated signal transduction.

BACKGROUND OF THE INVENTION
[0006] Cartilage is an avascular tissue of which chondrocytes are the main cellular component. The chondrocytes in normal articular cartilage occupy approximately 5% of the tissue volume, while the extracellular matrix makes up the remaining 95% of the tissue. The chondrocytes secrete the components of the matrix, mainly proteoglycans and collagens, which in turn supply the chondrocytes with an environment suitable for their survival under mechanical stress. In cartilage, collagen type II, together with the protein collagen type IX, is arranged in solid fibril-like structures which provide cartilage with great mechanical strength. The proteoglycans can absorb water and are responsible for the resilient and shock absorbing properties of the cartilage.

[0007] One of the functional roles of cartilage in the joint is to allow bones to articulate on each other smoothly. Loss of articular cartilage, therefore, causes the bones to rub against each other leading to pain and loss of mobility. The degradation of cartilage can have various causes. In inflammatory arthritides, as rheumatoid arthritis for example, cartilage degradation is caused by the secretion of proteases (e.g. collagenases) by inflamed tissues (the inflamed synovium for example). Cartilage degradation can also be the result of an injury of the cartilage, due to an accident or surgery, or exaggerated loading or ‘wear and tear’. The ability of cartilage tissue to regenerate after such insults is limited. Chondrocytes in injured cartilage often display reduced cartilage synthesizing (anabolic) activity and / or increased cartilage degrading (catabolic) activity.

[0008] The degeneration of cartilage is the hallmark of various diseases, among which rheumatoid arthritis and osteoarthritis are the most prominent. Rheumatoid arthritis (RA) is a chronic joint degenerative disease, characterized by inflammation and destruction of the joint structures. When the disease is unchecked, it leads to substantial disability and pain due to loss of joint functionality and even premature death. The aim of an RA therapy, therefore, is not only to slow down the disease but to attain remission in order to stop the joint destruction. Besides the severity of the disease outcome, the high prevalence of RA (~ 0.8% of the adults are affected worldwide) means a high socio-economic impact. (For reviews on RA, we refer to Smolen and Steiner (2003); Lee and Weinblatt (2001); Choy and Panayi (2001); O’Dell (2004) and Firestein (2003)).

[0009] Osteoarthritis (also referred to as OA, or wear-and-tear arthritis) is the most common form of arthritis and is characterized by loss of articular cartilage, often associated with hypertrophy of the bone and pain. The disease mainly affects hands and weight-bearing joints such as knees, hips and spines. This process thins the cartilage. When the surface area has disappeared due to the thinning, a grade I osteoarthritis is reached; when the tangential surface area has disappeared, grade II osteoarthritis is reached. There are further levels of degeneration and destruction, which affect the deep and the calcified cartilage layers that border with the subchondral bone. For an extensive review on osteoarthritis, we refer to Wieland et al., 2005.

[0010] The clinical manifestations of the development of the osteoarthritis condition are: increased volume of the joint, pain, crepitation and functional disability that lead to pain and reduced mobility of the
joints. When disease further develops, pain at rest emerges. If the condition persists without correction and/or therapy, the joint is destroyed leading to disability. Replacement surgery with total prosthesis is then required.

Therapeutic methods for the correction of the articular cartilage lesions that appear during the osteoarthritic disease have been developed, but so far none of them have been able to mediate the regeneration of articular cartilage in situ and in vivo.

Osteoarthritis is difficult to treat. At present, no cure is available and treatment focuses on relieving pain and preventing the affected joint from becoming deformed. Common treatments include the use of non-steroidal anti-inflammatory drugs (NSAIDs). Although dietary supplements such as chondroitin and glucosamine sulphate have been advocated as safe and effective options for the treatment of osteoarthritis, a recent clinical trial revealed that both treatments did not reduce pain associated to osteoarthritis. (Clegg et al., 2006). Taken together, no disease modifying osteoarthritic drugs are available.

In severe cases, joint replacement may be necessary. This is especially true for hips and knees. If a joint is extremely painful and cannot be replaced, it may be fused. This procedure stops the pain, but results in the permanent loss of joint function, making walking and bending difficult.

Another possible treatment is the transplantation of cultured autologous chondrocytes. Here, chondral cellular material is taken from the patient, sent to a laboratory where it is expanded. The material is then implanted in the damaged tissues to cover the tissue's defects.

Another treatment includes the intra-articular instillation of Hylan G-F 20 (e.g. Synvisc®, Hyalgan®, Artz®), a substance that improves temporarily the rheology of the synovial fluid, producing an almost immediate sensation of free movement and a marked reduction of pain.

Other reported methods include application of tendinous, periosteal, fascial, muscular or perichondral grafts; implantation of fibrin or cultured chondrocytes; implantation of synthetic matrices, such as collagen, carbon fiber; administration of electromagnetic fields. All of these have reported minimal and incomplete effects, resulting in a poor quality tissue that can neither support the weighted load nor allow the restoration of an articular function with normal movement.

Stimulation of the anabolic processes, blocking catabolic processes, or a combination of these two, may result in stabilization of the cartilage, and perhaps even reversion of the damage, and therefore prevent further progression of the disease. Various triggers may stimulate anabolic stimulation of chondrocytes. Insulin-like growth factor-I (IGF-I) is the predominant anabolic growth factor in synovial fluid and stimulates the synthesis of both proteoglycans and collagen. It has also been shown that members of the bone morphogenetic protein (BMP) family, notably BMP2, BMP4, BMP6, and BMP7, and members of the human transforming growth factor-β (TGF-β) family can induce chondrocyte anabolic stimulation (Chubinskaya and Kuettner, 2003). A compound has recently been identified that induces anabolic stimulation of chondrocytes (US 6,500,854; EP 1 391 211). However, most of these compounds show severe side effects and, consequently, there is a strong need for compounds that stimulate chondrocyte differentiation without these side effects.
Vandeghinste et al. (WO 2005/124342) discovered JAK1 as a target whose inhibition might have therapeutic relevance for several diseases including OA. JAK1 belongs to the Janus kinase (JAK) family of cytoplasmic tyrosine kinases, involved in cytokine receptor-mediated intracellular signal transduction. The JAK family consists of 4 members: JAK1, JAK2, JAK3 and TYK2. JAKs are recruited to cytokine receptors, upon binding of the cytokine, followed by heterodimerization of the cytokine receptor and a shared receptor subunit (common gamma-c chain, gp130). JAKs are then activated by auto- and/or transphosphorylation by another JAK, resulting in phosphorylation of the receptors and recruitment and phosphorylation of members of the signal transducer and activator of transcription (STATs). Phosphorylated STATs dimerize and translocate to the nucleus where they bind to enhancer regions of cytokine-responsive genes. Knockout of the JAK1 gene in mice demonstrated that JAK1 plays essential and nonredundant roles during development: JAK1/- mice died within 24h after birth and lymphocyte development was severely impaired. Moreover, JAK1-/- cells were not, or less, reactive to cytokines that use class II cytokine receptors, cytokine receptors that use the gamma-c subunit for signaling and the family of cytokine receptors that use the gp130 subunit for signaling (Rodig et al., 1998).

Various groups have implicated JAK-STAT signaling in chondrocyte biology. Li et al. (2001) showed that Oncostatin M induces MMP and TIMP3 gene expression in primary chondrocytes by activation of JAK/STAT and MAPK signaling pathways. Osaki et al. (2003) showed that interferon-gamma mediated inhibition of collagen II in chondrocytes involves JAK-STAT1 signaling. IL1-beta induces cartilage catabolism by reducing the expression of matrix components, and by inducing the expression of collagenases and inducible nitric oxide synthase (NOS2), which mediates the production of nitric oxide (NO). Otero et al., (2005) showed that leptin and IL1-beta synergistically induced NO production or expression of NOS2 mRNA in chondrocytes, and that that was blocked by a JAK inhibitor. Legendre et al. (2003) showed that IL6/IL6Receptor induced downregulation of cartilage-specific matrix genes collagen II, aggrecan core and link protein in bovine articular chondrocytes, and that this was mediated by JAK/STAT signaling. Therefore, these observations suggest a role for JAK kinase activity in cartilage homeostasis and therapeutic opportunities for JAK kinase inhibitors.

JAK family members have been implicated in additional conditions including myeloproliferative disorders (O’Sullivan et al., 2007, Mol Immunol. 44(10):2497-506), where mutations in JAK2 have been identified. This indicates that inhibitors of JAK in particular JAK2 may also be of use in the treatment of myeloproliferative disorders. Additionally, the JAK family, in particular JAK1, JAK2 and JAK3, has been linked to cancers, in particular leukaemias e.g. acute myeloid leukaemia (O’Sullivan et al., 2007, Mol Immunol. 44(10):2497-506; Xiang et al., 2008, “Identification of somatic JAK1 mutations in patients with acute myeloid leukemia” Blood First Edition Paper, prepublished online December 26, 2007; DOI 10.1182/blood-2007-05-090308) and acute lymphoblastic leukaemia (Mullighan et al, 2009) or solid tumours e.g. uterine leiomyosarcoma (Constantinescu et al., 2007, Trends in Biochemical Sciences 33(3): 122-131), prostate cancer (Tam et al., 2007, British Journal of Cancer, 97, 378 – 383). These results indicate that
inhibitors of JAK, in particular of JAK1 and/or JAK2, may also have utility in the treatment of cancers (leukaemias and solid tumours e.g. uterine leiomyosarcoma, prostate cancer).

[0021] In addition, Castleman’s disease, multiple myeloma, mesangial proliferative glomerulonephritis, psoriasis, and Kapoś’s sarcoma are likely due to hypersecretion of the cytokine IL-6, whose biological effects are mediated by intracellular JAK-STAT signaling (Tetsuji Naka, Norihiro Nishimoto and Tadamitsu Kishimoto, Arthritis Res 2002, 4 (suppl 3):S233-S242). This result shows that inhibitor of JAK, may also find utility in the treatment of said diseases.

[0022] A link with autoimmune diseases has been established for JAK3 and Tyk2. Mutations in JAK3 but also in the upstream signaling components gamma-c receptor chain and IL7 receptor account in aggregate for ~70% of cases of human severe combined immunodeficiency (‘OShea et al., 2004). Note that JAK1 cooperates with JAK3 in transducing signals from the gamma-c receptor chain. Tyk2 polymorphisms are seen in systemic lupus erythematosus (SLE) (O’Sullivan et al., 2007, Mol Immunol. 44(10):2497-506). Hence, targeting the JAK family may provide a therapeutic opportunity in the immuno-inflammation area.

[0023] The current therapies are not satisfactory and therefore there remains a need to identify further compounds that may be of use in the treatment of diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). The present invention therefore provides compounds, methods for their manufacture and a pharmaceutical comprising a compound of the invention together with a suitable pharmaceutical carrier. The present invention also provides for the use of a compound of the invention in the preparation of a medicament for the treatment of degenerative joint diseases.

**SUMMARY OF THE INVENTION**

[0024] The present invention is based on the discovery that inhibitors of JAK are useful for the treatment of diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin
states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g.
diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases
associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors
of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK
find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine
leiomyosarcoma, prostate cancer). The present invention also provides methods for the production of these
compounds, pharmaceutical compositions comprising these compounds and methods for treating diseases
involving cartilage degradation, joint degradation and/or inflammation by administering a compound of the
invention.

Accordingly, in a first aspect of the invention, substituted bicycloheteroaryl compounds are
disclosed having a formula according to Formula (I):

![Chemical Structure](image)

wherein
each R¹ is independently selected from C₁-C₆ alkyl, substituted C₁-C₆ alkyl, acyl, substituted acyl,
substituted or unsubstituted acylamino, substituted or unsubstituted C₁-C₆ alkoxy, substituted or
unsubstituted amido, substituted or unsubstituted amino, substituted sulfanyl, substituted sulfonyl,
substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano,
substituted or unsubstituted C₅-C₇ cycloalkyl, substituted or unsubstituted 4-7 membered
heterocycloalkyl, halo, and hydroxyl;
R³ is selected from substituted or unsubstituted C₁-C₆ alkyl or C₅-C₇ cycloalkyl;
Cy1 is selected from aryl and heteroaryl;
L1 is selected from a single bond, -O-, -N(R⁴a)-, -C(=O)-, -CON(R⁴a) -, -(SO₂)-, -SO₂N(R⁴a) -, -N(R⁴a)CO-, or -N(R⁴a)SO₂-;
each R³ is independently selected from C₁-C₆ alkyl, substituted C₁-C₆ alkyl, acyl, substituted acyl,
substituted or unsubstituted acylamino, substituted or unsubstituted C₁-C₆ alkoxy, substituted or
unsubstituted amido, alkoxy carbonyl, substituted alkoxy carbonyl, aryalkyloxy, substituted
aryalkyloxy, substituted or unsubstituted amino, aryl, substituted aryl, arylalkyl, substituted sulfanyl,
substituted sulfanyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid,
sulfonic acid ester, azido, carboxy, cyano, substituted or unsubstituted C₅-C₇ cycloalkyl, substituted or
unsubstituted 4-7 membered heterocycloalkyl, halo, substituted or unsubstituted heteroaryl, hydroxyl,
nitro, and thiol;
R\(^{3b}\) is substituted or unsubstituted C\(_1\)–C\(_6\) alkyl, substituted or unsubstituted C\(_7\)–C\(_{10}\) cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C\(_1\)–C\(_6\) alkoxy, substituted or unsubstituted amino, substituted or unsubstituted acylamino, cyano or –O-aryl;

R\(^{4b}\), R\(^{5b}\), R\(^{6c}\) are independently selected from H, C\(_1\)–C\(_6\) alkyl;
m\(_1\) is 0, 1, or 2; m\(_2\) is 0, 1, 2, or 3; and n\(_1\) is 0, 1, 2, or 3;

provided that

when L\(_1\) is –O-, -N(R\(^{6b}\)-), -CON(R\(^{6a}\)-), or -SO\(_2\)N(R\(^{6b}\)-), and R\(^{3b}\) is other than cycloalkyl, aryl or 5-10 membered heteroaryl, then n\(_1\) is 1, 2 or 3;

or pharmaceutically acceptable salts or solvates thereof, or solvates of the pharmaceutically acceptable salts.

[0026] In a further aspect, the present invention discloses substituted bicycloheteroaryl compounds that are capable of modulating the activity of JAK \textit{in vivo}.

[0027] In a further aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. In this aspect of the invention, the pharmaceutical composition can comprise one or more of the compounds described herein. Moreover, the compounds of the present invention useful in the pharmaceutical compositions and treatment methods disclosed herein, are all pharmaceutically acceptable as prepared and used.

[0028] In a further aspect of the invention, this invention provides a method of treating a mammal susceptible to or afflicted with a condition from among those listed herein, and particularly, such condition as may be associated with aberrant JAK activity, for example diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In a particular embodiment the present invention provides a method for treating conditions selected from inflammation, such as rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn's disease, colitis), endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and organ transplant rejection; and cartilage, bone and/or joint degradation or degeneration, such as osteoarthritis, which
method comprises administering an effective amount of one or more of the pharmaceutical compositions or compounds herein described.

[0029] In a further aspect, the present invention provides a method of treating a mammal susceptible to or afflicted with proliferative disorders in particular cancer, (e.g. solid tumours), leukaemias, multiple myeloma or psoriasis.

[0030] In a further aspect, the present invention provides a compound of the invention for use in the treatment or prevention of a condition selected from those listed herein, particularly such conditions as may be associated with aberrant JAK activity such as diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In a specific embodiment, the condition is selected from inflammation, such as rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn’s disease, colitis), endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and organ transplant rejection; and cartilage, bone and/or joint degradation or degeneration, such as osteoarthritis.

[0031] In a further aspect, the present invention provides a compound of the invention for use in the treatment or prevention of proliferative disorders, in particular cancer, (e.g. solid tumours), leukaemias, multiple myeloma or psoriasis.

[0032] In yet another method of treatment aspect, this invention provides a method for treating a mammal susceptible to or afflicted with a condition that is causally related to abnormal JAK activity as described herein, and comprises administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds herein described.

[0033] In a further aspect, the present invention provides a compound of the invention for use in the treatment or prevention of a condition that is causally related to abnormal JAK activity.

[0034] In additional aspects, this invention provides methods for synthesizing the compounds of the invention, with representative synthetic protocols and pathways disclosed later on herein.
Accordingly, it is a principal object of this invention to provide a novel series of compounds, which can modify the activity of JAK and thus prevent or treat any maladies that may be causally related thereto.

It is further an object of this invention to provide a series of compounds that can treat or alleviate maladies or symptoms of same, such as cartilage and/or bone degradation and related inflammation, and joint diseases, that may be causally related to the activity of JAK.

A still further object of this invention is to provide pharmaceutical compositions that may be used in the treatment or prevention of a variety of disease states, including the diseases associated with JAK activity such as diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In a specific embodiment the condition is selected from inflammation, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and organ transplant rejection; and cartilage, bone and/or joint degradation or degeneration, such as osteoarthritis or cancers (e.g. solid tumours or leukaemias).

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

**DETAILED DESCRIPTION OF THE INVENTION**

**Definitions**

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.

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.

[0041] 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.

[0042] ‘Acyl’ or ‘Alkanoyl’ refers to a radical -C(O)R\textsuperscript{20}, where R\textsuperscript{20} is hydrogen, C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{3}-C\textsubscript{10} cycloalkyl, C\textsubscript{2}-C\textsubscript{10} cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylmethyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzy1carbonyl. Exemplary ‘acyl’ groups are –C(O)H, –C(O)-C\textsubscript{1}-C\textsubscript{8} alkyl, –C(O)-(CH\textsubscript{2})\textsubscript{2}(C\textsubscript{6}-C\textsubscript{10} aryl), –C(O)-(CH\textsubscript{2})\textsubscript{4}(5-10 membered heteroaryl), –C(O)-(CH\textsubscript{2})\textsubscript{2}(C\textsubscript{2}-C\textsubscript{10} cycloalkyl), and –C(O)-(CH\textsubscript{2})\textsubscript{4}(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

[0043] ‘Substituted Acyl’ or ‘Substituted Alkanoyl’ refers to a radical -C(O)R\textsuperscript{21}, wherein R\textsuperscript{21} is independently
  - C\textsubscript{1}-C\textsubscript{4} alkyl, substituted with halo or hydroxy; or
  - C\textsubscript{3}-C\textsubscript{10} cycloalkyl, 4-10 membered heterocycloalkyl, C\textsubscript{6}-C\textsubscript{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylmethyl, each of which is substituted with unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl, halo, unsubstituted C\textsubscript{1}-C\textsubscript{4} alkoxy, unsubstituted C\textsubscript{1}-C\textsubscript{4} haloalkyl, unsubstituted C\textsubscript{1}-C\textsubscript{4} hydroxyalkyl, or unsubstituted C\textsubscript{1}-C\textsubscript{4} haloalkoxy or hydroxy.

[0044] ‘Acylamino’ refers to a radical -NR\textsuperscript{22}C(O)R\textsuperscript{23}, where R\textsuperscript{22} is hydrogen, C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{3}-C\textsubscript{10} cycloalkyl, 4-10 membered heterocycloalkyl, C\textsubscript{6}-C\textsubscript{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylmethyl and R\textsuperscript{23} is hydrogen, C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{2}-C\textsubscript{10} cycloalkyl, 4-10 membered heterocycloalkyl, C\textsubscript{6}-C\textsubscript{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylmethyl, as defined herein. Exemplary ‘acylamino’ include, but are not limited to, formylanino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethylcarbonylamino, benzoylamino and benzy1carbonylamino. Exemplary ‘acylamino’ groups are –NR\textsuperscript{21}C(O)-C\textsubscript{1}-C\textsubscript{8} alkyl, –NR\textsuperscript{21}C(O)-(CH\textsubscript{2})\textsubscript{2}(C\textsubscript{6}-C\textsubscript{10} aryl), –NR\textsuperscript{21}C(O)-(CH\textsubscript{2})\textsubscript{2}(5-10 membered heteroaryl), –NR\textsuperscript{21}C(O)-(CH\textsubscript{2})\textsubscript{2}(C\textsubscript{2}-C\textsubscript{10} cycloalkyl), and –NR\textsuperscript{21}C(O)-(CH\textsubscript{2})\textsubscript{2}(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, each R\textsuperscript{21} independently represents H or C\textsubscript{1}-C\textsubscript{4} alkyl.

[0045] ‘Substituted Acylamino’ refers to a radical -NR\textsuperscript{24}C(O)R\textsuperscript{25}, wherein:
  - R\textsuperscript{24} is independently
    - H, C\textsubscript{1}-C\textsubscript{8} alkyl, substituted with halo or hydroxy; or
    - C\textsubscript{3}-C\textsubscript{10} cycloalkyl, 4-10 membered heterocycloalkyl, C\textsubscript{6}-C\textsubscript{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylmethyl, each of which is substituted with unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl, halo,
unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy; and

R²⁵ is independently

- H, C₁₋₃ alkyl, substituted with halo or hydroxy; or
- C₅₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylmalkyl, each of which is substituted with unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxyl;

provided at least one of R²⁴ and R²⁵ is other than H.

[0046] ‘Alkoxy’ refers to the group –OR²⁶ where R²⁶ is C₁₋₃ alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isoproxy, 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.

[0047] ‘Substituted alkoxy’ refers to an alkoxy group substituted with one or more of those groups recited in the definition of “substituted” herein, and particularly refers to an alkoxy group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C₆₋₁₀ aryl, -O-aryl, carboxyl, cyano, C₅₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, halogen, 5-10 membered heteroaryl, hydroxyl, nitro, thioalkoxy, thio-O-aryl, thiol, alkyl-S(O)₂-, aryl-S(O)₂-, alkyl-S(O)₂- and aryl-S(O)₂-. Exemplary ‘substituted alkoxy’ groups are –O-(CH₂)₆(C₆₋₁₀ aryl), –O-(CH₂)₉(5-10 membered heteroaryl), –O-(CH₂)₉(C₅₋₁₀ cycloalkyl), and –O-(CH₂)₉(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁₋₄ alkyl, halo, unsubstituted C₁₋₄ alkoxy, unsubstituted C₁₋₄ haloalkyl, unsubstituted C₁₋₄ hydroxyalkyl, or unsubstituted C₁₋₄ haloalkoxy or hydroxy. Particular exemplary ‘substituted alkoxy’ groups are OCF₃, OCH₂CF₃, OCH₂Ph, OCH₂-cyclopropyl, OCH₂CH₂OH, OCH₂CH₂NMe₂.

[0048] ‘Alkoxy carbonyl’ refers to a radical -C(O)-OR²⁷ where R²⁷ represents an C₁₋₃ alkyl, C₃₋₁₀ cycloalkyl, C₅₋₁₀ cycloalkylalkyl, 4-10 membered heterocycloalkylalkyl, aralkyl, or 5-10 membered heteroarylmalkyl as defined herein. Exemplary “alkoxy carbonyl” groups are C(O)O-C₁₋₃ alkyl, C(O)O-(CH₂)₆(C₆₋₁₀ aryl), -C(O)O-(CH₂)₉(5-10 membered heteroaryl), -C(O)O-(CH₂)₉(C₅₋₁₀ cycloalkyl), and -C(O)O-(CH₂)₉(4-10 membered heterocycloalkyl), wherein t is an integer from 1 to 4.

[0049] ‘Substituted Alkoxy carbonyl’ refers to a radical -C(O)-OR²⁸ where R²⁸ represents:

- C₁₋₃ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkylalkyl, or 4-10 membered heterocycloalkylalkyl, each of which is substituted with halo, substituted or unsubstituted amino, or hydroxy; or
• C₆-C₁₀ aralkyl, or 5-10 membered heteroarylalkyl, each of which is substituted with unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxyl.

[0050] ‘Alkyl’ means straight or branched aliphatic hydrocarbon having 1 to 20 carbon atoms. Particular alkyl has 1 to 12 carbon atoms. More particular is lower alkyl which has 1 to 6 carbon atoms. A further particular group has 1 to 4 carbon atoms. Exemplary straight chain groups include methyl, ethyl, propyl, and n-butyl. Branched means that one or more lower alkyl groups such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain, exemplarily branched chain groups include isopropyl, iso-butyl, t-butyl and isomyl.

[0051] ‘Substituted alkyl’ refers to an alkyl group as defined above substituted with one or more of those groups recited in the definition of “substituted” herein, and particularly refers to an alkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of acyl, acylamino, acyloxy (-O-acyl or -OC(O)R), alkoxycarbonyl, alkoxycarbonylamino (-NR₂-alkoxycarbonyl or -NH-C(O)-OR), amino, substituted amino, aminocarbonyl (carbamoyl or amido or -C(O)-NR₂), aminocarbonylamino (-NR₂-C(O)-NR₂), aminocarbonyloxy (-O-C(O)-NR₂), aminosulfonyl, sulfonylamino, aryloxy, O-aryl, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, heteroaryl, nitro, thiol, S-alkyl, S-aryl, S(O)-alkyl, S(O)-aryl, S(O)-alkyl, and S(O)-aryl. In a particular embodiment ‘substituted alkyl’ refers to a C₁-C₈ alkyl group substituted with halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -NR₂SO₂R, -SO₂NR₂R, -C(O)R, -C(O)OR, -NR₂C(O)R, -NR₂C(O)NR₂R, -NR₂R, or -(CR₃R)₆OR; wherein each R₂ is independently selected from H, C₁-C₈ alkyl, -(CH₂)(C₆-C₁₀ aryl), -(CH₂)$_n$(5-10 membered heteroaryl), -(CH₂)$_n$(C₁-C₁₀ cycloalkyl), and -(CH₂)$_n$(4-10 membered heterocycloalkyl), wherein n is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy. Each of R₂ and R₃ independently represents H or C₁-C₈ alkyl.

[0052] ‘Amino’ refers to the radical -NH₂.

[0053] ‘Substituted amino’ refers to an amino group substituted with one or more of those groups recited in the definition of ‘substituted’ herein, and particularly refers to the group -N(R3)$^3$; where each R₃ is independently selected from:

- hydrogen, C₁-C₈ alkyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, or C₃-C₁₀ cycloalkyl; or
- C₁-C₈ alkyl, substituted with halo or hydroxy; or
- -(CH₂)$_n$(C₆-C₁₀ aryl), -(CH₂)$_n$(5-10 membered heteroaryl), -(CH₂)$_n$(C₃-C₁₀ cycloalkyl) or -(CH₂)$_n$(4-10 membered heterocycloalkyl) wherein n is an integer between 0 and 8, each of
which is substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy,
unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄
haloalkoxy or hydroxy; or

- both R₃³ groups are joined to form an alkenylene group.

When both R₃³ groups are hydrogen, -N(R₃³)₂ is an amino group. Exemplary ‘substituted amino’
groups are -NR₃³-C₁-C₈ alkyl, -NR₃³-(CH₂)(C₆-C₁₀ aryl), -NR₃³-(CH₂)(5-10 membered heteroaryl),
-NR₃³-(CH₂)(C₅-C₁₀ cycloalkyl), and -NR₃³-(CH₂)(4-10 membered heterocycloalkyl), wherein t is
an integer from 0 to 4, each R₃³ independently represents H or C₁-C₈ alkyl; and any alkyl groups
present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and
any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by
unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl,
unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0054] “Aminosulfonyl” or “Sulfonamide” refers to the radical –S(O₂)NH₂.

[0055] “Substituted aminosulfonyl” or “substituted sulfonamide” refers to a radical such as –
S(O₂)N(R₄⁸)₂ wherein each R₄⁸ is independently selected from:

- H, C₁-C₈ alkyl, C₅-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10
membered heteroaryl, and heteroaralkyl; or

- C₁-C₄ alkyl substituted with halo or hydroxy; or

- C₅-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10 membered heteroaryl,
or heteroaralkyl, substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy,
unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or
hydroxy;

provided that at least one R₄⁸ is other than H.

[0056] Exemplary ‘substituted aminosulfonyl’ or ‘substituted sulfonamide’ groups are –S(O₂)N(R₄⁸)₃-
C₁-C₈ alkyl, –S(O₂)N(R₄⁸)-(CH₂)(C₆-C₁₀ aryl), –S(O₂)N(R₄⁸)-(CH₂)(5-10 membered heteroaryl), –
S(O₂)N(R₄⁸)-(CH₂)(C₅-C₁₀ cycloalkyl), and –S(O₂)N(R₄⁸)-(CH₂)(4-10 membered heterocycloalkyl), wherein
the t is an integer from 0 to 4; each R₄⁸ independently represents H or C₁-C₈ alkyl; and any aryl, heteroaryl,
cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl,
halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or
unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0057] ‘Aralkyl’ or ‘arylalkyl’ refers to an alkyl group, as defined above, substituted with one or
more aryl groups, as defined above. Particular aralkyl or arylalkyl groups are alkyl groups substituted with one
aryl group.

[0058] ‘Substituted Aralkyl’ or ‘substituted arylalkyl’ refers to an alkyl group, as defined above,
substituted with one or more aryl groups; and at least one of any aryl group present, may themselves be
substituted by unsubstituted C₁-C₄ alkyl, halo, cyano, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0059] ‘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, mono-cyclic or poly-cyclic that includes from 5 to 12 ring members, more usually 6 to 10. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene and trinaphthalene. Particularly aryl groups include phenyl, napthyl, indenyl, and tetrahydronaphthyl.

[0060] ‘Substituted Aryl’ refers to an aryl group substituted with one or more of those groups recited in the definition of ‘substituted’ herein, and particularly refers to an aryl group that may optionally be substituted with 1 or more substituents, for instance from 1 to 5 substituents, particularly 1 to 3 substituents, in particular 1 substituent. Particularly, ‘Substituted Aryl’ refers to an aryl group substituted with one or more of groups selected from halo, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, cyano, hydroxy, C₁-C₈ alkoxy, and amino.

[0061] Examples of representative substituted aryls include the following

![Diagram](image-url)

[0062] In these formulae one of R⁴⁹ and R⁵₀ may be hydrogen and at least one of R⁴⁹ and R⁵₀ is each independently selected from C₁-C₈ alkyl, 4-10 membered heterocycloalkyl, alkanoyl, C₁-C₈ alkoxy, hetero-O-aryl, alkylamino, arylamino, heteroarylamino, NR⁵¹COR⁵², NR⁵¹SOR⁵² NR⁵¹SO₂R⁵², COOalkyl, COOaryl, CONR⁵¹R⁵², CONR⁵¹OR⁵², NR⁵¹R⁵², SO₂NR⁵¹R⁵², S-alkyl, SO₂aryl, SO₂alkyl, Saryl, SO₂aryl, SO₂aryl; or R⁴⁹ and R⁵₀ may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O or S. R⁵¹, and R⁵² are independently hydrogen, C₁-C₈ alkyl, C₁-C₄ haloalkyl, C₅-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, substituted aryl, 5-10 membered heteroaryl.

[0063] ‘Arylalkyloxy’ refers to an -O-alkylaryl radical where alkylaryl is as defined herein.

[0064] ‘Substituted Arylalkyloxy’ refers to an -O-alkylaryl radical where alkylaryl is as defined herein; and any aryl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl, halo, cyano,
unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[0065] ‘Azido’ refers to the radical -N3.

[0066] ‘Carbamoyl or amido’ refers to the radical -C(O)NH2.

[0067] ‘Substituted Carbamoyl or substituted amido’ refers to the radical -C(O)N(R53)2 wherein each R53 is independently

- H, C1-C8 alkyl, C9-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C1-C8 alkyl substituted with halo or hydroxy; or
- C9-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy;

provided that at least one R53 is other than H.

Exemplary ‘Substituted Amido / Carbamoyl’ groups are -C(O)NR53-C1-C8 alkyl, -C(O)NR53-(CH2)n(C6-C10 aryl), -C(O)N53-(CH2)n(5-10 membered heteroaryl), -C(O)NR53-(CH2)n(C1-C10 cycloalkyl), and -C(O)NR53-(CH2)n(4-10 membered heterocycloalkyl), wherein n is an integer from 0 to 4, each R53 independently represents H or C1-C8 alkyl and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

[0068] ‘Carboxy’ refers to the radical -C(O)OH.

[0069] ‘Cycloalkyl’ refers to cyclic non-aromatic hydrocarbon groups having from 3 to 10 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

[0070] ‘Substituted cycloalkyl’ refers to a cycloalkyl group as defined above substituted with one or more of those groups recited in the definition of ‘substituted’ herein, and particularly refers to a cycloalkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent.

[0071] ‘Cyan’ refers to the radical -CN.

[0072] ‘Halo’ or ‘halogen’ refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

[0073] ‘Hetero’ when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbonyl groups described above such as alkyl, e.g.
heteroalkyl, cycloalkyl, e.g. heterocycloalkyl, aryl, e.g. heteroaryl, cycloalkenyl, e.g. cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0074] 'Heteroaryl' means an aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms and 5 to 12 ring members, more usually 5 to 10 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole and imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoazoxole, isobenzoxazoles, benzisoxazole, benzthiazoles, benzisothiazoles, isobenzofurans, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiocroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoazaine, benzdiaizene, pyridopyridin, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

[0075] Examples of representative aryl having hetero atoms containing substitution include the following:

![Diagram]

wherein each W is selected from C(R^6)_2, NR^4, O and S; and each Y is selected from carbonyl, NR^4, O and S; and R^4 is independently hydrogen, C_1-C_8 alkyl, C_3-C_10 cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_10 aryl, and 5-10 membered heteroaryl.
Examples of representative heteroaryl s include the following:

wherein each Y is selected from carbonyl, N, NR, O and S; and R is independently hydrogen, C₁-C₈ alkyl, C₇-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl.

As used herein, the term ‘heterocycloalkyl’ refers to a 4-10 membered, stable heterocyclic non-aromatic ring and/or including rings containing one or more heteroatoms independently selected from N, O and S, fused thereto. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazine, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:

wherein each W is selected from CR, C(R), NR, O and S; and each Y is selected from NR, O and S; and R is independently hydrogen, C₁-C₈ alkyl, C₇-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl.
aryl, 5-10 membered heteroaryl, These heterocycloalkyl rings may be optionally substituted with one or more groups selected from the group consisting of aeryl, acylamino, acyloxy (-O-acyl or -OC(O)R), alkoxycarbonyl, alkoxycarbonylamino (-NR alkoxycarbonyl or -NH-C(O)-OR), amino, substituted amino, aminocarbonyl (amido or -C(O)-NR), aminocarbonylamino (-NR C(O)-NR), aminocarbonylxy (-O-C(O)-NR), aminosulfonfyl, sulfonlamino, aryl, -O-aryl, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, nitro, thiol, -S-alkyl, -S-aryl, -S(=O)(O)-aryl, -S(O)-alkyl, and -S(O)-aryl. Substituting groups include carbonyl or thio carbonyl which provide, for example, lactam and urea derivatives.

[0078] ‘Hydroxy’ refers to the radical -OH.

[0079] ‘Nitro’ refers to the radical –NO₂.

[0080] ‘Substituted’ refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituents(s). Typical substituents may be selected from the group consisting of:

- halogen, -R, -O, =O, -OR, -SR, -S, =S, -NR₂R, =NR, -CCl₃, -CF₃, -CN, -OCN, -SCN, -NO₂, =N₂, -N₃, -S(O)₂O, -S(O)₂OH, -S(O)R₂, =O(S(O)₂)O, =O(S(O)₂)R, =P(O)(O)R₂, =P(O)(OR), =OP(O)(O)R, =C(S)R, =C(=O)OR, =C(=O)NR₂R, =C(=O)N,R₅R₅, =C(=O)OR, =C(S)OR, =NR₂NR₅R₅, =NR₅C(S)NR₅R₅, =NR₅C(NR₅)NR₅R₅ and =C(NR₅)NR₅R₅;

wherein each R, R, R and R are independently:

- hydrogen, C₁-C₈ alkyl, C₆-C₁₀ aryl, arylalkyl, C₃-C₄ cycloalkyl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, heteroarylalkyl; or
- C₁-C₈ alkyl substituted with halo or hydroxy; or
- C₆-C₁₀ aryl, 5-10 membered heteroaryl, C₆-C₁₀ cycloalkyl or 4-10 membered heterocycloalkyl substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₂ haloalkoxy or hydroxy.

In a particular embodiment, substituted groups are substituted with one or more substituents, particularly with 1 to 3 substituents, in particular with one substituent group.

In a further particular embodiment the substituent group or groups are selected from: halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -NR SO₂R, -SO₂NR R, -C(O)R, -C(O)OR, -OC(O)R, -NR C(O)R, -C(O)NR R, -NR R, -(CR R) OR, wherein each R is independently selected from H, C₁-C₈ alkyl, -(CH₂)(C₆-C₁₀ aryl), -(CH₂)(S-10 membered heteroaryl), -(CH₂)(C₃-C₁₀ cycloalkyl), and -(CH₂)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4; and

- any alkyl groups present, may themselves be substituted by halo or hydroxy; and
- any heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄...
haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.
Each Rᵢ independently represents H or C₁-C₆ alky.

[0081] ‘Substituted sulfanyl’ refers to the group –SR₆¹, wherein R₆¹ is selected from:

- C₁-C₈ alkyl, C₂-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C₁-C₆ alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C₂-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0082] Exemplary ‘substituted sulfanyl’ groups are –S-(C₁-C₆ alkyl) and –S-(C₂-C₁₀ cycloalkyl), –S-(CH₂)(C₆-C₁₀ aryl), –S-(CH₂)₈(5-10 membered heteroaryl), –S-(CH₂)(C₂-C₁₀ cycloalkyl), and –S-(CH₂)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0083] ‘Substituted sulfanyl’ refers to the group –S(O)R₆₈, wherein R₆₈ is selected from:

- C₁-C₈ alkyl, C₂-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C₁-C₆ alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C₂-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0084] Exemplary ‘substituted sulfanyl’ groups are –S(O)–(C₁-C₆ alkyl) and –S(O)–(C₂-C₁₀ cycloalkyl), –S(O)–(CH₂)(C₆-C₁₀ aryl), –S(O)–(CH₂)(5-10 membered heteroaryl), –S(O)–(CH₂)(C₂-C₁₀ cycloalkyl), and –S(O)–(CH₂)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy.

[0085] ‘Substituted sulfonyl’ refers to the group –S(O)₂R₇₅, wherein R₇₅ is selected from:

- C₁-C₈ alkyl, C₂-C₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₆-C₁₀ aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C₁-C₆ alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_{1-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_{1-4} alky1, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy.

Exemplary ‘substituted sulfonyl’ groups are \(-S(O)_{2}-(C_{1-4} alky1)\) and \(-S(O)_{2}-(C_{3-10} cycloalkyl)\), \(-S(O)_{2}-(CH)_{n}(C_{6-10} aryl)\), \(-S(O)_{2}-(CH)_{n}(5-10 membered heteroaryl)\), \(-S(O)_{2}-(CH)_{n}(C_{1-10} cycloalkyl)\), and \(-S(O)_{2}-(CH)_{n}(4-10 membered heterocycloalkyl)\), wherein \(n\) is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_{1-4} alky1, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy.

‘Sulfo’ or ‘sulfonic acid’ refers to a radical such as \(-SO_{2}H\).

‘Substituted sulfo’ or ‘sulfonic acid ester’ refers to the group \(-S(O)_{2}OR^{E}\), wherein \(R^{E}\) is selected from:
- C_{1-4} alky1, C_{2-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, aralkyl, 5-10 membered heteroaryl, and heteroaralkyl; or
- C_{1-4} alky1 substituted with halo, substituted or unsubstituted amino, or hydroxy; or
- C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C_{6-10} aryl, aralkyl, 5-10 membered heteroaryl, or heteroaralkyl, each of which is substituted by unsubstituted C_{1-4} alky1, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy.

Exemplary ‘Substituted sulfo’ or ‘sulfonic acid ester’ groups are \(-S(O)_{2}O-(C_{1-4} alky1)\) and \(-S(O)_{2}O-(C_{3-10} cycloalkyl)\), \(-S(O)_{2}O-(CH)_{n}(C_{6-10} aryl)\), \(-S(O)_{2}O-(CH)_{n}(5-10 membered heteroaryl)\), \(-S(O)_{2}O-(CH)_{n}(C_{3-10} cycloalkyl)\), and \(-S(O)_{2}O-(CH)_{n}(4-10 membered heterocycloalkyl)\), wherein \(n\) is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C_{1-4} alky1, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy.

‘Thiol’ refers to the group \(-SH\).

One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms.

In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

‘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.

[0093] ‘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, cyclopentaneacetic acid, glycine 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-toluensulfonic 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 sulfonic acid, gluconic acid, glutamic acid, hydroxyxynaphthoic 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.

[0094] ‘Pharmaceutically acceptable vehicle’ refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0095] ‘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.

[0096] ‘Solvate’ refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The 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. ‘Solvent’ encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0097] ‘Subject’ includes humans. The terms ‘human’, ‘patient’ and ‘subject’ are used interchangeably herein.

[0098] ‘Therapeutically effective amount’ means the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0099] ‘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.

[0100] 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.

[0101] ‘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.

[0102] As used herein the term ‘condition(s) involving inflammation’ refers to the group of conditions including, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, psoriasis, allergic airway disease (e.g. asthma, rhinitis), inflammatory bowel diseases (e.g. Crohn’s disease, 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) and inflammatory bowel diseases.

[0103] As used herein the term ‘condition(s) involving an immune response’ or “autoimmune diseases” are used interchangeably and refer to any of 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), multiple
sclerosis, type 1 diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly the term refers to COPD, asthma, systemic lupus erythematosus, type I diabetes mellitus and inflammatory bowel disease.

[00104] 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.

[00105] As used herein the term 'proliferative diseases' refers to conditions such as cancer (e.g. uterine leiomyosarcoma or prostate cancer), myeloproliferative disorders (e.g. polycythemia vera, essential thrombocytosis and myelofibrosis), leukemia (e.g. acute myeloid leukaemia and acute lymphoblastic leukemia), multiple myeloma, psoriasis, restenosis, sclerodermitis or fibrosis. In particular the term refers to cancer, leukemia, multiple myeloma and psoriasis.

[00106] As used herein, the term 'cancer' refers to a malignant or benign growth of cells in skin or in body organs, for example 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.

[00107] As used herein the term ‘leukaemia’ 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).

[00108] As used herein the term ‘diseases involving impairment of cartilage turnover’ and specifically ‘diseases involving the anabolic stimulation of chondrocytes’ 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, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis.

[00109] 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.
As used herein the term ‘disease(s) associated with hypersecretion of IL6’ includes conditions such as Castleman’s disease, multiple myeloma, psoriasis, Kaposi’s sarcoma and/or mesangial proliferative glomerulonephritis.

‘Compound(s) of the invention’, and equivalent expressions, are meant to embrace compounds of the Formula(e) as hereinbefore 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.

When ranges are referred to herein, for example but without limitation, C₁₋C₈ alkyl, the citation of a range should be considered a representation of each member of said range.

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 (see, Bundgaard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 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 ((alkoxy)carboxyl)oxy)alkylesters. Particular such prodrugs 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.

As used herein, the term ‘isotopic variant’ refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an ‘isotopic variant’ of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (²H or D), carbon-13 (¹³C), nitrogen-15 (¹⁵N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ²H/D, any carbon may be ¹³C, or any nitrogen may be ¹⁵N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may 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. Further, compounds may be prepared that are substituted with 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.
All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

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’.

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’.

‘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.

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

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

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.

THE COMPOUNDS

The present invention is based on the discovery that inhibitors of JAK are useful for the treatment of diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g.
diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In particular diseases involving cartilage degradation, bone and/or joint degradation and/or inflammation, for example osteoarthritis. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating diseases involving cartilage degradation, bone and/or joint degradation and/or inflammation by administering a compound of the invention. The present compounds may be inhibitors of one or more members of the JAK family; specifically they may inhibit the activity of one or more of JAK1, JAK2, JAK3 and/or TYK2.

Accordingly, in a first aspect of the invention, substituted bicycloheteroaryl compounds are disclosed according to Formula I:

$\text{Cy1}$

wherein

each $R^1$ is independently selected from $C_1$-$C_6$ alkyl, substituted $C_1$-$C_6$ alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted $C_1$-$C_6$ alkoxy, substituted or unsubstituted amido, substituted or unsubstituted amino, substituted sulfinyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano, substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, and hydroxyl;

$R^{3b}$ is selected from substituted or unsubstituted $C_1$-$C_6$ alkyl or $C_3$-$C_7$ cycloalkyl;

$\text{Cy1}$ is selected from aryl and heteroaryl;

$L^1$ is selected from a single bond, -O-, -N(R^{4a})-, -C(=O)-, -CON(R^{4a})-, -(SO_{2})-, -SO_{2}N(R^{4a})-, -N(R^{4a})CO-, or -N(R^{4a})SO_{2}-;

each $R^{3b}$ is independently selected from $C_1$-$C_6$ alkyl, substituted $C_1$-$C_6$ alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted $C_1$-$C_6$ alkoxy, substituted or unsubstituted amido, alkoxyxoylbonyl, substituted alkoxyxocn, arylalkylxoy, substituted aryalkoxy, substituted or unsubstituted amino, aryl, substituted aryl, aryalkyl, substituted sulfanyl, substituted sulfinyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, substituted or
unsubstituted 4-7 membered heterocycloalkyl, halo, substituted or unsubstituted heteroaryl, hydroxyl, nitro, and thiol;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_5-C_7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted amino, substituted or unsubstituted acylamino, cyano or -O-aryl;

R^{ab}, R^{ch}, R^{ac} are independently selected from H, C_1-C_6 alkyl;

m1 is 0, 1, or 2; m2 is 0, 1, 2, or 3; and n1 is 0, 1, 2, or 3;

provided that

when L1 is -O-, -N(R^{ta})-, -CON(R^{ta})-, or -SO_2N(R^{ta})-, and R^{ab} is other than cycloalkyl, aryl or 5-10 membered heteroaryl, then n1 is 1, 2 or 3;

or pharmaceutically acceptable salts or solvates thereof, or solvates of the pharmaceutically acceptable salts.

[00124] In a particular embodiment, the compound is according to Formula I, wherein

each R^1 is independently selected from unsubstituted C_1-C_6 alkyl, unsubstituted acyl, unsubstituted acylamino, unsubstituted C_1-C_6 alkoxy, unsubstituted amido, unsubstituted amino, unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano, unsubstituted C_5-C_7 cycloalkyl, unsubstituted 4-7 membered heterocycloalkyl, halo, and hydroxyl;

R^{sa} is selected from unsubstituted C_1-C_6 alkyl or unsubstituted C_5-C_7 cycloalkyl;

Cy1 is selected from aryl and heteroaryl;

L1 is selected from a single bond, -O-, -N(R^{ta})-, -C(=O)-, -CON(R^{ta})-, -(SO_2)- -SO_2N(R^{ta})-, -N(R^{ta})CO-, or -N(R^{ta})SO_2-; -CR^{ch}=CR^{ac};

each R^{sa} is independently selected from unsubstituted C_1-C_6 alkyl, unsubstituted acyl, unsubstituted acylamino, unsubstituted C_1-C_6 alkoxy, unsubstituted amido, unsubstituted alkoxy carbonyl, unsubstituted aryalkyloxy, unsubstituted amino, unsubstituted aryl, unsubstituted sulfanyl, unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, unsubstituted C_5-C_7 cycloalkyl, unsubstituted 4-7 membered heterocycloalkyl, halo, unsubstituted heteroaryl, hydroxyl, nitro, and thiol;

R^{ch} is H, C_1-C_6 alkyl (which C_1-C_6 alkyl may be substituted with cyano), C_5-C_7 cycloalkyl (which C_5-C_7 cycloalkyl may be substituted with unsubstituted C_1-C_4 alkyl), 4-7 membered heterocycloalkyl (which 4-7 membered heterocycloalkyl may be substituted with unsubstituted C_1-C_4 alkyl, cyano, OH), aryl (which aryl may be substituted with unsubstituted C_1-C_4 alkyl, cyano), heteroaryl (which heteroaryl may be substituted with unsubstituted C_1-C_4 alkyl, unsubstituted C_1-C_4 alkoxy, cyano, halo, OH, unsubstituted aryl), C_1-C_6 alkoxy (which C_1-C_6 alkoxy may be substituted with cyano), amino (which
amino may be substituted with unsubstituted aryl, substituted or unsubstituted acylamino (which
acylamino may be substituted with unsubstituted C₈-C₄ alkyl), cyano or unsubstituted -O-aryl;
R²₄, R⁴₀, and R⁴₄ are independently selected from H, unsubstituted C₈-C₆ alkyl, acyl (which acyl may be
substituted with unsubstituted C₈-C₄ alkyl);
m₁ is 0, 1, or 2; m₂ is 0, 1, 2, or 3; and n₁ is 0, 1, 2, or 3;
provided that
when L₁ is -N(R⁴₄)-, -CON(R⁴₄)-, or -SO₂N(R⁴₄)-, and R²₂ is other than H, C₈-C₆ alkyl, C₅-C₇
cycloalkyl, aryl or heteroaryl, then n₁ is 1, 2, 3, or 4;
or pharmaceutically acceptable salts thereof, solvates of the compounds, and solvates of the
pharmaceutically acceptable salts.

[00125] In one embodiment, with respect to Formula I, R²₄ is substituted or unsubstituted cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[00126] In one embodiment, with respect to Formula I, R²₄ is cyclopropyl.

[00127] In one embodiment, with respect to Formula I, each R¹ is independently halo, C₈-C₆ alkyl or
C₅-C₆ haloalkyl.

[00128] In further embodiment, with respect to Formula I, m₁ is 0.

[00129] In one embodiment, with respect to Formula I, Cy₁ is aryl.

[00130] In a particular embodiment, with respect to Formula I, Cy₁ is phenyl.

[00131] In another embodiment with respect to Formula I, Cy₁ is heteroaryl.

[00132] In a particular embodiment, with respect to Formula I, Cy₁ is selected from pyridyl, pyrrolyl,
pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzodioxanyl, quinolinyl and
isoquinolinyl.

[00133] In one embodiment, with respect to Formula I, each R²₂ is selected from C₈-C₆ alkyl, C₅-C₆
haloalkyl, halo, C₅-C₆ alkoxy, -O-aryl, hydroxyl, substituted or unsubstituted amino, substituted or
unsubstituted amidio, carboxy, substituted or unsubstituted acylamino, substituted or unsubstituted aryl,
substituted or unsubstituted heteroaryl, substituted or unsubstituted C₅-C₇ cycloalkyl, substituted or
unsubstituted 4-7 membered heterocycloalkyl, and m₂ is 0, 1, 2 or 3.

[00134] In a particular embodiment, with respect to Formula I, each R³₂ is selected from Me, Et, CF₃,
Cl, F, OMe, OEt, O-iPr, O-nPr, -OCF₃, -CO₂H, -NHAc, -Ph or -OH and m₂ is 0, 1, 2 or 3.

[00135] In another embodiment, with respect to Formula I, the compound is according to Formula IIa,
IIb, IIc, IID, IIe, IIf, IIG, IIH or III:
wherein $R^{3a}$, $R^{3b}$, $R^{4a}$, $R^{4c}$, and $n1$ are as described above.

[00136] In one embodiment with respect to Formulae Ila, IIb, IIC, IID, IIE, IIF, IIG, IIH or III, $R^{7b}$ is selected from Me, Et, i-Pr, OMe, CF$_3$, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, cyano, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy, substituted or unsubstituted piperidinyl, substituted
or unsubstituted piperazinyl, substituted or unsubstituted azepinyl, substituted or unsubstituted diazepinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted tetrahydroquinolinyl, substituted or unsubstituted tetrahydroisoquinolinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted imidazolyl, and substituted or unsubstituted oxadiazolyl.

[00137] In a particular embodiment with respect to Formulae Ia, IIb, IIc, IID, IIe, IIi, IIg, IIh or III, R_{3b} is selected from phenyl, phenoxy, pyridinyl, pyrrolyl, pyrazolyl, oxazolyl, imidazolyl, and oxadiazolyl unsubstituted or substituted with one or more groups selected from Me, Cl, F, CF₃, substituted or unsubstituted acyl, substituted or unsubstituted benzyl, and substituted or unsubstituted phenyl.

[00138] In another embodiment, with respect to compounds of Formulae Ia, IIg, IIe, IIf, III or IIIi; m₁ is 0; and R_{3b} is selected from substituted or unsubstituted pyrrolidin-1-yl, piperidin-1-yl, piperizin-1-yl, 1,4-diazepan-1-yl, morpholin-1-yl and tetrahydroquinolin-1-yl.

[00139] In a particular embodiment, with respect to compounds of Formulae Ia, IIg, IIe, III and IIIi; m₁ is 0; and R_{3b} is selected from pyrrolidin-1-yl, piperidin-1-yl, piperizin-1-yl, 1,4-diazepan-1-yl, morpholin-1-yl, and tetrahydroquinolin-1-yl substituted with one or more groups selected from Me, Cl, F, CF₃, substituted or unsubstituted acyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzoyl, and substituted or unsubstituted phenyl.

[00140] In another embodiment with respect to Formula I, the compound is according to Formula IIIa, IIIb, IIIc, IIId, IIIe, IIIf, IIIg, IIIh, and IIIi:
wherein n1 is 0, 1, 2 or 3; R^{3a}, R^{3b}, and R^{3c} are as described previously; each R^{5a} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, amino, acylamino, cyano, C_{1-6} alkoxy and C_{1-6} haloalkyl-O-; and m3 is 0, 1, 2, 3, 4 or 5.
In one embodiment with respect to Formulae IIIa, IIIb, IIIc, IIId, IIle, IIIf, IIIg, IIIh, and IIIi, m3 is 1 or 2; and each R⁴ is independently Me, CF₃, OMe, NH₂, NHAc, OCF₃, Cl, or F.

In a particular embodiment with respect to Formulae IIIa, IIIb, IIIc, IIId, IIle, IIIf, IIIg, IIIh, and IIIi, n₁ is 0, 1, 2 or 3.

In another embodiment with respect to Formula I, the compound is according to Formula IVa, IVb, IVc, IVd, IVe or IVf:

![Chemical Structures](attachment:chemical_images.png)

wherein R⁵, R⁶, and R⁷ are as described previously; L is –O–, –NH–, or –CONH–; each R⁸ is independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, Ph, benzyl and halo; n₁ is 0, 1, 2, 3 or 4; and m₃ is 0, 1, 2, 3 or 4.

In one embodiment with respect to compounds of Formulae IVa, IVb, IVc, IVd, IVe or IVf, L is –O–.

In one embodiment with respect to compounds of Formulae IVa, IVb, IVc, IVd, IVe or IVf, L is –NH–.

In one embodiment with respect to compounds of Formulae IVa, IVb, IVc, IVd, IVe or IVf, L is –CONH–.
In one embodiment with respect to compounds of Formulae IVa, IVb, IVc, IVd, IVe or IVf, n1 is 0, 1 or 2.

In another embodiment with respect to Formula I, the compound is according to Formula Va:

wherein $R^{3a}$, $R^{3b}$, $R^{4c}$ are as described above; n1 is 1 or 2; each $R^{3a}$ is independently selected from C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl and halo; $R^{4c}$ is selected from C$_1$-C$_6$ alkyl; and m3 is 0, 1, 2, 3, 4 or 5.

In a particular embodiment with respect to Formula Va, $R^{4c}$ is Me.

In a particular embodiment with respect to Formula Va, $R^{4c}$ is H.

In one embodiment, with respect to Formulae IVa-Va, m3 is 1 or 2; and each $R^{3a}$ is independently selected from Me, Cl, F and CF$_3$.

In a particular embodiment, with respect to Formulae I-Va, $R^{3b}$ and $R^{4c}$ are independently selected from H and Me.

In one embodiment with respect to Formula I, the compound is according to Formula VIa, VIb, VIc, VId, VJe, VIf, VIg, or VIh.
wherein $R^{3a}$ is as described above.

[00154] In one embodiment with respect to Formula I, the compound is according to Formulae VIIa, VIIb, VIIc, VII, VIIa, VIIb, VIIc, VIId, Vlle, VII, VIIe, VIIf, VIIg, VIIh, or VIIi:
wherein \( R^{3a} \) is as described above.

[00155] In one embodiment with respect to Formula I, the compound is according to Formula VIq, or VIr:
wherein $R^{3a}$ is as described above.

[00156] In another embodiment with respect to Formula I, the compound is according to Formula VIIa, VIIb, VIIc, VIIId, VIIe, or VIIf:

![Chemical structures](image)

wherein $R^{3a}$ is as described above.

[00157] In another embodiment with respect to Formula I, the compound is according to Formula VIIIa, VIIIb or VIIlc:
wherein $R^{3a}$ is as described above.

[00158] In another embodiment with respect to Formula I, the compound is according to Formula IXa, IXb, or IXc:

wherein $R^{3a}$ is as described above.

[00159] In another embodiment with respect to Formula I, the compound is according to Formula Xa, Xb, or Xc:

wherein $R^{3a}$ is as described above.
[00160] In another embodiment with respect to Formula I, the compound is according to Formula Xd, Xe, Xf, Xg, Xh or Xi:

\[
\begin{align*}
&\text{Xd} &\text{Xe} &\text{Xf} \\
&\text{Xg} &\text{Xh} &\text{Xi}
\end{align*}
\]

wherein \( R^{3a} \) is as described above; and Q is N or CH.

[00161] In another embodiment with respect to Formula I, the compound is according to Formula XIa, XIb, XIc, XId, XIe or XIf.
wherein $R^{3a}$ is as described above.

In another embodiment with respect to Formula I, the compound is according to Formula XIIa

wherein $R^{3a}$ is as described above.

In one embodiment with respect to Formulae I-XIIa and the preferred embodiments described above, $R^{3a}$ is selected from H, Me, Cl, F and CF$_3$.

In one embodiment with respect to Formulae I-XIIa and the preferred embodiments described above, $R^{3a}$ is H.

In one embodiment the compound of the invention is not an isotopic variant.

In one embodiment, the compound is selected from compounds listed in Table 1.
In one aspect a compound of the invention according to any one of the embodiments herein described is present as the free base.

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

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

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 the compound.

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.

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.

Other derivatives of the compounds of the invention have activity in both their acid and acid derivative forms, but the acid sensitive form offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 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 ((alkoxy)carbonyloxy)alkylesters. Particularly useful are the C₁ to C₈ alkyl, C₂-C₆ alkenyl, aryl, C₇-C₁₂ substituted aryl, and C₇-C₁₂ arylalkyl esters of the compounds of the invention.

PHARMACEUTICAL COMPOSITIONS

When employed as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of the invention
are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient’s symptoms, and the like.

[00175] The pharmaceutical compositions of the invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds of the invention are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[00176] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include pre-filled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the furansulfonic acid compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[00177] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00178] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[00179] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal
formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[00180] The compounds of this invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[00181] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington’s Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[00182] The compounds of this invention may also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington’s Pharmaceutical Sciences.

[00183] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

**Formulation 1 - Tablets**

[00184] A compound of the invention 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 amide compound per tablet) in a tablet press.

**Formulation 2 - Capsules**

[00185] A compound of the invention 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 amide compound per capsule).

**Formulation 3 - Liquid**

[00186] A compound of the invention (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. Sufficient water is then added to produce a total volume of 5 mL.
Formulation 4 - Tablets

[00187] A compound of the invention 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 is formed into 450-900 mg tablets (150-300 mg of active amide compound) in a tablet press.

Formulation 5 - Injection

[00188] A compound of the invention may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[00189] 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 (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) is added and the resulting mixture is stirred until it congeals.

METHODS OF TREATMENT

[00190] The present compounds are used as therapeutic agents for the treatment of conditions in mammals that are causally related or attributable to aberrant activity of JAK. In particular, conditions related to aberrant activity of one or more of JAK1, JAK2, JAK3 and/or TYK2. Accordingly, a compound of the invention and pharmaceutical compositions of this invention find use as therapeutics for preventing and/or treating diseases involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn’s disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6 and transplantation rejection (e.g. organ transplant rejection). Inhibitors of JAK can also find application in the treatment of proliferative diseases. In particular the inhibitors of JAK find application in the treatment of cancers, especially leukaemias and solid tumours (e.g. uterine leiomyosarcoma, prostate cancer). In particular the conditions are selected from inflammatory conditions, conditions related to cartilage and/or joint degradation in mammals including humans. In another embodiment, the compounds and pharmaceutical compositions of the invention find use as therapeutics for preventing and/or treating proliferative disorders in mammals, including humans. In a specific embodiment a compound of the invention and pharmaceutical compositions thereof find use as therapeutics for preventing and/or treating cancer in mammals including humans.

[00191] In additional method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with condition involving an immune response or an autoimmune disease.
The methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosus, type 1 diabetes mellitus and inflammatory bowel disease.

[00192] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of a condition involving an autoimmune response or an autoimmune disease. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosus, type 1 diabetes mellitus and inflammatory bowel disease.

[00193] In a method of treatment aspect, this invention provides a method of treatment, prevention or prophylaxis in a mammal susceptible to or afflicted with diseases involving impairment of cartilage turnover (e.g. a condition associated with, or diseases involving the anabolic stimulation of chondrocytes), for example, 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, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis, which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[00194] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of diseases involving impairment of cartilage turnover (e.g. a condition associated with, or diseases involving the anabolic stimulation of chondrocytes), for example, 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, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis.

[00195] The present invention also provides a method of treatment of congenital cartilage malformations, including hereditary chondrolysis, chondrodysplasias and pseudochondrodysplasias, in particular, but without limitation, microtia, anotia, metaphyseal chondrodysplasia, and related disorders, which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[00196] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of congenital cartilage malformations, including hereditary chondrolysis, chondrodysplasias and pseudochondrodysplasias, in particular, but without limitation, microtia, anotia, metaphyseal chondrodysplasia, and related disorders.
In another aspect, this invention provides a method of treating a mammal susceptible to or afflicted with a condition involving inflammation. In additional method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with diseases and disorders which are mediated by or result in inflammation such as, for example rheumatoid arthritis and osteoarthritis, allergic airway disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, 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. In a specific embodiment, the condition involving inflammation is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (e.g. asthma) and inflammatory bowel diseases, which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

In another aspect, this invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of a condition involving inflammation. In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of diseases and disorders which are mediated by or result in inflammation such as, for example rheumatoid arthritis and osteoarthritis, allergic airway disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, 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. In a specific embodiment, the condition involving inflammation is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (e.g. asthma) and inflammatory bowel diseases.

In further method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with a proliferative disease, in particular cancer (e.g. solid tumors such as uterine leiomyosarcoma or prostate cancer), leukemia (e.g. AML or ALL), multiple myeloma and/or psoriasis which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described. In further method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with cancer (e.g. solid tumors such as uterine leiomyosarcoma or prostate cancer) and/or leukemias.

In another aspect the present invention provides the compound of the invention for use in the treatment, prevention or prophylaxis of a proliferative disease, in particular cancer (e.g. solid tumors such as uterine leiomyosarcoma or prostate cancer), leukemia (e.g. AML or ALL), multiple myeloma and/or psoriasis. In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of cancer (e.g. solid tumors such as uterine leiomyosarcoma or prostate cancer) and/or leukemias.

In further method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with diseases associated with hypersecretion of IL6, in particular Castleman's disease.
or mesangial proliferative glomerulonephritis which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[00202] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of diseases associated with hypersecretion of IL6, in particular Castleman's disease or mesangial proliferative glomerulonephritis.

[00203] In further method of treatment aspects, this invention provides methods of treating a mammal susceptible to or afflicted with transplantation rejection which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described. In a specific embodiment, the invention provides methods of treating organ transplant rejection.

[00204] In another aspect the present invention provides a compound of the invention for use in the treatment, prevention or prophylaxis of transplantation rejection. In a specific embodiment, the invention provides methods of treating organ transplant rejection.

[00205] As a further aspect of the invention there is provided the present compounds for use as a pharmaceutical especially in the treatment or prevention of the aforementioned conditions and diseases. Also provided herein is the use of the present compounds in the manufacture of a medicament for the treatment or prevention of one of the aforementioned conditions and diseases.

[00206] A particular regimen of the present method comprises the administration to a subject in suffering from a disease involving inflammation, of an effective amount of a compound of the present invention for a period of time sufficient to reduce the level of inflammation in the patient, and preferably terminate, the processes responsible for said inflammation. A special embodiment of the method comprises administering of an effective amount of a compound of the invention to a subject patient suffering from or susceptible to the development of rheumatoid arthritis, for a period of time sufficient to reduce or prevent, respectively, inflammation in the joints of said patient, and preferably terminate, the processes responsible for said inflammation.

[00207] A further particular regimen of the present method comprises the administration to a subject in suffering from a disease condition characterized by cartilage or joint degradation (e.g. osteoarthritis) of an effective amount of a compound of the invention for a period of time sufficient to reduce and preferably terminate, the self-perpetuating processes responsible for said degradation. A special embodiment of the method comprises administering of an effective amount of a compound of the invention to a subject patient suffering from or susceptible to the development of osteoarthritis, for a period of time sufficient to reduce or prevent, respectively, cartilage degradation in the joints of said patient, and preferably terminate, the self-perpetuating processes responsible for said degradation. In a particular embodiment said compounds exhibit cartilage anabolic and/or anti-catabolic properties.
Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. 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 2 g/day for a 40 to 80 kg human patient.

For the prevention 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 five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of the compound of the invention, with particular doses each providing from about 0.1 to about 10 mg/kg and especially 1 to about 5 mg/kg.

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

When used to prevent the onset of an inflammatory condition, the compounds of this 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.

The compounds of the invention can be administered as the sole active agent or they can be administered in combination with other agents, including other compounds that demonstrate the same or a similar therapeutic activity, and that are determined to 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.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of a disease involving inflammation; particular agents include, but are not limited to, immunoregulatory agents e.g. azathioprine, corticosteroids (e.g. prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, Mycophenolate Mofetil, muromonab-CD3 (OKT3, e.g. Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention 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, and ciclosporin), and biological DMARDS (for example but without limitation Infliximab, Etanercept, Adalimumab, Rituximab, and Abatacept).

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of proliferative disorders; particular agents include but are not limited
to: methotrexate, leukovorin, adriamycin, prenisone, 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® or hsp90 inhibitors (e.g. 17-AAG). Additionally, a compound of the invention may be administered in combination with other therapies including, but not limited to, radiotherapy or surgery. In a specific embodiment the proliferative disorder is selected from cancer, myeloproliferative disease or leukaemia.

[00216] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of autoimmune diseases, particular agents include but are not limited to: glucocorticoids, cytostatic agents (e.g. purine analogs), alkylating agents, (e.g nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds, and others), antimetabolites (e.g. methotrexate, azathioprine and mercaptopurine), cytotoxic antibiotics (e.g. daclomycin anthracyclines, mitomycin C, bleomycin, and mithramycin), antibodies(e.g., anti-CD20, anti-CD25 or anti-CD3 (OKT3) monoclonal antibodies, Atgam® and Thymoglobulin®), cyclosporin, tacrolimus, rapamycin (sirolimus), interferons (e.g. IFN-β), TNF binding proteins (e.g. infliximab (Remicade), etanercept (Enbrel), or adalimumab (Humira)), mycophenolate, Fingolimod, Myriocin.

[00217] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of transplantation 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-2Rα receptor antibodies, basiliximab, daclizumab), polyclonal anti-T-cell antibodies (e.g. anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG)).

[00218] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention 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 β₂-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. cromoglicate and ketotifen), biological regulators of IgE response (e.g. omalizumab), antihistamines (e.g. ceterizine, cinnarizine, fexofenadine), vasoconstrictors (e.g. oxymethazoline, xylometazoline, nafazoline and tramazoline).

[00219] 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, nonspecific beta-agonists, injected or inhaled (e.g. epinephrine, isoetharine, isoproterenol, metaproterenol), anticholinergics (IV or nebulized, e.g. glycopyrrolate, atropine, ipratropium), methylxanthines (theophylline, aminophylline, bambiphylline), inhalation anesthetics that have a bronchodilatory effect (e.g. isoflurane, halothane, enflurane), ketamine, intravenous magnesium sulfate.

[00220] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of IBD, particular agents include but are not limited to: glucocorticoids (e.g. prednisone, budesonide) synthetics disease modifying, immunomodulatory agents (e.g. methotrexate, leflunomide, sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and ciclosporin) and biological disease modifying, immunomodulatory agents (infliximab, adalimumab, rituximab, and abatacept).

[00221] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention of SLE, particular agents include but are not limited to: 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.

[00222] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prevention 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 Ameveive, Enbrel, Humira, Remicade, Raptiva and ustekinumab (a 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)).

[00223] 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 this is not essential. The agents may be administered in different formulations and at different times.

**GENERAL SYNTHETIC PROCEDURES**

**General**
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.

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. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

The following methods are presented with details as to the preparation of representative bicycloheteroarylts that have been listed hereinabove. The compounds of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

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 was performed on silica gel 60 (35-70 μm). Thin layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). 1H NMR spectra were recorded on a Bruker DPX 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. CHCl3 (δ 7.27), as internal reference. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Coupling constants (J) are given in Hz. Electrospray MS spectra were obtained on a Micromass platform LC/MS spectrometer. Column Used for all LCMS analysis: Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 50mm L. (Part No.186002350)). Preparative HPLC :Waters XBridge Prep C18 5μm ODB 19mm ID x 100mm L (Part No.186002978). All the methods are using MeCN/H2O gradients. H2O contains either 0.1% TFA or 0.1% NH3.

List of abbreviations used in the experimental section:

| DCM | Dichloromethane |
| DiPEA | N,N-diisopropylethylamine |
| MeCN | Acetonitrile |
| BOC | tert-Butyloxy-carbonyl |
| MF | N,N-dimethylformamide |

<p>| Cat. | Catalytic amount |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| NMR | Nuclear Magnetic Resonance |</p>
<table>
<thead>
<tr>
<th>DMSO</th>
<th>Dimethylsulfoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC-MS</td>
<td>Liquid Chromatography-Mass Spectrometry</td>
</tr>
<tr>
<td>Ppm</td>
<td>part-per-million</td>
</tr>
<tr>
<td>Pd/C</td>
<td>Palladium on Charcoal 10%</td>
</tr>
<tr>
<td>PMB</td>
<td>Para-methoxy-benzyl</td>
</tr>
<tr>
<td>PyBOP</td>
<td>benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluoroborate</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
</tr>
<tr>
<td>Rt</td>
<td>retention time</td>
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<td>s</td>
<td>singlet</td>
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<tr>
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</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Triethylamine</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix Metallo Proteinase</td>
</tr>
<tr>
<td>NHAC</td>
<td>Normal Human Articular Chondrocytes</td>
</tr>
<tr>
<td>shRNA</td>
<td>short hairpin RNA</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>Ad-Si RNA</td>
<td>Adenoviral encoded siRNA</td>
</tr>
<tr>
<td>PBST</td>
<td>Phosphate buffered saline with Tween 3.2 mM Na₂HPO₄, 0.5 mM KH₂PO₄, 1.3 mM KCl, 135 mM NaCl, 0.05% Tween 20, pH 7.4</td>
</tr>
<tr>
<td>APMA</td>
<td>4-aminophenylmercuric acetate</td>
</tr>
<tr>
<td>DMEM</td>
<td>Dulbecco's Modified Eagle Medium</td>
</tr>
<tr>
<td>FBS</td>
<td>Fetal bovine serum</td>
</tr>
<tr>
<td>hCAR</td>
<td>human cellular adenovirus receptor</td>
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<td>3- MOI</td>
<td>multiplicity of infection of 3</td>
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<tr>
<td>dNTP</td>
<td>deoxyribonucleoside triphosphate</td>
</tr>
<tr>
<td>QPCR</td>
<td>quantitative polymerase chain reaction</td>
</tr>
<tr>
<td>cDNA</td>
<td>copy deoxyribonucleic acid</td>
</tr>
<tr>
<td>GAPDH</td>
<td>Glyceraldehyde phosphate dehydrogenase</td>
</tr>
</tbody>
</table>

**Synthetic Preparation of Compounds of the Invention**

[00229] A compound of the invention can be produced according to the following scheme.

**General Synthetic Method**

**Scheme 1**

8-Substituted-[1,2,4]triazolo[1,5-a]pyridin-2-ylamine


1.1.1 1-(3-Bromo-pyridin-2-yl)-3-carboxethoxy-thiourea (2)

[00230] To a solution of 2-amino-3-bromopyridine (1) (253.8 g, 1.467 mol) in DCM (2.5 L) cooled to 5°C was added ethoxycarbonyl isothiocyanate (173.0 mL, 1.467 mol) dropwise over 15 min. The reaction mixture was then allowed to warm to room temp. (20°C) and stirred for 16 h. Evaporation in vacuo gave a solid which was collected by filtration, thoroughly washed with petrol (3 x 600 mL) and air-dried to afford (2). No further purification was required. NMR (1H, DMSO) 11.45 (2H, d, NH); 8.49 (1H, d, ArH); 8.17 (1H, d, ArH), 7.33 (1H, m, ArH), 4.22 (2H, q, CH2); 1.20 (3H, t, CH3).

1.1.2 8-Bromo-[1,2,4]triazolo[1,5-a]pyridin-2-ylamine (3)

[00231] To a suspension of hydroxylamine hydrochloride (101.8 g, 1.465 mol) in EtOH/MeOH (1:1, 900 mL) was added N,N-diisopropylethylamine (145.3 mL, 0.879 mol) and the mixture was stirred at room temp. (20°C) for 1 h. 1-(3-Bromo-pyridin-2-yl)-3-carboxethoxy-thiourea (2) (89.0 g, 0.293 mol) was then added and the mixture slowly heated to reflux (Note: bleach scrubber is required to quench H2S evolved). After 3 h at
reflux, the mixture was allowed to cool and filtered to collect the precipitated solid. Further product was collected by evaporation in vacuo of the filtrate, addition of H₂O (250 mL) and filtration. The combined solids were washed successively with H₂O (250 mL), EtOH/MeOH (1:1, 250 mL) and Et₂O (250 mL) then dried in vacuo to afford (3) as a solid. No further purification was required. NMR (¹H, DMSO) 8.57 (1H, d, ArH); 7.72 (1H, d, ArH), 6.79 (1H, m, ArH), 6.27 (2H, s, NH₂).

1.2 General procedure for mono-acylation to afford intermediate (4):

[00232] To a solution of the 2-amino-triazolopyridine (3) (7.10 g, 33.3 mmol) in dry CH₃CN (150 mL) at 5°C is added Et₃N (11.6 mL, 83.3 mmol) followed by the appropriate acid chloride (83.3 mmol). The reaction mixture is then allowed to warm to ambient temperature and stirred until all starting material (3) is consumed. If required, further Et₃N (4.64 mL, 33.3 mmol) and acid chloride (33.3 mmol) may be added to ensure complete reaction. Following solvent evaporation in vacuo the resultant residue is treated with 7 N methanolic ammonia solution (50 mL) and stirred at ambient temp. (for 1-16 h) to hydrolyse any bis-acylated product. Product isolation is made by removal of volatiles in vacuo followed by trituration with Et₂O (50 mL). The solids may be collected by filtration, washed with H₂O (2×50 mL), acetone (50 mL) and Et₂O (50 mL), then dried in vacuo to give the required intermediate (4). In some cases column chromatography (petrol/EtOAc) may be required to obtain pure compounds.

General Synthetic Methods for Preparation of the Compounds of Invention

Method A

Suzuki reaction (General Method)
Boronic acid (2 eq.) is added to a solution of the above bromo intermediate (2) in 1,4-dioxane/water (5:1). K₂CO₃ (2 eq.) and Pd(dpff)Cl₂ (5%) (dpff = 1,1'-Bis(diphenylphosphino)ferrocene) are added to the solution. The resulting mixture is then heated in a microwave oven (CEM discover) in a sealed tube at 140 °C for 30 min or heated at 90°C in oil bath for 16h. Water is added and the solution is extracted with ethyl acetate. The organic layers are dried over MgSO₄ and evaporated in vacuo. The final compound is obtained after purification by preparative HPLC. Analytical: Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 50mm L (Part No.186002350).

Preparative HPLC: Waters XBridge Prep C18 5μm ODB 19mm ID x 100mm L (Part No.186002978). All the methods are using MeCN/H₂O gradients. H₂O contains either 0.1% TFA or 0.1% NH₃.

**Method B**

![Chemical Structures]

wherein R²ₐ, R²ₖ and m1 are as described herein.

**B1. 4-[2-(Cyclopropanecarbonyl-amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl]-benzoyl chloride**

![Chemical Structure]

**[00235]** 2 Drops of DMF are added to a solution of 4-[2-(cyclopropanecarbonyl-amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl]-benzoic acid (1 eq) obtained by Method A in DCM under N₂ atmosphere. Then oxalyl chloride (2 eq) is added dropwise to this resulting solution (gas release). The mixture is stirred at rt for 2 hours. After completion of the reaction by LCMS, the solvent are removed. The crude acid chloride is used without further purification in next step.

**B2. Amide formation (General Method)**
[00236] An appropriate amine (1.1 eq; R²ₑ, R²ᶠ and m₁ are as described herein) and Et₃N (5 eq) are dissolved in DCM under N₂ and cooled at 0°C. The acid chloride (B₁, 1 eq) dissolved in DCM is added dropwise to this solution. The reaction is stirred at room temperature for 3h to 16 h. After this time, reaction is complete. The compound is extracted with EtOAc and water, washed with brine and dried over MgSO₄. Organic layers are filtered and evaporated. The final compound is isolated by preparative HPLC. Preparative HPLC: Waters XBridge Prep C18 5μm ODB 19mm ID x 100mm L (Part No.186002978). All the methods are using MeCN/H₂O gradients. H₂O contains either 0.1% TFA or 0.1% NH₃.

Method C

Wherein m₁ and R²ᵇ are as described herein.

Reaction of alkylation (General Method)

[00237] Cyclopropanecarboxylic acid [8-(4-hydroxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide (1.1 eq) obtained by Method A and K₂CO₃ (5 eq) (or AgCO₃) are dissolved in DMF under N₂ and an alkylating agent (1.1 eq) is added dropwise. The resulting suspension is heated at 50°C for 16h. After this time, the reaction is complete. The compound is extracted with EtOAc and water, washed with brine and dried over MgSO₄. Organic layers are filtered...
and evaporated. The final compound is isolated by preparative HPLC. Preparative HPLC: Waters XBridge Prep C18 5μm ODB 19mm ID x 100mm L (Part No.186002978). All the methods are using MeCN/H₂O gradients. H₂O contains either 0.1% TFA or 0.1% NH₃.

[00238] The exemplary compounds that have been or can be prepared according to the synthetic methods described herein are listed in Table I below. The NMR spectral data of some representative compounds of the invention is given in Table II.

Compound 1
[00239] This compound was prepared via Method A using 4-ethoxyphenylboronic acid.

Compound 2
[00240] This compound was prepared via Method A using 4-benzyloxyphenylboronic acid.

Compound 3
[00241] This compound was prepared via Method A using 4-(methoxymethyl)phenylboronic acid.

Compound 4
[00242] This compound was prepared via Method A using 1-N-methylindole-5-boronic acid.

Compound 5
[00243] This compound was prepared via Method A using 4-benzylophenylboronic acid.

Compound 6
[00244] This compound was prepared via Method A using 4-isopropoxyphenylboronic acid.

Compound 7
[00245] This compound was prepared via Method A using 4-(Piperidine-1-carbonyl)phenylboronic acid.

Compound 8
[00246] This compound was prepared via Method B using phenethylamine.

Compound 9
[00247] This compound was prepared via Method B using 2-phenoxy-ethylamine.
Compound 10

This compound was prepared via Method A using 1-benzyl-1H-pyrazole-4-boronic acid.

Compound 11

Step 11.1: 3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-ylmethyl]-pyridine

To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (2.27 mmol; 1.0 equiv.) in acetone (10.0 mL) at room temperature were added under argon 3-chloromethyl-pyridine hydrochloride (3.18 mmol; 1.4 equiv.) and cesium carbonate (2.8 equiv.). The reaction mixture was heated for 4 hours at reflux. The mixture was then cooled to room temperature, quenched by addition of a saturated aqueous solution of sodium hydrogen carbonate (100 mL) and extracted with dichloromethane (2 x 100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography over silica gel (dichloromethane/ethyl acetate) to afford the expected boronate as a white solid which was used in the next step without further purification.

Step 11.2

The title compound is prepared by Method A using 3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-ylmethyl]-pyridine obtained in Step 11.1.

Compound 12
Step a:

[00251] In a microwave vessel, a solution of 5-bromo-1,3-dihydro-isooindole-2-carboxylic acid tert-butyl ester (1.5 equiv.), di(pinacolato) diborane (2.0 equiv.), potassium acetate (2.0 equiv.) in 1,4-dioxane (2.0 mL) is flushed with nitrogen. [1,1’-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 equiv.) was then added and the reaction mixture was flushed again with argon (and heated up to 90°C) for 20 hours until the reaction is complete on TLC. No purification was carried out.

Step b

[00252] Cyclopropanecarboxylic acid (8-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-amide (1.0 equiv.), K$_2$CO$_3$ (2.0 equiv.), [1,1’-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 equiv.) and 1,4-dioxane/water 4:1 (1.5 mL) were added to the mixture. The reaction mixture was heated at 90°C for 16 h until complete consumption of the starting material. The precipitate was filtered, washed with H$_2$O, dried under vacuum. The product was obtained which was used in the next step without further purification.

Step c
[00253] TFA (excess) was added dropwise to a solution of 5-[2-(Cyclopropanecarbonyl-amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl]-1,3-dihydro-isooindole-2-carboxylic acid tert-butyl ester in DCM. After stirring at room temperature for 16h, the solvent was removed under vacuum. Compound precipitated in NAOH solution (2 N) and was filtered. Compound was used in the next step without further purification.

Step d

[00254] Cyclopropanecarboxylic acid [8-(2,3-dihydro-1H-isooindol-5-yl)]=[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide (1 eq) was treated with benzaldehyde (2 eq.) and TiOiPr4 (4eq.) for 2 hr under N2. Then ethanol and NaCNBH3 (1eq) were stirred at RT for 16 hr. Water was added to the reaction mixture. A precipitate formed and was filtered, washed with EtOH. The filtrate was concentrated and the residue was purified by preparative HPLC to afford the expected product.

Compound 13

[00255] This compound was prepared via Method B using 4-benzyl-piperidin-4-ol.

Compound 14

[00256] This compound was prepared via Method B using 3,3-dimethyl-piperidine.

Compound 15

[00257] This compound was prepared via Method B using 2-(1-phenyl-1H-pyrazol-4-yl)-ethylamine.

Compound 16

\[
\begin{align*}
\text{Step 16.1: Preparation of 1-(3-Phenyl-propyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole} \\
[00258] \text{To 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.0 equiv.) in acetone (250 mL) at room temperature were added under argon (3-bromo-propyl)-benzene (1.1 equiv.) and cesium carbonate (2 equiv.). The reaction mixture was heated for 78 hours at reflux. The mixture was then cooled to room temperature, the acetone was evaporated. Water was added and the product was extracted with EtOAc. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. The resulting residue was}
\end{align*}
\]
purified by chromatography over silica gel (petrol: EtOAc 10:1) to afford the expected boronate as a white solid.

Step 16.2:

[00259] This compound was prepared via Method A using the intermediate obtained in Step 16.1.

Compound 17

[00260] This compound was prepared via Method A using 4-hydroxyphenylboronic acid.

Compound 18

[00261] This compound was prepared via Method C using bromo-acetonitrile.

Compound 19

[00262] This compound was prepared via Method C using 2-bromomethyl-pyridine.

Compound 20

[00263] This compound was prepared via Method C using 3-(chloromethyl)-1,5-dimethyl-1H-pyrazole.

Compound 21

[00264] This compound was prepared via Method A using 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-1,4-benzoxazine.

Compound 22
Step 22.1: Preparation of 1-(2-Phenoxy-ethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole

[00265] To 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.0 equiv.) in acetone at room temperature were added under argon (2-bromo-ethoxy)-benzene (1.1 equiv.) and cesium carbonate (2 equiv.). The reaction mixture was heated for 78 hours at reflux. The mixture was then cooled to room temperature, the acetone was evaporated. Water was added and the product was extracted with EtOAc. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness.

Step 22.2

[00266] This compound was prepared via Method A using the intermediate obtained in Step 22.1.

Compound 23

[00267] This compound was prepared via Method B using 3-methyl piperidine.

Compound 24

[00268] This compound was prepared via Method C using 1-(2-bromo-ethyl)-1H-pyrazole.

Compound 25

[00269] This compound was prepared via Method C using 2-chloropropionitrile.

Compound 26

[00270] This compound was prepared via Method A using 3-cyanomethoxyphenylboronic acid.
Compound 27

Step 27.1:

Cyclopropanecarboxylic acid [8-(2-methoxy-pyridin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide prepared by Method A was heated at 110°C for 2 hrs in HCl one/ 1,4-dioxane (1:1). The reaction mixture was allowed to cool to room temperature. The excess solvent was evaporated under reduced pressure. The crude product was used without further purification in the next step.

Step 27.2:

To a solution of 4-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-8-yl)-pyridin-2-ol (1 eq.) in dry CH₂CN at 5°C was added Et₃N (3eq.) followed by cyclopropanecarbonyl chloride (3 eq.). The reaction mixture was then allowed to warm to ambient temperature and stirred until all starting material was consumed. Following solvent evaporation in vacuo the resultant residue was treated with 7N methanolic ammonia solution and stirred at ambient temp. (for 2 h) to hydrolyse any bis-acylated product. Product isolation was made by removal of volatiles in vacuo followed by trituration with Et₂O. The solids were collected by filtration, washed with H₂O, acetone and Et₂O.

Compound 28

This compound was prepared via Method A using indole-5-boronic acid.

Compound 29

This compound was prepared via Method A using indazole-5-boronic acid pinacol ester.

Compound 30

This compound was prepared via Method C using methanesulfonic acid 6-methoxy-pyridin-3-ylmethyl ester made by mesylation of (6-methoxy-pyridin-3-yl)-methanol in presence of mesylate chloride.

Compound 31

This compound was prepared via Method C using methanesulfonic acid 1-(6-methoxy-pyridin-3-yl)-ethyl ester made by mesylation of 1-(6-methoxy-pyridin-3-yl)-ethanol in presence of mesylate chloride.
Compound 32

[00277] This compound was prepared via Method A using 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol.

Compound 33

[00278] This compound was prepared via Method A using 4-benzzyloxy-3-fluorophenylboronic acid.

Compound 34

[00279] This compound was prepared via Method A using (3-fluro-4-hydroxyphenyl)boronic acid.

Compound 35

[00280] Compound 30 was heated at 110°C for 2 hrs in HCl conc / 1,4-dioxane (1:1). The reaction mixture was allowed to cool to room temperature. The excess solvent was evaporated under reduced pressure. The crude product was purified by preparative HPLC.

Compound 36

[00281] To 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.0 equiv.) in acetone at room temperature were added under argon (3-Bromo-ethyl)-benzene (1.1 equiv.) and cesium carbonate (2 equiv.). The reaction mixture was heated for 78 hours at reflux. The mixture was then cooled to room temperature, the acetone was evaporated. Water was added and the product was extracted with EtOAc. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness.
Compound 37

This compound was prepared via Method A using 1-(2-morpholinoethyl)-1h-pyrazole-4-boronic acid, pinacol ester.

Compound 38

Potassium tert-butoxide (1.5 eq.) was added to an ice-cooled solution of diethyl cyanomethyl phosphate (1.5 eq.) in THF. The resulting mixture was stirred for 30 min at 0°C, then at room temperature for another 30 min. A solution of cyclopropanecarboxylic acid [8-(4-formyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide (1eq) in THF was added dropwise to the reaction mixture. The reaction mixture was stirred for 8h. The reaction was quenched with water, extracted with ethyl acetate. The organic phase was dried over MgSO₄, filtered and evaporated to afford the product as a yellow solid which was purified by methanol trituration.

Compound 39
Step 39.1: Preparation of 4-(n-butylsulfonyl)benzenebromide

[00284] A solution of 4-bromobenzenesulfonyl chloride 1 (1.0 equiv.), sodium sulfite (1.1 equiv.) and sodium hydrogen carbonate (5.0 equiv.) in water was heated to 100°C for 4 hours. The reaction mixture became clear and butyl bromide (1.2 equiv.) is added at 100°C. The mixture was stirred at this temperature for 16 hours. The reaction mixture was cooled to room temperature. Then, additional water was added (50 mL) and the resulting aqueous layer was extracted with dichloromethane (3 x 50mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude product was purified by chromatography over silica gel to afford the expected sulfone.

Step 39.2: coupling

[00285] In a microwave vessel, a solution of the sulfone obtained according to the procedure described above (1.5 equiv.), di(pinacolato)diaborane (2.0 equiv.) potassium acetate (2.0 equiv.) in dioxane was flushed with argon (3 times). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 equiv.) was then added and the reaction mixture was flushed again with argon (3 times) and heated up to 90°C for 20 hours until the reaction was complete on TLC. Then, cyclopropanecarboxylic acid (8-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-amide (1.0 equiv.), sodium hydrogen carbonate (equiv.), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20.0 mg, 0.03 mmol, 0.05 equiv.) and dioxane/water 2:1 (1.5 mL) were added to the mixture. The reaction mixture was then submitted several times (1-5 times) to microwave irradiations (P: 150 W, T=120°C, t=15 min.) until complete consumption of the starting material. Sodium sulfate was added to the reaction mixture before diluting the latter with dichloromethane (3.0 mL).
Purification by chromatography on silica gel followed by trituration of the collected compound in methanol afforded the expected product with a satisfactory HPLC purity.

**Compound 40**

[00286] This compound was prepared via Method A using 4-benzyloxy-3-methoxyboronic acid, pinacol ester.

**Compound 41**

[00287] This compound was prepared via the same procedure as for compound 39 using 2-bromomethyl-pyridine.

**Compound 42**

[00288] This compound was prepared via the same procedure as for compound 39 using 3-bromomethyl-pyridine.

**Compound 43**

[00289] This compound was prepared via Method B using 1-isopropyl-piperazine.

**Compound 44**

[00290] This compound was prepared via Method C using 5-chloromethyl-pyridine-2-carbonitrile.

**Compound 45**

[00291] This compound was prepared via Method C using 3-bromomethyl-pyridine.

**Compound 46**

[00292] This compound was prepared via Method C using 2-chloropropionitrile.

**Compound 47**

[00293] This compound was prepared via Method C using 3-(chloromethyl)-1-methyl-1H-pyrazole.

**Compound 48**

[00294] This compound was prepared via Method C using 2-bromomethyl-pyridine.

**Compound 49/Compound 50**
Compound 27 (1eq.) was treated with NaH (5eq.) in DMF for 30 min at rt. 3-bromomethylpyridine (1eq.) was added to the mixture and the resulting mixture was stirred at 60°C for 4hr. The reaction was allowed to cool to room temperature, water was added and the solution was extracted with ethyl acetate. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. Purification by preparative HPLC gave the expected products (ratio 3/1 compound 49/compound 50).

**Compound 51**

![Chemical structure diagram]

*Step 51.1: 5-Bromo-1-pyridin-3-ylmethyl-2,3-dihydro-1H-indole*

5-Bromo-2,3-dihydro-1H-indole (1 eq) was treated with pyridine-3-carbaldehyde (2 eq.) and Ti(OiPr)₄ (4 eq.) for 2 hr under N₂. Then ethanol and NaCNBH₃ (1eq) were stirred at RT for 16 hr. Water was added to the reaction mixture. A precipitate formed and was filtered and washed with EtOH. The filtrate was concentrated and used in the next step without further purification.

*Step 51.2: 1-Pyridin-3-ylmethyl-5-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-2,3-dihydro-1H-indole*

5-Bromo-1-pyridin-3-ylmethyl-2,3-dihydro-1H-indole (1eq), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2]bi[1,3,2]dioxaborolanyl (1.5eq) and potassium acetate (2 eq.) were mixed in a vial, purged with nitrogen. 1,4-Dioxane was added. Then Pd(dppf)Cl₂ was added, the reaction was sonicated and heated to 85°C overnight until full conversion. The reaction mixture was dissolved in DCM, filtered through celite, and washed 3 times with DCM. Solvents were removed under reduced pressure and the obtained residue was used in the next step without purification.

*Step 51.3*
[00298] This compound was prepared via Method A using 1-Pyridin-3-ylmethyl-5-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-y1)-2,3-dihydro-1H-indole obtained in step 51.2

**Compound 52**

[00299] Phthalimide (1eq) was added to a solution of 3-bromomethyl-pyridine (1.1eq) and K$_2$CO$_3$ (2eq) in DMF under N$_2$. The mixture was stirred at rt for 16 hrs. Reaction was diluted in water and the compound precipitated. The solid was filtered and dried under reduced pressure. Compound was used in the next step without further purification.

[00300] 5-Bromo-2-pyridin-3-ylmethyl-isoiindole-1,3-dione (1eq), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bis[1,3,2]dioxaborolanyl (1.5eq) and potassium acetate (2eq) were mixed in a vial, purged with nitrogen. 1,4-Dioxane is added. Then Pd(dppf)Cl$_2$ was added, the reaction was sonicated and it was heated at 85°C overnight until full conversion. The reaction mixture was dissolved in DCM, filtered through celite, and
washed 3 times with DCM. Solvents were removed under reduced pressure and the obtained residue was used in the next step without purification.

[00301] This compound was prepared via Method A using 2-Pyridin-3-ylmethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoindole-1,3-dione prepared above.

**Compound 53**

[00302] This compound was prepared via Method C using 3-(chloromethyl)-6-methyl pyridine.

**Compound 54**

[00303] This compound was prepared via Method A using 2-phenyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzooxazole.

**Compound 55**

[00304] Aniline (2 eq.), cyclopropanecarboxylic acid [8-(4-formyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide prepared by Method A (1 eq.) and Ti(OPr)₄ are mixed and stirred at room temperature for 3 hrs. The mixture is diluted in ethanol and Na(CN)BH₃ (1 eq.) is added. The resulting solution is stirred at room temperature for 16 hrs. The mixture is diluted in water and filtered. The solid is washed with ethanol. The combined solvent phases are evaporated under vacuum. The final compound is isolated by preparative HPLC.

**Compound 56**

[00305] This compound was prepared via Method B using piperidine-4-carbonitrile.

**Compound 57**

[00306] This compound was prepared via Method C using 3-(bromomethyl)-5-methylisoxazole.

**Compound 58**

[00307] This compound was prepared via Method C using 2-chloromethyl-5-methyl-pyridine.
Compound 59

[00308] This compound was prepared via Method A using 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-y1)-benzyl]-morpholine.

Compound 60

[00309] This compound was prepared via Method C using 1-iodo-propane.

Compound 61

61.1 *Synthesis of the boronic acid:*

![Structure](image)

[00310] To 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-y1)-1H-pyrazole (1.0 equiv.) in acetone at room temperature were added under nitrogen 4-bromomethyl-benzonitrile (2 equiv.) and cesium carbonate (3 equiv.). The reaction mixture was heated for 16 hours at reflux. The mixture was then cooled to room temperature, the acetone was evaporated. Water was added and the product was extracted with EtOAc. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness used in next step without further purification.

61.2 *Synthesis of compound 61*

[00311] This compound was prepared via Method A using 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-y1)-pyrazol-1-ylmethyl]-benzonitrile made as described above.

Compound 62

[00312] This compound was prepared via Method C using 5-chloromethyl-3-methyl-[1,2,4]oxadiazole.

Compound 63

[00313] This compound was prepared via Method C using 2-chloro-5-(chloromethyl)pyridine.

Compound 64

[00314] Compound 38 was dissolved in MeOH/pyridine(1:3). Then NaBH₄ (1.5 eq) was added portionwise. After refluxing for 2h, the mixture was allowed to cool to room temperature and then poured into
10% aqueous HCl solution, and the compound was extracted with ethyl acetate. The organic phase was dried over MgSO₄, filtered and removed under vacuum. Purification was carried out by preparative HPLC.

**Compound 65**

[00315] This compound was prepared via Method C using 3-bromomethyl-pyridine.

**Compound 66**

[00316] Cyclopropanecarboxylic acid-[8-(1H-pyrrol-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide (1eq.) prepared by Method A was treated with NaH (5eq.) in DMF for 30 min at rt. 4-bromomethyl-benzonitrile (1eq.) was added to the mixture and the resulting mixture was stirred at 60°C for 4hr. The reaction was allowed to cool to room temperature, water was added and the solution was extracted with ethyl acetate. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. Purification by preparative HPLC gave the expected product.

**Compound 67**
Step a

To a solution of 1 (13.5 g, 78 mmol) in CHCl₃ (5.63 mL, 70 mmol) and acetone (95 mL) was added NaOH (15 g, 375 mmol). The reaction mixture was heated at reflux for 4 h, concentrated in vacuo and the residue was diluted in 50 mL of water, stirred and acidified with 6M HCl. An oil was formed, from which the water was decanted. The oil solidified on standing and the resultant solid was washed with water and petroleum ether, and dried in vacuo to give the expected compound.

Step b

2 from the scheme above (1.4 g, 5.4 mmol), acetamide oxime HCl.NEt₃ (2.9 g, 13.7 mmol), EDCI.HCl (2.2 g, 13.7 mmol), DIPEA (5 mL, 28.7 mmol), in THF (100 mL) was heated at reflux for 18 h. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography to give the expected compound.

Step c

3 from the scheme above (225 mg, 0.75 mmol), bispinacolato diboron (255 mg, 1.00 mmol), KOAc (98 mg, 1.00 mmol), Pd(dppf)Cl₂ (18.2 mg, 0.022 mmol) and dioxane (1.8 mL) were combined, degassed and heated to 90 °C for 4 h. 4 (180 mg, 0.64 mmol), NaHCO₃ (200 mg, 2.38 mmol), Pd(dppf)Cl₂ (20 mg, 0.024 mmol) and dioxane/water (2:1, 1 mL) were then added. The reaction mixture was heated at 100 °C for 18 hr, concentrated in vacuo and purified by preparative HPLC to give the expected compound.

Compound 68

This compound was prepared via Method C using 2-chloromethyl-6-methoxy-pyridine.

Compound 69

This compound was prepared via Method C using 2-chloromethyl-6-methyl-pyridine.

Compound 70

This compound was prepared via Method C using 8-bromomethyl-pyridine-2-carbonitrile.

Compound 71
N-(8-Bromo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-acetamide

To a solution of the 8-bromo-2-amino-triazolopyridine (1 eq.) in dry CH₂CN at 5 °C was added Et₃N (2.5 eq.) followed by acetyl chloride (2.5 eq.). The reaction mixture was then allowed to warm to ambient temperature and stirred until all starting material was consumed. If required, further Et₃N (1 eq.) and acid chloride (1 eq.) were added to ensure complete reaction. Following solvent evaporation *in vacuo* the resultant residue was treated with 7 N methanolic ammonia solution and stirred at ambient temp. (for 16 h) to hydrolyse any bis-acylated product. Product isolation was made by removal of volatiles *in vacuo* followed by addition of water and extraction with ethyl acetate. The organic phase was then dried over MgSO₄, evaporated *in vacuo*. The compound was used without further purification.

* Suzuki reaction *

2-(4-Benzylxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2eq.) was added to a solution of N-(8-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-acetamide in 1,4-dioxane/water (5:1). K₂CO₃ (2 eq.)
and Pd(dppf)Cl₂ (5%) (dppf = 1,1'-bis(diphenylphosphino)ferrocene) were added to the solution. The resulting mixture was then heated at 90°C for 16 h. Water was added and the solution was extracted with ethyl acetate. The organic layers were dried over MgSO₄ and evaporated in vacuo. The final compound was obtained after purification by preparative HPLC. Analytical: Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 50mm L (Part No.186002350).

Preparative HPLC: Waters XBridge Prep C18 5μm ODB 19mm ID x 100mm L (Part No.186002978). All the methods were using MeCN/H₂O gradients. H₂O contained either 0.1% TFA or 0.1% NH₃.

**Compound 73**

![Chemical Structure](image)

5-Bromo-2,3-dihydro-isocarbostyril-1-one (1eq) was added to a solution of benzyl bromide (1.1eq) and K₂CO₃ (2eq) in DMF under N₂. The mixture was stirred at rt for 16 hrs. Reaction was diluted in water and the compound precipitated. The solid was filtered and dried under reduced pressure. Compound was used in the next step without further purification.

![Chemical Structure](image)

2-Benzyl-5-bromo-2,3-dihydro-isocarbostyril-1-one (1eq), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bis[(1,2,3)dioxaborolanyl] (1.5eq) and potassium acetate (2 eq) were mixed in a vial, purged with nitrogen. 1,4-Dioxane is added. Then Pd(dppf)Cl₂ was added, the reaction was sonicated and it was heated at 85°C overnight until full conversion. The reaction mixture was dissolved in DCM, filtered through celite, and washed 3 times with DCM. Solvents were removed under reduced pressure and the obtained residue was used in the next step without purification.
This compound was prepared via Method A using 2-benzyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoidol-1-one prepared above.

**Compound 74**

This compound was prepared via Method C using 3-chloromethyl-1-methyl-1H-[1,2,4]triazole.

**Compound 75**

*Step i)*  
To a solution of 1 (13.5 g, 78 mmol) in CHCl₃ (5.63 mL, 70 mmol) and acetone (95 mL) was added NaOH (15 g, 375 mmol). The reaction mixture was heated at reflux for 4 h, concentrated in vacuo and the residue was diluted in 50 mL of water, stirred and acidified with 6M HCl. An oil was formed, from which the water was decanted. The oil solidified on standing and the resultant solid was washed with water and petroleum ether, and dried *in vacuo* to give (2) as shown in the scheme above.
Step ii)  
[00331] 2 (1.4 g, 5.4 mmol), acetamide oxime HCl, NEt$_3$ (2.9 g, 13.7 mmol), EDCI.HCl (2.2 g, 13.7 mmol), DIPEA (5 mL, 28.7 mmol), in THF (100 mL) was heated at reflux for 18 h. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography to give (3) as shown in the scheme above.

Step iii) 
[00332] 3 (225 mg, 0.75 mmol), bispinacolato diboron (255 mg, 1.00 mmol), KOAc (98 mg, 1.00 mmol), Pd(dppf)Cl$_2$ (18.2 mg, 0.022 mmol) and dioxane (1.8 mL) were combined, degassed and heated to 90 °C for 4 h. 4 (180 mg, 0.64 mmol), NaHCO$_3$ (200 mg, 2.38 mmol), Pd(dppf)Cl$_2$ (20 mg, 0.024 mmol) and dioxane/water (2:1, 1 mL) were then added. The reaction mixture was heated at 100 °C for 18 hr, concentrated in vacuo and purified by preparative HPLC to give Compound 75.

Compound 76

Step i  
[00333] To a solution of 1 (1 eq.) and chloro-acetic acid (0.9 eq) and acetone was added NaOH (5 eq). The reaction mixture was heated at reflux for 4 h, concentrated in vacuo and the residue was diluted in 50 mL of water, stirred and acidified with 6M HCl. An oil was formed, from which the water was decanted. The oil solidified on standing and the resultant solid was washed with water and petroleum ether, and dried in vacuo to give (2) as shown in the scheme above.
Step ii)

2 (1 eq), acetonitrile HCl, NEt₃ (2 eq), EDCI.HCl (2 eq), DIPEA (4 eq), in THF (100 mL) was heated at reflux for 18 h. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography to give (3) as shown in the scheme above.

Step iii)

3 (1 eq), bispinacolato diboron (1.2 eq), KOAc (98 mg, 1.00 mmol), Pd(dppf)Cl₂ (0.05 eq) and dioxane (1.8 mL) were combined, degassed and heated to 90 °C for 4 h. 4 (1 eq), NaHCO₃ (2 eq), Pd(dppf)Cl₂ (0.05 eq) and dioxane/water (2:1) were then added. The reaction mixture was heated at 100 °C for 18 hr, concentrated in vacuo and purified by preparative HPLC to give compound 76.

Compound 77

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\[\text{\includegraphics[width=0.8\textwidth]{compound77.png}}\]
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Step a

3-(4-Bromo-phenoxy)-propionitrile (2.4 g, 10 mmol), NH₂OH·HCl (695 mg, 10 mmol), NaOH (400 mg, 10 mmol) and ethanol (100 mL) were combined and heated to 80 °C for 18 h. CH₃COCl (45 mL) was then added and the reaction mixture was heated for a further 18 h at 65 °C (57 % conversion). The solvents were removed in vacuo, CH₃COCl (45 mL) was added and the reaction mixture was heated for a further 30 min. The solvents were removed in vacuo and the residue dissolved in AcOH then heated at reflux for 18 h (70% conversion). The reaction mixture was concentrated to dryness using cyclohexane to remove AcOH to give the expected compound.

Step b

The product obtained above in Step a (250 mg, 0.84 mmol), bispinacolato diboron (283 mg, 1.11 mmol), KOAc (109 mg, 1.11 mmol), Pd(dppf)Cl₂ (20 mg, 0.024 mmol) and dioxane (2 mL) were combined, degassed and heated to 90 °C for 18 h. Cyclopropanecarboxylic acid (8-bromo-[1,2,4]triazolo[1,5-
alpyridin-2-yl)-amide (200 mg, 0.71 mmol), NaHCO₃ (233 mg, 2.77 mmol), Pd(dppf)Cl₂ (25 mg, 0.030 mmol) and dioxane/water (2:1, 1.5 mL) were then added. The reaction mixture was heated under microwave irradiation at 120 °C for 15 min four times, concentrated in vacuo and purified by preparative HPLC to give the expected compound.

**Compound 78**

This compound was prepared via Method A using 4-acetamidophenylboronic acid.

**Compound 79**

2-Bromomethyl-pyridine (1.5eq.) was added to a solution of the acetamide derivative (1eq.) obtained by method A and NaH (2eq.) in DMF at 0°C. The mixture was stirred for 16hrs at room temperature. The solution was then diluted in water at 0°C and the solution was extracted with EtOAc. The organic phases were dried over MgSO₄, filtered and the solvent was removed under vacuum. The final compound was isolated by preparative HPLC.

**Compound 80**

4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile (1.1eq.) was added to a solution of cyclopropanecarboxylic acid [8-(4-bromo-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide, prepared by
method A in 1,4-dioxane/water (5:1). K$_2$CO$_3$ (2 eq.) and Pd(dppf)Cl$_2$ (0.03 eq.) (dppf = 1,1’-Bis(diphenylphosphino)ferrocene) were added to the solution. The resulting mixture was then heated in a sealed tube at 90°C for 16 hrs. Water was added and the solution was extracted with ethyl acetate. The organic layers were dried over MgSO$_4$ and evaporated in vacuo. The final compound was obtained after purification by preparative HPLC. Analytical: Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 50mm L.

**Compound 81**

[00341] This compound was prepared via Method B using 2,6-dimethyl-morpholine.

**Compound 82**

[00342] This compound was prepared via Method B using thiomorpholine 1,1-dioxide.

**Compound 83**

[00343] This compound was prepared via Method B using 4-hydroxy-piperidine.

**Compound 84**

[00344] The benzylamine derivative (1 eq.) obtained by Method A and Et$_3$N (5 eq) were dissolved in DCM under N$_2$ and cooled at 0°C. Trifluoroacetyl chloride (1.5 eq.) dissolved in DCM was added dropwise to this solution. The reaction was stirred at room temperature for 16 h. After this time, the reaction was complete. The compound was extracted with EtOAc and water, washed with brine and dried over MgSO$_4$. Organic layers were filtered and evaporated. The final compound was isolated by preparative HPLC. Preparative HPLC: Waters XBridge Prep C18 5μm ODB 19mm ID x 100mm L (Part No.186002978). All the methods were using MeCN/H$_2$O gradients. H$_2$O contains either 0.1% TFA or 0.1% NH$_3$.

**Compound 85**
Step a

[00345] The boronic acid (1 eq) and pinacol (1 eq) were heated in toluene at reflux for 20h. The excess of solvent was evaporated under reduced pressure to afford a crude product which was used in the next step without further purification.

Step b

[00346] 2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (1 eq), 2,6-dimethylmorpholine (1.2 eq), EDC (1.2 eq), HOBt (1.2 eq) and NEt$_3$ (3 eq), were mixed in THF at room temperature. The reaction mixture was mixed for 24h. Water was added and the organics were extracted with DCM. The organic layer was separated, dried over MgSO$_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography.

Step c

[00347] (2,6-Dimethyl-morpholin-4-yl)-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone (1.3 eq), Cyclopropanecarboxylic acid (8-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-amide (1 eq), PdCl$_2$dpff (0.05 eq) and NaHCO$_3$ (4 eq) were mixed in 1,4-dioxane/H$_2$O (4:1). The reaction mixture was allowed to heated at 90°C for 16 hrs. Water was added the organics were extracted with EtOAc. The organic layer was separated, dried over MgSO$_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography, followed by trituration in Et2O/MeOH.

Compound 86

[00348] This compound was prepared via Method B using 3,3-dimethylazetidine.

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<td><img src="image5.png" alt="Structure 5" /></td>
<td>Cyclopropanecarboxylic acid [8-(4-benzoyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
<td>382.43</td>
<td>383.90</td>
</tr>
<tr>
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<tr>
<td>6</td>
<td><img src="image" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid [8-(4-isopropoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
<td>336.40</td>
<td>337.00</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid [8-[4-(piperidine-1-carbonyl)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
<td>389.46</td>
<td>390.10</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td>4-[2-(Cyclopropanecarbonyl-amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl]-N-phenethyl-benzamide</td>
<td>425.49</td>
<td>448.1 (M+23)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td>4-[2-(Cyclopropanecarbonyl-amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl]-N-(2-phenoxyethyl)-benzamide</td>
<td>441.49</td>
<td>464.1 (M+23)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(8-(1-benzyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>358.4</td>
<td>359.0</td>
</tr>
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<tr>
<td>11</td>
<td><img src="image1" alt="Structure" /></td>
<td>N-(8-(1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>359.4</td>
<td>360.0</td>
</tr>
<tr>
<td>12</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(8-(2-benzylisoindolin-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>409.5</td>
<td>410.1</td>
</tr>
<tr>
<td>13</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-(8-(4-(4-benzyl-4-hydroxypiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>495.6</td>
<td>496.1</td>
</tr>
<tr>
<td>14</td>
<td><img src="image4" alt="Structure" /></td>
<td>N-(8-(4-(3,3-dimethylpiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>417.5</td>
<td>418.1</td>
</tr>
<tr>
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<td>MW (calcd)</td>
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<tr>
<td>15</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>4-(2- (cyclopropanecarboxamido)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)-N-(2- (1-phenyl-1H-pyrazol-4-yl)ethyl)benzamide</td>
<td>491.5</td>
<td>492.1</td>
</tr>
<tr>
<td>16</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N-(8-((1-(3-phenylpropyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>386.5</td>
<td>387.0</td>
</tr>
<tr>
<td>17</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>N-(8-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>294.3</td>
<td>295.0</td>
</tr>
<tr>
<td>18</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>N-(8-(4-(cyanomethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>333.4</td>
<td>334.0</td>
</tr>
<tr>
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<tr>
<td>19</td>
<td><img src="image1.png" alt="Structure 19" /></td>
<td>N-(8-(4-(pyridin-2-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>385.4</td>
<td>386.0</td>
</tr>
<tr>
<td>20</td>
<td><img src="image2.png" alt="Structure 20" /></td>
<td>N-(8-(4-((1,5-dimethyl-1H-pyrazol-3-yl)methyldimethyl-1H-pyrazol-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>402.5</td>
<td>403.0</td>
</tr>
<tr>
<td>21</td>
<td><img src="image3.png" alt="Structure 21" /></td>
<td>N-(8-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>349.4</td>
<td>350.0</td>
</tr>
<tr>
<td>22</td>
<td><img src="image4.png" alt="Structure 22" /></td>
<td>N-(8-(1-(2-phenoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>388.4</td>
<td>389.1</td>
</tr>
<tr>
<td>ID</td>
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<td>NAME</td>
<td>MW (calc)</td>
<td>MS (obsd)</td>
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</tr>
<tr>
<td>23</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(8-(4-(3-methylpiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>403.5</td>
<td>404.1</td>
</tr>
<tr>
<td>24</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>N-(8-(4-(2-(1H-pyrazol-1-yl)ethyl1H-pyrazol-1-yl)ethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>388.4</td>
<td>389.0</td>
</tr>
<tr>
<td>25</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>N-(8-(4-(1-cyanoethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>347.4</td>
<td>348.0</td>
</tr>
<tr>
<td>26</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N-(8-(3-(cyanomethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>333.4</td>
<td>334.1</td>
</tr>
<tr>
<td>ID</td>
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<tr>
<td>27</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(8-(2-hydroxy pyridin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>295.3</td>
<td>296.0</td>
</tr>
<tr>
<td>28</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>N-(8-(1H-indol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>317.4</td>
<td>318.0</td>
</tr>
<tr>
<td>29</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>N-(8-(1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>318.3</td>
<td>319.0</td>
</tr>
<tr>
<td>30</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N-(8-((6-methoxy pyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>415.5</td>
<td>416.0</td>
</tr>
<tr>
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<td>NAME</td>
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<td>MS (obsd)</td>
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</tr>
<tr>
<td>31</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>N-(8-(4-(1-(6-methoxypyridin-3-yl)ethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>429.5</td>
<td>430.0</td>
</tr>
<tr>
<td>32</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N-(8-(4-hydroxy-3,5-dimethylphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>322.4</td>
<td>323.1</td>
</tr>
<tr>
<td>33</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>N-(8-(4-(benzyloxy)-3-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>402.4</td>
<td>403.0</td>
</tr>
<tr>
<td>34</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>N-(8-(3-fluoro-4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>312.3</td>
<td>313.0</td>
</tr>
<tr>
<td>ID</td>
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<td>NAME</td>
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<td>MS (obsd)</td>
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</tr>
<tr>
<td>35</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>N-(8-(4-(((6-oxo-1,6-dihydro[1,2,4]triazolo[1,5-a]pyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>401.4</td>
<td>402.0</td>
</tr>
<tr>
<td>36</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N-(8-(1-phenethyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>372.4</td>
<td>373.1</td>
</tr>
<tr>
<td>37</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>N-(8-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>381.4</td>
<td>382.1</td>
</tr>
<tr>
<td>38</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>(E)-N-(8-(4-(2-cyanovinyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>329.4</td>
<td>330.1</td>
</tr>
<tr>
<td>ID</td>
<td>STRUCTURE</td>
<td>NAME</td>
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</tr>
<tr>
<td>39</td>
<td></td>
<td>N-(8-(4-(butylsulfonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>398.5</td>
<td>399.1</td>
</tr>
<tr>
<td>40</td>
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<td>N-(8-(4-(benzyloxy)-3-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>414.5</td>
<td></td>
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<td>41</td>
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<td>N-(8-(4-(pyridin-2-ylmethylsulfonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>433.5</td>
<td>434.1</td>
</tr>
<tr>
<td>42</td>
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<td>N-(8-(4-(pyridin-3-ylmethylsulfonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>433.5</td>
<td>434.1</td>
</tr>
<tr>
<td>ID</td>
<td>STRUCTURE</td>
<td>NAME</td>
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<td>MS (obsd)</td>
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<tr>
<td>43</td>
<td><img src="image" alt="Structure 1" /></td>
<td>N-(8-(4-(4-isopropylpiperazine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>432.5</td>
<td>433.1</td>
</tr>
<tr>
<td>44</td>
<td><img src="image" alt="Structure 2" /></td>
<td>N-(8-(4-((5-cyanopyridin-2-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>410.4</td>
<td>411.0</td>
</tr>
<tr>
<td>45</td>
<td><img src="image" alt="Structure 3" /></td>
<td>N-(8-(3,5-dimethyl-4-(pyridin-3-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>413.5</td>
<td>414.1</td>
</tr>
<tr>
<td>46</td>
<td><img src="image" alt="Structure 4" /></td>
<td>N-(8-(4-(1-cyanoethoxy)-3,5-dimethylphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>375.4</td>
<td>376.1</td>
</tr>
<tr>
<td>ID</td>
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<td>NAME</td>
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<td>MS (obsd)</td>
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</tr>
<tr>
<td>47</td>
<td><img src="image" alt="Structure 47" /></td>
<td>N-(8-(3,5-dimethyl-4-((1-methyl-1H-pyrazol-3-yl)methyl)methyl-1H-pyrazol-3-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>416.5</td>
<td>417.1</td>
</tr>
<tr>
<td>48</td>
<td><img src="image" alt="Structure 48" /></td>
<td>N-(8-(3,5-dimethyl-4-(pyridin-2-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>413.5</td>
<td>414.0</td>
</tr>
<tr>
<td>49</td>
<td><img src="image" alt="Structure 49" /></td>
<td>N-(8-(2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>386.4</td>
<td>387.0</td>
</tr>
<tr>
<td>50</td>
<td><img src="image" alt="Structure 50" /></td>
<td>N-(8-(2-(pyridin-3-ylmethoxy)pyridin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>386.4</td>
<td>387.0</td>
</tr>
<tr>
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<td>NAME</td>
<td>MW (calcd)</td>
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<tr>
<td>51</td>
<td><img src="image1" alt="Structure 51" /></td>
<td>N-(8-(1-(pyridin-3-ylmethyl)indolin-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>410.5</td>
<td>411.0</td>
</tr>
<tr>
<td>52</td>
<td><img src="image2" alt="Structure 52" /></td>
<td>N-(8-(1,3-dioxo-2-(pyridin-3-ylmethyl)isoindolin-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>438.5</td>
<td>439.0</td>
</tr>
<tr>
<td>53</td>
<td><img src="image3" alt="Structure 53" /></td>
<td>N-(8-(4-((6-methylpyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>399.5</td>
<td>400.0</td>
</tr>
<tr>
<td>54</td>
<td><img src="image4" alt="Structure 54" /></td>
<td>N-(8-(2-phenylbenzo[d]oxazol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>395.4</td>
<td>396.0</td>
</tr>
<tr>
<td>ID</td>
<td>STRUCTURE</td>
<td>NAME</td>
<td>MW (calcd)</td>
<td>MS (obsd)</td>
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</tr>
<tr>
<td>55</td>
<td><img src="image" alt="Structure 55" /></td>
<td>N-(8-(4-((phenylamino)methyl)phenyl)-1,2,4-triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>383.5</td>
<td>384.1</td>
</tr>
<tr>
<td>56</td>
<td><img src="image" alt="Structure 56" /></td>
<td>N-(8-(4-(4-cyanopiperidine-1-carbonyl)phenyl)-1,2,4-triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>414.5</td>
<td>415.0</td>
</tr>
<tr>
<td>57</td>
<td><img src="image" alt="Structure 57" /></td>
<td>N-(8-(4-((5-methylisoxazol-3-yl)methoxy)phenyl)-1,2,4-triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>389.4</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td><img src="image" alt="Structure 58" /></td>
<td>N-(8-(4-((5-methylpyridin-2-yl)methoxy)phenyl)-1,2,4-triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>399.5</td>
<td>400.1</td>
</tr>
<tr>
<td>ID</td>
<td>STRUCTURE</td>
<td>NAME</td>
<td>MW (calc.)</td>
<td>MS (obsd.)</td>
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</tr>
<tr>
<td>59</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>N-(8-(4-(morpholinomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>377.5</td>
<td>378.1</td>
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<td>60</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>N-(8-(4-propoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>336.4</td>
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<td>63</td>
<td><img src="image" alt="Structure 63" /></td>
<td>N-(8-(4-((6-chloropyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>419.9</td>
<td>420.0</td>
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<td>64</td>
<td><img src="image" alt="Structure 64" /></td>
<td>N-(8-(4-(2-cyanethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>331.4</td>
<td>332.1</td>
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<td>65</td>
<td><img src="image" alt="Structure 65" /></td>
<td>N-(8-(4-(pyridin-3-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>385.4</td>
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<td>66</td>
<td><img src="image" alt="Structure 66" /></td>
<td>N-(8-(1-(4-cyanobenzyl)-1H-pyrrol-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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<tr>
<td>67</td>
<td><img src="image1" alt="Structure" /></td>
<td>N-(8-(4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)propan-2-yloxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>418.5</td>
<td>419</td>
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<td>68</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(8-(4-((6-methoxy)pyridin-2-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>415.5</td>
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<td><img src="image3" alt="Structure" /></td>
<td>N-(8-(4-((6-methyl)pyridin-2-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>399.5</td>
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<td><img src="image4" alt="Structure" /></td>
<td>N-(8-(4-((6-cyanopyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>410.4</td>
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<td>71</td>
<td><img src="image1.png" alt="Structure 71" /></td>
<td>N-[8-(4-Benzyl oxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-acetamide</td>
<td>358.40</td>
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<td>73</td>
<td><img src="image2.png" alt="Structure 73" /></td>
<td>Cyclopropanecarboxylic acid [8-(2-benzyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
<td>423.48</td>
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<td>74</td>
<td><img src="image3.png" alt="Structure 74" /></td>
<td>Cyclopropanecarboxylic acid [8-[4-(1-methyl-1H-[1,2,4]triazol-3-ylmethoxy)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
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<td>75</td>
<td><img src="image4.png" alt="Structure 75" /></td>
<td>N-(8-(4-(2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yloxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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<td>76</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(8-(4-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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<td><img src="image2.png" alt="Structure" /></td>
<td>N-(8-(4-((5-methyl-1,2,4-oxadiazol-3-yl)ethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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<td><img src="image3.png" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid [8-(4-acetylamino-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
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<td><img src="image4.png" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid [8-[4-(acetylpyridin-2-ylmethylamino)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
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<td>80</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid {8-[(4-(6-cyano-pyridin-3-yl)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
<td>380.41</td>
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<td><img src="image2.png" alt="Structure" /></td>
<td>N-(8-(4-(2,6-dimethylmorpholine-4-carbonyl)phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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<td>82</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid {8-[(4-(1,1-dioxo-lambda^6*-thiomorpholine-4-carbonyl)phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
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<td><img src="image4.png" alt="Structure" /></td>
<td>N-(8-(4-(4-hydroxypiperidine-1-carbonyl)phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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### Table II: NMR Data of Representative Compounds of the Invention

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<td>84</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(8-(4-((2,2,2-trifluoroacetamido) methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
<td>403</td>
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<td>85</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(8-(4-(2,6-dimethylmorpholine-4-carbonyl)-3-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide</td>
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<td>86</td>
<td><img src="image" alt="Structure" /></td>
<td>Cyclopropanecarboxylic acid [8-[4-(3,3-dimethyl-azetidine-1-carbonyl)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide</td>
<td>549.60</td>
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<td>1</td>
<td>'H NMR δ (ppm)(CDCl₃): 9.25 (1H, b, NH), 8.56 (1H, b, ArH), 7.88 (2H, d, ArH), 7.61 (1H, d, ArH), 7.04 (3H, m, ArH), 4.11 (2H, q, CH₂), 1.60 (1H, b, CH), 1.46 (3H, t, CH₃), 1.14 (2H, b, CH₂), 0.84 (2H, b, CH₃)</td>
</tr>
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<td>'H NMR δ (ppm)(CDCl₃): 8.61 (1H, b, NH), 8.53 (1H, d, ArH), 7.92 (2H, d, ArH), 7.60 (1H, d, ArH), 7.50-7.35 (5H, m, ArH), 7.12 (2H, d, ArH), 7.05 (1H, m, ArH), 5.16 (2H, d, CH₂), 1.5 (1H, b, CH), 1.18 (2H, m, CH₂), 0.90 (2H, m, CH₂)</td>
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<td>3</td>
<td>1H NMR δ (ppm)(CDCl₃): 8.75 (1H, b, NH), 8.58 (1H, d, ArH), 7.94 (2H, d, ArH), 7.67 (1H, d, ArH), 7.50 (2H, d, ArH), 7.09 (1H, m, ArH), 4.55 (2H, s, CH₂), 3.45 (3H, s, CH₃), 1.90 (1H, under water peak, CH), 1.17 (2H, m, CH₂), 0.88 (2H, m, CH₂)</td>
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<td>1H NMR δ (ppm)(CDCl₃): 9.70 (1H, b, NH), 7.59 (1H, d, ArH), 8.20 (1H, s, ArH), 7.80 (1H, d, ArH), 7.76 (1H, d, ArH), 7.46 (1H, d, ArH), 7.13 (2H, m, ArH), 6.57 (1H, s, ArH), 3.86 (3H, s, CH₃), 1.25 (1H, b, CH), 0.99 (2H, b, CH₂), 0.66 (2H, b, CH₂)</td>
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<td>1H NMR δ (ppm)(CDCl₃): 8.63 (1H, b, NH), 8.45 (1H, b, ArH), 8.10 (2H, d, ArH), 7.99 (2H, d, ArH), 7.76 (1H, b, ArH), 7.64 (1H, m, ArH), 7.54 (2H, m, ArH), 7.14 (1H, b, ArH), 1.50 (1H, b, CH), 1.22 (2H, b, CH₂), 0.96 (2H, b, CH₂)</td>
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<td>1H NMR δ (ppm)(DMSO-d₆): 8.65 (1H, b, NH), 7.90 (2H, d, ArH), 7.60 (1H, d, ArH), 7.04 (3H, m, ArH), 4.64 (1H, sept, CH), 1.39 (6H, d, 2xCH₃), 1.25 (1H, b, CH), 1.18 (2H, m, CH₂), 0.90 (2H, m, CH₂)</td>
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<td>1H NMR δ (ppm)(DMSO-d₆): 11.16 (1H, b, NH), 8.86 (1H, d, ArH), 8.64 (1H, m, NH), 8.22 (2H, d, ArH), 7.96 (3H, dd, ArH), 7.33-7.19 (6H, m, ArH), 3.52 (2H, m, CH₂), 2.88 (2H, m, CH₂), 2.02 (1H, b, CH), 0.83 (4H, m, 2xCH₂)</td>
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<td>1H NMR δ (ppm)(DMSO-d₆): 11.17 (1H, s, NH), 8.87 (1H, d, ArH), 8.80 (1H, m, ArH), 8.24(2H, d, ArH), 8.01 (3H, m, ArH), 7.30-7.20 (3H, m, ArH), 7.00-6.94 (3H, m, ArH), 4.16 (2H, m, CH₂), 3.68 (2H, m, CH₂), 2.02 (1H, m, CH), 0.84 (4H, m, 2xCH₂)</td>
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<td>1H NMR δ (ppm)(DMSO-d₆): 11.01 (1H, b, NH), 8.67 (2H, m, ArH), 8.35 (1H, s, ArH), 7.92 (1H, dd, ArH), 7.34 (5H, m, ArH), 5.44 (2H, s, CH₂), 2.06 (1H, b, CH), 0.82 (4H, m, 2xCH₂).</td>
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<td>1H NMR δ (ppm)(DMSO-d₆): 11.01 (1H, b, NH), 8.67 (4H, m, ArH), 8.38 (1H, s, ArH), 7.92 (1H, dd, ArH), 7.85 (1H, d, ArH), 7.55 (1H, dd, ArH), 7.15 (1H, t, ArH), 5.55 (2H, s, CH₂), 2.07 (1H, b, CH), 0.84 (4H, m, 2xCH₂).</td>
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<td>1H NMR δ (ppm)(DMSO-d₆): 11.16 (1H, b, NH), 8.81 (1H, dd, ArH), 7.93 (2H, s, ArH), 7.83 (1H, dd, ArH), 7.37 (5H, m, ArH), 7.28 (1H, m, ArH), 7.20 (1H, t, ArH), 3.90 (6H, s, 3xCH₂), 2.01 (1H, b, CH), 0.82 (4H, m, 2xCH₂).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d6): 11.20 (1H, b, NH), 8.86 (1H, dd, ArH), 8.16 (2H, d, ArH), 7.94 (1H, dd, ArH), 7.50 (2H, d, ArH), 7.23 (6H, m, ArH), 4.51 (1H, b, CH$_2$), 4.23 (1H, b, CH$_2$), 3.11 (1H, b, CH), 2.72 (2H, s, CH$_2$), 2.03 (1H, b, CH), 1.50 (2H, b, CH$_2$), 1.34 (1H, b, CH), 0.83 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d6): 11.21 (1H, b, NH), 8.86 (1H, dd, ArH), 8.18 (2H, d, ArH), 7.95 (1H, d, ArH), 7.50 (2H, b, ArH), 7.24 (1H, m, ArH), 3.58 (1H, b, CH$_2$), 3.27 (2H, b, CH$_2$), 3.08 (1H, b, CH$_2$), 2.02 (1H, b, CH), 1.56 (2H, b, CH$_2$), 1.41 (2H, b, CH$_2$), 0.83 (10H, m, 2xCH$_2$, 2xCH$_3$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d6): 11.20 (1H, b, NH), 8.87 (1H, dd, ArH), 8.72 (1H, t, NH), 8.38 (1H, s, ArH), 8.22 (2H, dd, ArH), 7.98 (3H, m, ArH), 7.79 (2H, m, ArH), 7.64 (1H, s, ArH), 7.46 (2H, m, ArH), 7.25 (1H, m, ArH), 3.54 (2H, t, CH$_2$), 2.79 (2H, t, CH$_2$), 2.03 (1H, b, CH), 0.82 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d6): 11.03 (1H, b, NH), 8.67 (1H, dd, ArH), 8.59 (1H, s, ArH), 8.33 (1H, s, ArH), 7.91 (1H, dd, ArH), 7.22 (7H, m, ArH), 4.20 (2H, t, CH$_2$), 2.60 (2H, t, CH$_2$), 2.14 (2H, t, CH$_2$), 2.08 (1H, b, CH), 0.83 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d6): 11.14 (1H, b, NH), 9.78 (1H, s, OH), 8.74 (1H, q, ArH), 7.99 (2H, d, ArH), 7.78 (1H, d, ArH), 7.17 (1H, t, ArH), 6.89 (2H, d, ArH), 2.03 (1H, b, CH), 0.82 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d6): 11.21 (1H, b, NH), 8.79 (1H, q, ArH), 8.15 (2H, d, ArH), 7.87 (1H, q, ArH), 7.23 (2H, d, ArH), 7.19 (1H, q, ArH), 5.27 (2H, s, ArH), 2.02 (1H, b, CH), 0.83 (4H, m, 2xCH$_2$).</td>
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<td>21</td>
<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.17 (1H, b, NH), 8.69 (1H, dd, ArH), 7.77 (1H, dd, ArH), 7.62 (2H, m, ArH), 7.15 (2H, m, ArH), 6.79 (1H, d, ArH), 4.27 (3H, t, CH$_3$), 3.31 (2H, t, CH$_3$), 2.90 (3H, s, CH$_3$), 2.02 (1H, b, CH), 0.82 (4H, m, 2xCH$_3$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.21 (1H, b, NH), 8.86 (1H, dd ArH), 8.18 (2H, d, ArH), 7.95 (1H, d, ArH), 7.51 (2H, d, ArH), 7.24 (1H, m, ArH), 4.32 (1H, b, CH), 3.51 (1H, b, CH), 3.16 (3H, s, CH$_3$), 3.01 (1H, b, CH$_3$), 2.80 (1H, b, CH$_3$), 2.03 (1H, b, CH), 1.18 (1H, b, CH$_2$), 1.60 (2H, b, CH$_2$), 1.44 (1H, b, CH$_2$), 0.83 (1H, b, CH$_2$), 0.82 (4H, m, 2xCH$_3$), 0.75 (1H, b, CH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.21 (1H, b, NH), 8.81 (1H, q, ArH), 8.15 (2H, d, ArH), 7.88 (1H, q, ArH), 7.25 (2H, d, ArH), 7.22 (1H, q, ArH), 5.57 (1H, q, CH), 2.02 (1H, b, CH), 1.73 (3H, d, CH$_3$), 0.82 (4H, m, 2xCH$_3$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.22 (1H, b, NH), 8.86 (1H, q, ArH), 7.95 (1H, q, ArH), 7.85 (1H, d, ArH), 7.83 (1H, t, ArH), 7.53 (1H, t, ArH), 7.24 (1H, t, ArH), 7.18 (1H, q, ArH), 5.27 (2H, s, CH$_2$), 2.03 (1H, b, CH), 0.83 (4H, m, 2xCH$_3$).</td>
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<td>27</td>
<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.65 (1H, b, NH), 11.23 (1H, b, OH), 8.90 (1H, d ArH), 8.01 (1H, d, ArH), 7.49 (1H, d, ArH), 7.33 (1H, s, ArH), 7.22 (1H, t, ArH), 6.83 (1H, dd, ArH), 2.03 (1H, b, CH), 0.83 (4H, m, 2xCH$_3$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.22 (1H, b, NH), 11.11 (1H, b, NH), 8.74 (1H, dd, ArH), 8.38 (1H, d, ArH), 7.84 (1H, d, ArH), 7.79 (1H, m, ArH), 7.51 (1H, d, ArH), 7.41 (1H, t, ArH), 7.21 (1H, d, ArH), 6.52 (1H, s, ArH), 2.05 (1H, b, CH), 0.82 (4H, m, 2xCH$_3$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 13.19 (1H, b, NH), 11.14 (1H, b, NH), 8.80 (1H, dd, ArH), 8.60 (1H, s, ArH), 8.18 (1H, s, ArH), 8.03 (1H, dd, ArH), 7.90 (1H, dd, ArH), 7.67 (1H, d, ArH), 7.22 (1H, t, ArH), 2.05 (1H, b, CH), 0.84 (4H, m, 2xCH$_3$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.17 (1H, b, NH), 8.78 (1H, dd, ArH), 8.30 (1H, d, ArH), 8.11 (2H, d, ArH), 7.84 (1H, dd, ArH), 7.83 (1H, dd, ArH), 7.19 (1H, dd, ArH), 7.16 (2H, d, ArH), 6.87 (1H, dd, ArH), 5.14 (2H, s, CH$_2$), 3.86 (3H, s, CH$_3$), 2.03 (1H, b, CH), 0.82 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.16 (1H, b, NH), 8.75 (1H, dd, ArH), 8.27 (1H, d, ArH), 8.00 (2H, d, ArH), 7.78 (1H, dd, ArH), 7.77 (1H, dd, ArH), 7.16 (1H, dd, ArH), 7.07 (2H, d, ArH), 6.81 (1H, dd, ArH), 6.55 (1H, s, ArH), 5.65 (1H, s, CH), 3.82 (3H, s, CH$_3$), 2.01 (1H, b, CH), 1.59 (3H, d, CH$_3$), 0.81 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.43 (1H, b, NH), 9.86 (1H, b, NH or OH), 8.83 (1H, dd, ArH), 7.98 (2H, d, ArH), 7.86 (1H, dd, ArH), 7.45 (1H, dd, ArH), 7.26 (2H, d, ArH), 6.92 (2H, d, ArH), 6.27 (1H, d, ArH), 4.80 (2H, s, CH$_2$), 2.31 (1H, b, CH), 0.89 (2H, m, CH$_2$), 0.80 (2H, m, CH$_2$).</td>
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<td>38</td>
<td>H NMR δ (ppm)(DMSO-d6): 11.17 (1H, b, NH), 8.86 (1H, d, ArH), 8.23 (2H, d, ArH), 7.98 (1H, d, ArH), 7.80 (2H, d, ArH), 7.71 (1H, d, ArH), 7.24 (1H, m, ArH), 6.57 (1H, d, ArH), 2.04 (1H, b, CH), 0.83 (4H, m, CH3).</td>
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<td>H NMR δ (ppm)(DMSO-d6): 11.19 (1H, s, NH), 8.85 (1H, d, ArH), 8.37 (2H, d, ArH), 8.03 (3H, d, ArH), 7.24 (1H, m, ArH), 3.4 (2H, under water peak, CH2), 2.01 (1H, m, CH), 1.40 (4H, 2xCH2), 0.84 (7H, m, CH3, 2xCH3).</td>
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<td>H NMR δ (ppm)(DMSO-d6): 11.09 (1H, b, NH), 8.5 (1H, m, ArH), 8.41 (1H, m, ArH), 8.28 (2H, d, ArH), 7.95 (2H, d, ArH), 7.78 (2H, m, ArH), 7.70 (1H, d, ArH), 7.42 (2H, m, ArH), 4.90 (2H, s, CH2), 2.01 (1H, m, CH), 0.82 (4H, m, 2xCH2).</td>
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<td>44</td>
<td>H NMR δ (ppm)(DMSO-d6): 11.12 (1H, b, NH), 9.05 (1H, d, ArH), 8.77 (1H, dd, ArH), 8.37 (1H, d, ArH), 8.10 (2H, d, ArH), 7.84 (1H, dd, ArH), 7.75 (1H, dd, ArH), 7.19 (3H, m, ArH), 5.38 (2H, s, CH2), 2.03 (1H, b, CH), 0.82 (4H, m, 2xCH2).</td>
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<td>48</td>
<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.12 (1H, b, NH), 8.78 (1H, dd, ArH), 8.59 (1H, m, ArH), 7.90 (1H, m, ArH), 7.80 (1H, dd, ArH), 7.77 (2H, s, ArH), 7.70 (1H, d, ArH), 7.39 (1H, m, ArH), 7.19 (1H, m, ArH), 4.95 (2H, s, CH$_2$), 2.33 (6H, s, 2xCH$_3$), 2.06 (1H, b, CH), 0.83 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.23 (1H, b, NH), 8.92 (1H, dd, ArH), 8.66 (1H, b, ArH), 8.55 (1H, dd, ArH), 8.05 (2H, q, ArH), 7.83 (1H, d, ArH), 7.47 (2H, m, ArH), 7.22 (1H, m, ArH), 5.20 (2H, s, CH$_2$), 2.03 (1H, b, CH), 0.84 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.20 (1H, b, NH), 8.92 (1H, dd, ArH), 8.73 (1H, b, ArH), 8.56 (1H, dd, ArH), 8.33 (2H, dd, ArH), 8.14 (1H, d, ArH), 7.94 (1H, m, ArH), 7.85 (1H, m, ArH), 7.77 (1H, m, ArH), 7.45 (1H, q, ArH), 7.25 (1H, m, ArH), 5.47 (2H, s, CH$_2$), 2.03 (1H, b, CH), 0.84 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.07 (1H, b, NH), 8.68 (1H, m, ArH), 8.60 (1H, d, ArH), 8.49 (1H, m, ArH), 7.87 (2H, m, ArH), 7.73 (2H, m, ArH), 7.39 (1H, m, ArH), 7.13 (1H, tapp, ArH), 6.76 (1H, d, ArH), 4.43 (2H, s, CH$_2$), 3.40 (2H, t, CH$_2$), 3.01 (2H, t, CH$_2$), 2.04 (1H, b, CH), 0.82 (4H, m, 2xCH$_2$).</td>
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<td>$^1$H NMR δ (ppm)(DMSO-d$_6$): 11.25 (1H, b, NH), 8.93 (1H, m, ArH), 8.67 (1H, s, ArH), 8.59 (2H, m, ArH), 8.48 (1H, m, ArH), 8.12 (1H, dd, ArH), 8.05 (1H, dd, ArH), 7.74 (1H, m, ArH), 7.36 (1H, m, ArH), 7.27 (1H, tapp ArH), 4.86 (2H, s, CH2), 2.05 (1H, b, CH), 0.83 (4H, m, 2xCH$_2$).</td>
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<td>¹H NMR δ (ppm)(DMSO-d6): 11.16 (1H, b, NH), 8.85 (1H, dd, ArH), 8.18 (2H, d, ArH), 7.94 (1H, dd, ArH), 7.55 (2H, d, ArH), 7.24 (1H, m, ArH), 3.30 (2H, b, CH₃), 3.17 (3H, m, CH₃), 1.92 (3H, b, CH₃), 1.77 (2H, b, CH₂), 0.74 (4H, m, 2xCH₂).</td>
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<td>61</td>
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<td>¹H NMR δ (ppm)(DMSO-d6): 10.94 (1H, b, NH), 8.58 (1H, dd, ArH), 7.95 (1H, m, ArH), 7.80 (3H, m, ArH), 7.32 (2H, m, ArH), 7.09 (2H, m, ArH), 7.01 (2H, m, ArH), 7.88 (1H, m, ArH), 5.34 (2H, s, CH₂), 2.02 (1H, b, CH), 0.80 (2H, m, 2xCH₂).</td>
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<td>&quot;H NMR (ppm)(DMSO-d6): 0.86 (4 H, d, CH), 1.84 (6 H, s, CH3), 2.06 (1 H, m, CH), 2.43 (3 H, br s, CH3), 6.88 (2 H, d, ArH), 7.21 (1 H, dd, ArH), 7.87 (1 H, d, ArH), 8.06 (2 H, d, ArH), 8.83 (1 H, d, ArH), 11.18 (1 H, s, NH).</td>
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<td>&quot;H NMR (ppm)(DMSO-d6): 11.21 (1H, b, NH) 8.86 (1H, dd, ArH) 8.24 (2H, m, 2xArH) 7.91 (2H, dd, 2xArH) 7.31 (6H, m, 6xArH) 4.77 (2H, s, CH2) 4.45 (2H, s, CH2) 2.00 (1H, b, CH) 0.82 (4H, m, 2xCH2)</td>
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<td>&quot;H NMR (ppm)(DMSO-d6): 0.86 (4 H, d, CH), 1.75 (6 H, s, CH3), 2.06 (1 H, m, CH), 2.68 (3 H, s, CH3), 6.93 (2 H, d, ArH), 7.22 (1 H, dd, ArH), 7.85 (1 H, d, ArH), 8.05 (2 H, d, ArH), 8.80 (1 H, d, ArH), 11.17 (1 H, s, NH).</td>
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<td>&quot;H NMR (ppm)(CHCl3-d): 0.89 (2 H, m, CH), 1.17 (2 H, m, CH), 2.64 (3 H, s, CH3), 5.22 (2 H, s, CH), 7.04 (1 H, dd, ArH), 7.15 (2 H, d, ArH), 7.59 (1 H, d, ArH), 7.92 (2 H, d, ArH), 8.51 (2 H, d, ArH, NH).</td>
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<td>&quot;H NMR (ppm)(DMSO-d6): 0.86 (4 H, m, CH), 2.09 (1 H, m, CH), 2.62 (3 H, s, CH3), 3.22 (2 H, t, CH2), 4.46 (2 H, t, CH2), 7.12 (2 H, d, ArH), 7.19-7.27 (1 H, m, ArH), 7.85-7.93 (1 H, m, ArH), 8.13 (2 H, d, ArH), 8.81 (1 H, d, ArH), 11.18 (1 H, s, NH).</td>
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<td>&quot;H NMR (ppm)(DMSO-d6): 11.09 (1H, b, NH), 10.10 (1H, b, NH), 8.78 (1H, dd, ArH), 8.09 (2H, d, ArH), 7.85 (1H, dd, ArH), 7.71 (1H, dd, ArH), 7.20 (1H, dd, ArH), 2.08 (3H, b, CH3), 2.03 (1H, b, CH), 0.83 (4H, m, CH2).</td>
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<td>&quot;H NMR (ppm)(DMSO-d6): 11.16 (1H, b, NH), 8.82 (1H, dd, ArH), 8.47 (1H, d, ArH), 8.11 (2H, d, ArH), 7.88 (1H, d, ArH), 7.76 (1H, ddd, ArH), 7.50 (2H, d, ArH), 7.41 (1H, d, ArH), 7.25 (1H, dd, ArH), 7.20 (1H, dd, ArH), 5.01 (2H, s, CH2), 1.96 (4H, b, CH3+CH), 0.82 (4H, m, CH2).</td>
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Example 1.1  JAK1 inhibition assay

[00351] Recombinant human JAK1 catalytic domain (amino acids 850-1154; catalog number 08-144) was purchased from Carna Biosciences. 10 ng of JAK1 was incubated with 12.5 μg polyGT substrate (Sigma catalog number P0275) in kinase reaction buffer (15 mM Tris-HCl pH 7.5, 1 mM DTT, 0.01% Tween-20, 10 mM MgCl₂, 2 μM non-radioactive ATP, 0.25 μCi 33P-gamma-ATP (GE Healthcare, catalog number AH9968) at 37°C for 15 min. The reactions were stopped by adding of 25 μL of 10% phosphoric acid. All of the terminated kinase reaction was transferred to prewashed (75 mM phosphoric acid) 96 well filter plates (Perkin Elmer catalog number 6005177) using a cell harvester (Perkin Elmer). Plates were washed 6 times with 300 μL per well of a 75 mM phosphoric acid solution and the bottom of the plates was sealed. 40 μL/well of Microscint-20 was added, the top of the plates was sealed and readout was performed using the Topcount (Perkin Elmer). Kinase activity was calculated by subtracting counts per minute (cpm) obtained in the presence of a positive control inhibitor (10 μM staurosporine) from cpm obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:

[00352] Percentage inhibition = ((cpm determined for sample with test compound present – cpm determined for sample with positive control inhibitor) divided by (cpm determined in the presence of vehicle – cpm determined for sample with positive control inhibitor)) * 100%.

[00353] Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the JAK1 assay and the calculation of the IC₅₀ for each compound. Each compound was routinely tested at concentration of 20μM followed by a 1/3 serial dilution, 8 points (20μM - 6.67μM - 2.22μM - 740nM - 247nM - 82nM - 27nM - 9nM) in a final concentration of 1% DMSO. When potency of compound series increased, more dilutions were prepared and/or the top concentration was lowered (e.g. 5 μM, 1 μM).

[00354] Semi-quantitative score:
* > 1001 nM  
** 501-1000 nM  
*** 101-500 nM  
**** 0.01-100 nM

**TABLE III: JAK1 IC₅₀ Values of Compounds**

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**Example 1.2 JAK2 inhibition assay**

Recombinant human JAK2 catalytic domain (amino acids 808-1132; catalog number PV4210) was purchased from Invitrogen. 0.025mU of JAK2 was incubated with 2.5 µg polyGT substrate (Sigma catalog number P0275) in kinase reaction buffer (5 mM MOPS pH 7.5, 9 mM MgAc, 0.3mM EDTA, 0.06% Brij and 0.6 mM DTT, 1 µM non-radioactive ATP, 0.25µCi 33P-gamma-ATP (GE Healthcare, catalog number AH9968) final concentrations) with or without 5µL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 25 µL, in a polypropylene 96-well plate (Greiner, V-bottom). After 90 min at 30 °C, reactions were stopped by adding of 25 µL/well of 150 mM phosphoric acid. All of the terminated kinase reaction was transferred to prewashed (75 mM phosphoric acid) 96 well filter plates (Perkin Elmer catalog number 6005177) using a cell harvester (Perkin Elmer). Plates were washed 6 times with 300 µL per well of a 75 mM phosphoric acid solution and the bottom of the plates was sealed. 40 µL/well of Microscint-20 was added, the top of the plates was sealed and readout was performed using the TopCount (Perkin Elmer). Kinase activity was calculated by subtracting counts per minute (cpm) obtained in the presence of a positive control inhibitor (10 µM staurosporine) from cpm obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:
Percentage inhibition = ((cpm determined for sample with test compound present – cpm determined for sample with positive control inhibitor) divided by (cpm determined in the presence of vehicle – cpm determined for sample with positive control inhibitor)) * 100%.

Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the JAK2 assay and the calculation of the IC₅₀ for each compound. Each compound was routinely tested at concentration of 20µM followed by a 1/3 serial dilution, 8 points (20µM - 6.67µM - 2.22µM - 740nM - 247nM - 82nM - 27nM - 9nM) in a final concentration of 1% DMSO. When potency of compound series increased, more dilutions were prepared and/or the top concentration was lowered (e.g. 5 µM, 1 µM).

Semi-quantitative score:

# > 1001 nM
## 501-1000 nM
### 101-500 nM
#### 0.01-100 nM

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Example 1.3  JAK3 inhibition assay

Recombinant human JAK3 catalytic domain (amino acids 781-1124; catalog number PV3855) was purchased from Invitrogen. 0.025mU of JAK3 was incubated with 2.5 μg polyGT substrate (Sigma catalog number P0275) in kinase reaction buffer (25 mM Tris pH 7.5, 0.5 mM EGTA, 0.5 mM Na3VO4, 5 mM β-glycerolphosphate, 0.01% Triton X-100, 1 μM non-radioactive ATP, 0.25μCi 33P-gamma-ATP (GE Healthcare, catalog number AH9968) final concentrations) with or without 5μL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 25 μL, in a polypropylene 96-well plate (Greiner, V-bottom). After 105 min at 30 °C, reactions were stopped by adding of 25 μL/well of 150 mM phosphoric
acid. All of the terminated kinase reaction was transferred to prewashed (75 mM phosphoric acid) 96 well filter plates (Perkin Elmer catalog number 6005177) using a cell harvester (Perkin Elmer). Plates were washed 6 times with 300 μL per well of a 75 mM phosphoric acid solution and the bottom of the plates was sealed. 40 μL/well of Microscint-20 was added, the top of the plates was sealed and readout was performed using the Topcount (Perkin Elmer). Kinase activity was calculated by subtracting counts per minute (cpm) obtained in the presence of a positive control inhibitor (10 μM staurosporine) from cpm obtained in the presence of vehicle.

The ability of a test compound to inhibit this activity was determined as:

\[
\text{Percentage inhibition} = \left( \frac{\text{cpm determined for sample with test compound present} - \text{cpm determined for sample with positive control inhibitor}}{\text{cpm determined in the presence of vehicle} - \text{cpm determined for sample with positive control inhibitor}} \right) \times 100\%.
\]

Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the JAK3 assay and the calculation of the IC_{50} for each compound. Each compound was routinely tested at concentration of 20μM followed by a 1/3 serial dilution, 8 points (20μM - 6.67μM - 2.22μM - 740nM - 247nM - 82nM - 27nM - 9nM) in a final concentration of 1% DMSO. When potency of compound series increased, more dilutions were prepared and/or the top concentration was lowered (e.g. 5 μM, 1 μM).

Semi-quantitative score:

+ 1001 nM
++ 501-1000 nM
+++ 101-500 nM
++++ 0.01-100 nM

TABLE V: JAK3 IC_{50} Values of Compounds

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Example 1.4  TYK2 inhibition assay

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Recombinant human TYK2 catalytic domain (amino acids 871-1187; catalog number 08-147) was purchased from Carna biosciences. 5 ng of TYK2 was incubated with 12.5 μg polyGT substrate (Sigma catalog number P0275) in kinase reaction buffer (25 mM Hapes pH 7.5, 100 mM NaCl, 0.2 mM Na3VO4, 0.1% NP-40, 0.1 μM non-radioactive ATP, 0.125 μCi 33P-gamma-ATP (GE Healthcare, catalog number AH9968) final concentrations) with or without 5μL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 25 μL, in a polypropylene 96-well plate (Greiner, V-bottom). After 90 min at 30 °C, reactions were stopped by adding of 25 μL/well of 150 mM phosphoric acid. All of the terminated kinase reaction was transferred to prewashed (75 mM phosphoric acid) 96 well filter plates (Perkin Elmer catalog number 6005177) using a cell harvester (Perkin Elmer). Plates were washed 6 times with 300 μL per well of a 75 mM phosphoric acid solution and the bottom of the plates was sealed. 40 μL/well of Microscint-20 was added, the top of the plates was sealed and readout was performed using the Topcount (Perkin Elmer). Kinase activity was calculated by subtracting counts per minute (cpm) obtained in the presence of a positive control inhibitor (10 μM staurosporine) from cpm obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:

\[
\text{Percentage inhibition} = \left( \frac{\text{cpm determined for sample with test compound present} - \text{cpm determined for sample with positive control inhibitor}}{\text{cpm determined in the presence of vehicle} - \text{cpm determined for sample with positive control inhibitor}} \right) \times 100\%.
\]

Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the TYK2 assay and the calculation of the IC₅₀ for each compound. Each compound was routinely tested at concentration of 20μM followed by a 1/3 serial dilution, 8 points (20μM - 6.67μM - 2.22μM - 740nM - 247nM - 82nM - 27nM - 9nM) in a final concentration of 1% DMSO. When potency of compound series increased, more dilutions were prepared and/or the top concentration was lowered (e.g. 5 μM, 1 μM).

Semi-quantitative score:

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Example 2.1  JAK-STAT signalling assay:

[00371] HeLa cells were maintained in Dulbecco’s Modified Eagle’s Medium (DMEM) containing 10% heat inactivated fetal calf serum, 100 U/mL penicillin and 100 μg/mL streptomycin. HeLa cells were used at 70% confluence for transfection. 20,000 cells in 87 μL cell culture medium were transiently transfected with 40 ng pSTAT1(2)-luciferase reporter (Panomics), 8 ng of LacZ reporter as internal control reporter and 52 ng of pBSK using 0.32 μL Jet-PEI (Polyplus) as transfection reagent per well in 96-well plate format. After overnight incubation at 37°C, 10% CO2, transfection medium was removed. 75 μL of DMEM + 1.5% heat inactivated fetal calf serum was added. 15 μL of compound at 6.7x concentration was added for 60 min and then 10 μL of human OSM (Peprotech) at 33 ng/mL final concentration.

[00372] All compounds were tested in duplicate starting from 20 μM followed by a 1/3 serial dilution, 8 doses in total (20 μM - 6.6 μM - 2.2 μM - 740 nM - 250 nM - 82 nM - 27 nM - 9 nM) in a final concentration of 0.2% DMSO.

[00373] After overnight incubation at 37°C, 10% CO2, cells were lysed in 100 μL lysis buffer/well (PBS, 0.9 mM CaCl2, 0.5 mM MgCl2, 5% Trehalose, 0.025% Tergitol NP9, 0.15% BSA).

[00374] 40 μL of cell lysate was used to read β-galactosidase activity by adding 180 μL βGal solution (30μl ONPG 4mg/mL + 150 μL β-Galactosidase buffer (0.06 M Na2HPO4, 0.04 M NaH2PO4, 1 mM MgCl2)) for 20 min. The reaction was stopped by addition of 50 μL Na2CO3 1 M. Absorbance was read at 405 nm.

[00375] Luciferase activity was measured using 40 μL cell lysate plus 40 μL of Steadylite® as described by the manufacturer (Perkin Elmer), on the Envision (Perkin Elmer).

[00376] 10 μM of a pan-JAK inhibitor was used as a positive control (100% inhibition). As negative control 0.5% DMSO (0% inhibition) was used. The positive and negative controls were used to calculate z’ and ‘percent inhibition’ (PIN) values.

[00377] Percentage inhibition = ((fluorescence determined in the presence of vehicle - fluorescence determined for sample with test compound present) divided by (fluorescence determined in the presence of vehicle – fluorescence determined for sample without trigger)) * 100 %.
PIN values were plotted for compounds tested in dose-response and EC_{50} values were derived.

* > 1001 nM
** 501-1000 nM
*** 1-500 nM

**TABLE VII: STAT signalling EC_{50} Values of Compounds**

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Example 2.2  OSM/IL-1β signaling Assay

[00380]  OSM and IL-1β were shown to synergistically upregulate MMP13 levels in the human chondrosarcoma cell line SW1353. The cells were seeded in 96 well plates at 15,000 cells/well in a volume of 120 μL DMEM (Invitrogen) containing 10% (v/v) FBS and 1% penicillin/streptomycin (Invitrogen) incubated at 37°C 5% CO2. Cells were preincubated with 15 μL compound in M199 medium with 2% DMSO 1 hr before triggering with 15 μL OSM and IL-1β to reach 25 ng/mL OSM and 1 ng/mL IL-1β, and MMP13 levels were measured in conditioned medium 48 hours after triggering.  MMP13 activity was measured using an antibody capture activity assay. For this purpose, 384 well plates (NUNC, 460518, MaxiSorb black) were coated with 35 μL of a 1.5 μg/mL anti-human MMP13 antibody (R&D Systems, MAB511) solution for 24 hours at 4°C. After washing the wells 2 times with PBS + 0.05% Tween, the remaining binding sites were blocked with 100 μL 5% non-fat dry milk (Santa Cruz, sc-2325, Blotto) in PBS for 24 hours at 4°C. Next, the wells were washed 2 times with PBS + 0.05% Tween and 35 μL of 1/10 dilution of culture supernatant containing MMP13 in 100-fold diluted blocking buffer was added and incubated for 4 hours at room temperature. Next the wells were washed twice with PBS + 0.05% Tween followed by MMP13 activation by addition of 35 μL of a 1.5 mM 4-Aminophenylmercuric acetate (APMA) (Sigma, A9563) solution and incubation at 37 °C for 1 hour. The wells were washed again with PBS + 0.05% Tween and 35 μL MMP13 substrate (Biomol, P-126, OmniMMP fluorogenic substrate) was added. After incubation for 24 hours at 37°C fluorescence of the converted substrate was measured in a Perkin Elmer Wallac EnVision 2102 Multilabel Reader (wavelength excitation: 320 nm, wavelength emission: 405 nm).

[00381]  Percentage inhibition = ((fluorescence determined in the presence of vehicle - fluorescence determined for sample with test compound present) divided by (fluorescence determined in the presence of vehicle – fluorescence determined for sample without trigger)) * 100 %.

* > 1001 nM
** 501-1000 nM
*** 1-500 nM

[00382]  TABLE VIII: MMP13 EC_{50} Values of Compounds

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**Example 2.3  PBL Proliferation assay**

Human peripheral blood lymphocytes (PBL) are stimulated with IL-2 and proliferation measured using a BrdU incorporation assay. The PBL are first stimulated for 72 hrs with PHA to induce IL-2 receptor, fasted for 24 hrs to stop cell proliferation followed by IL-2 stimulation for another 72 hrs (including 24hr BrdU labeling). Cells are preincubated with test compounds 1 hr before IL-2 addition. Cells are cultured in RPMI 1640 containing 10% (v/v) FBS.

**Example 3. In vivo models**

**Example 3.1  CIA model**

3.1.1  Materials

Completed Freund’s adjuvant (CFA) and incomplete Freund’s adjuvant (IFA) are purchased from Difco. Bovine collagen type II (CII), lipopolysaccharide (LPS), and Enbrel are obtained from Chondrex.
(Isle d’Abeau, France); Sigma (P4252, L'Isle d'Abeau, France), Whyett (25mg injectable syringe, France) Aeros Organics (Palo Alto, CA), respectively. All other reagents used are of reagent grade and all solvents are of analytical grade.

3.1.2 Animals

[00385] Dark Agouti rats (male, 7-8 weeks old) are obtained from Harlan Laboratories (Maison-Alfort, France). DBA/1J mice (male, 7 weeks old) are obtained from Centre d’Elevage et de Reproduction JANVIER (CERJ) (Laval, France). Rats and mice are kept on a 12 hours light/dark cycle (0700 - 1900). The temperature is maintained at 22°C, and food and water are provided ad libitum.

3.1.3 Collagen induced arthritis (CIA)

[00386] One day before the experiment, CII solution (2 mg/mL) is prepared with 0.05 M acetic acid and stored at 4°C. Just before the immunization, equal volumes of adjuvant (IFA) and CII are mixed by a homogenizer in a pre-cooled glass bottle in an ice water bath. Extra adjuvant and prolonged homogenization might be required if an emulsion is not formed.

[00387] Mice: 0.1 mL of the emulsion is injected intradermally at the base of the tail of each mouse on day 1, a second booster intradermal injection (CII solution at 1 mg/mL in CFA 0.1 mL saline) is performed on day 21. This immunization method is modified from published methods (David D Brand Kary A Latham, & Edward F Rosloniec. Collagen-induced arthritis. Nature Methods 2 (5): 1269-1275, 2007).

[00388] Rat: 0.2 mL of the emulsion is injected intradermally at the base of the tail of each rat on day 1, a second booster intradermal injection (CII solution at 2 mg/mL in CFA 0.1 mL saline) is performed on day 9. This immunization method is modified from published methods (Sims NA et al., (2004) Targeting osteoclasts with zoledronic acid prevents bone destruction in collagen-induced arthritis, Arthritis Rheum. 50 2338-2346; Jou et al., 2005).

3.1.4 Study design

[00389] The therapeutic effects of the test compounds are tested in the rat or mouse CIA model. Animals are randomly divided into equal groups and each group contained 10 animals. All rats are immunized on day 1 and boosted on day 9. All mice are immunized on day 1 and boosted on day 21. Therapeutic dosing last from day 16 to day 30. The negative control group is treated with vehicle (MC 0,5%) and the positive control group with Enbrel (10 mg/kg, 3x week., s.c.). A compound of interest is typically tested at 3 doses, e.g. 3, 10, 30 mg/kg, p.o.
3.1.5 Clinical assessment of arthritis

[00390] Arthritis is scored according the method of Khachigian 2006, Lin et al 2007 and Nishida et al. 2004). The swelling of each of the four paws is ranked with the arthritis score as follows: 0-no symptoms; 1-mild, but definite redness and swelling of one type of joint such as the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits; 2-moderate redness and swelling of two or more types of joints; 3-severe redness and swelling of the entire paw including digits; 4-maximally inflamed limb with involvement of multiple joints (maximum cumulative clinical arthritis score 16 per animal) (Nishida et al., 2004).

3.1.6 Change in body weight (%) after onset of arthritis

[00391] Clinically, body weight loss is associated with arthritis (Shelton et al., 2005; Argiles et al., 1998; Rall, 2004; Walsmith et al., 2004). Hence, changes in body weight after onset of arthritis can be used as a non-specific endpoint to evaluate the effect of therapeutics in the rat model. The change in body weight (%) after onset of arthritis is calculated as follows:

\[
\frac{\text{Body Weight}_{\text{(week 6)}} - \text{Body Weight}_{\text{(week 5)}}}{\text{Body Weight}_{\text{(week 5)}}} \times 100\%
\]

[00392] Mice:

\[
\frac{\text{Body Weight}_{\text{(week 4)}} - \text{Body Weight}_{\text{(week 3)}}}{\text{Body Weight}_{\text{(week 3)}}} \times 100\%
\]

[00393] Rats:

3.1.7 Radiology

[00394] X-ray photos are taken of the hind paws of each individual animal. A random blind identity number is assigned to each of the photos, and the severity of bone erosion is ranked by two independent scorers with the radiological Larsen's score system as follows: 0- normal with intact bony outlines and normal joint space; 1- slight abnormality with any one or two of the exterior metatarsal bones showing slight bone erosion; 2-definite early abnormality with any three to five of the exterior metatarsal bones showing bone erosion; 3-medium destructive abnormality with all the exterior metatarsal bones as well as any one or two of the interior metatarsal bones showing definite bone erosions; 4-severe destructive abnormality with all the metatarsal bones showing definite bone erosion and at least one of the inner metatarsal joints completely eroded leaving some bony joint outlines partly preserved; 5-mutilating abnormality without bony outlines. This scoring system is a modification from Salvarini et al., 2001; Bush et al., 2002; Sims et al., 2004; Jou et al., 2005.

3.1.8 Histology

[00395] After radiological analysis, the hind paws of mice are fixed in 10% phosphate-buffered formalin (pH 7.4), decalcified with rapid bone decalcifant for fine histology (Laboratories Eurobio) and
embedded in paraffin. To ensure extensive evaluation of the arthritic joints, at least four serial sections (5 μm thick) are cut and each series of sections were 100 μm in between. The sections are stained with hematoxylin and eosin (H&E). Histologic examinations for synovial inflammation and bone and cartilage damage are performed double blind. In each paw, four parameters are assessed using a four-point scale. The parameters are cell infiltration, pannus severity, cartilage erosion and bone erosion. Scoring is performed as follows: 1-normal, 2-mild, 3-moderate, 4-marked. These four scores are summed together and represented as an additional score, namely the 'RA total score'.

3.1.9 Micro-computed tomography (μCT) analysis of calcaneus (heel bone):

Bone degradation observed in RA occurs especially at the cortical bone and can be revealed by μCT analysis (Sims NA et al., 2004; Oste L et al., ECTC Montreal 2007). After scanning and 3D volume reconstruction of the calcaneus bone, bone degradation is measured as the number of discrete objects present per slide, isolated in silico perpendicular to the longitudinal axis of the bone. The more the bone is degraded, the more discrete objects are measured. 1000 slices, evenly distributed along the calcaneus (spaced by about 10.8 μm), are analyzed.

Example 3.2 Septic shock model

Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF-alpha) into the periphery. This model is used to analyse prospective blockers of TNF release in vivo.

Six BALB/cJ female mice (20 g) per group were treated at the intended dosing once, po. Thirty minutes later, LPS (15 μg/kg; E. Coli serotype 0111:B4) was injected ip. Ninety minutes later, mice were euthanized and blood was collected. Circulating TNF alpha levels were determined using commercially available ELISA kits. Dexamethasone (5 μg/kg) was used as a reference anti-inflammatory compound. Selected compounds are tested at one or multiple doses, e.g. 3 and/or 10 and/or 30 mg/kg, po.

Selected compounds were tested in the septic shock model; Compounds 13, 25, 53, 60 and 62 were active at 30 mg/kg.

Example 3.3 MAB model

The MAB model allows a rapid assessment of the modulation of an RA-like inflammatory response by therapeutics (Kachigian LM. Nature Protocols (2006) 2512-2516: Collagen antibody-induced arthritis). DBA/J mice are injected i.v. with a cocktail of mAbs directed against collagen II. One day later, compound treatment is initiated (vehicle: 10% (v/v) HPβCD). Three days later, mice receive an i.p. LPS injection (50 μg/mouse), resulting in a fast onset of inflammation. Compound treatment is continued until 10 days after the mAb injection. Inflammation is read by measuring paw swelling and recording the clinical score of each paw. The cumulative clinical arthritis score of four limbs is presented to show the severity of
inflammation. A scoring system is applied to each limb using a scale of 0–4, with 4 being the most severe inflammation.

0  Symptom free
1  Mild, but definite redness and swelling of one type of joint such as the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits
2  Moderate redness and swelling of two or more types of joints
3  Severe redness and swelling of the entire paw including digits
4  Maximally inflamed limb with involvement of multiple joints

Example 3.4  Oncology models


Example 3.5  Mouse IBD model

[00402]  *In vitro* and *in vivo* models to validate efficacy of small molecules towards IBD are described by Wirtz *et al.* 2007.

Example 3.6  Mouse Asthma model

[00403]  *In vitro* and *in vivo* models to validate efficacy of small molecules towards asthma are described by Nials *et al.*, 2008; Ip *et al.*, 2006; Pernis *et al.*, 2002; Kudlacz *et al.*, 2008.

Example 4:  Toxicity, DMPK and Safety Models

Example 4.1  Thermodynamic solubility

[00404]  A solution of 1 mg/mL of the test compound is prepared in a 0.2M phosphate buffer pH7.4 or a 0.1M citrate buffer pH3.0 at room temperature in a glass vial.

[00405]  The samples are rotated in a Rotator drive STR 4 (Stuart Scientific, Bibby) at speed 3.0 at room temperature for 24 hours.

[00406]  After 24 hours, 800µL of the sample is transferred to an eppendorf tube and centrifuged 5 min at 14000rpm. 200 µL of the supernatant of the sample is then transferred to a MultiscreenR Solubility Plate (Millipore, MSSLBPC50) and the supernatant is filtered (10-12” Hg) with the aid of a vacuum manifold into a clean Greiner polypropylene V-bottom 96well plate (Cat no.651201). 5 µL of the filtrate is diluted into 95 µL (F20) of the same buffer used to incubate in the plate containing the standard curve (Greiner,Cat no.651201).

[00407]  The standard curve for the compound is prepared freshly in DMSO starting from a 10mM DMSO stock solution diluted factor 2 in DMSO (5000µM) and then further diluted in DMSO up to 19.5µM.
3μL of the dilution series as from 5000μM is then transferred to a 97μL acetonitrile-buffer mixture (50/50). The final concentration range is 2.5 to 150 μM.

The plate is sealed with sealing mats (MA96RD-04S, www.kinesis.co.uk) and samples are measured at room temperature on LCMS (ZQ 1525 from Waters) under optimized conditions using Quanoptimiz to determine the appropriate mass of the molecule.

The samples are analyzed on LCMS with a flow rate of 1mL/min. Solvent A is 15mM ammonia and solvent B is acetonitrile. The sample is run under positive ion spray on an XBridge C18 3.5μM (2.1 x 30mm) column, from Waters. The solvent gradient has a total run time of 2 minutes and ranges from 5% B to 95% B.

Peak areas are analyzed with the aid of Masslynx software package and peak areas of the samples are plotted against the standard curve to obtain the solubility of the compound.

Solubility values are reported in μM or μg/mL.

**Example 4.2 Aqueous Solubility**

Starting from a 10mM stock in DMSO, a serial dilution of the compound is prepared in DMSO. The dilution series is transferred to a 96 NUNC Maxisorb plate F-bottom (Cat no. 442404) and 0.2M phosphate buffer pH7.4 or 0.1M citrate buffer pH3.0 at room temperature is added.

The final concentration ranged from 200μM to 2.5μM in 5 equal dilution steps. The final DMSO concentration did not exceed 2%. 200μM Pyrene is added to the corner points of each 96 well plate and serves as a reference point for calibration of Z-axis on the microscope.

The assay plates are sealed and incubated for 1 hour at 37°C while shaking at 230rpm. The plates are then scanned under a white light microscope, yielding individual pictures of the precipitate per concentration. The precipitate is analyzed and converted into a number which is plotted onto a graph. The first concentration at which the compound appears completely dissolved is the concentration reported, however the true concentration lies somewhere between this concentration and one dilution step higher.

Solubility values are reported in μg/mL.

**Example 4.3 Plasma Protein Binding (Equilibrium Dialysis)**

A 10mM stock solution of the compound in DMSO is diluted with a factor 5 in DMSO. This solution is further diluted in freshly thawed human, rat, mouse or dog plasma (BioReclamation INC) with a final concentration of 10μM and final DMSO concentration of 0.5% (5.5μl in 1094.5μl plasma in a PP-Masterblock 96well (Greiner, Cat no. 780285))

A Pierce Red Device plate with inserts (ThermoScientific, Cat no. 89809) is prepared and filled with 750μL PBS in the buffer chamber and 500μL of the spiked plasma in the plasma chamber. The plate is incubated for 4 hours at 37°C while shaking at 230rpm. After incubation, 120μL of both chambers is
transferred to 360μL acetonitrile in a 96-well round bottom, PP deep-well plates (Nunc, Cat no. 278743) and sealed with an aluminum foil lid. The samples are mixed and placed on ice for 30min. This plate is then centrifuged 30 min at 1200 × gref at 4°C and the supernatant is transferred to a 96 v-bottom PP plate (Greiner, 651201) for analysis on LCMS.

The plate is sealed with sealing mats (MA96RD-04S) of www.kinesis.co.uk and samples are measured at room temperature on LCMS (ZQ 1525 from Waters) under optimized conditions using Quanoptimizer to determine the appropriate mass of the molecule.

The samples are analyzed on LCMS with a flow rate of 1mL/min. Solvent A was 15mM ammonia and solvent B was acetonitrile. The sample was run under positive ion spray on an XBridge C18 3.5μM (2.1 x 30mm) column, from Waters. The solvent gradient has a total run time of 2 minutes and ranges from 5% B to 95% B.

Peak area from the compound in the buffer chamber and the plasma chamber are considered to be 100% compound. The percentage bound to plasma is derived from these results and was reported to the LIIMS as percentage bound to plasma.

The solubility of the compound in the final test concentration in PBS is inspected by microscope to indicate whether precipitation is observed or not.

**Example 4.4 Liability for QT prolongation**

Potential for QT prolongation is assessed in the hERG patch clamp assay.

**4.4.1 Conventional whole-cell patch-clamp**

Whole-cell patch-clamp recordings are performed using an EPC10 amplifier controlled by Pulse v8.77 software (HEKA). Series resistance is typically less than 10 MΩ and compensated by greater than 60%, recordings are not leak subtracted. Electrodes are manufactured from GC150TF pipette glass (Harvard).

The external bathing solution contains: 135 mM NaCl, 5 mM KCl, 1.8 mM CaCl₂, 5 mM Glucose, 10 mM HEPES, pH 7.4.

The internal patch pipette solution contains: 100mM Kgluconate, 20 mM KCl, 1mM CaCl₂, 1 mM MgCl₂, 5mM Na₂ATP, 2mM Glutathione, 11 mM EGTA, 10 mM HEPES, pH 7.2.

Drugs are perfused using a Biologic MEV-9/EVH-9 rapid perfusion system.

All recordings are performed on HEK293 cells stably expressing hERG channels. Cells are cultured on 12 mm round coverslips (German glass, Bellco) anchored in the recording chamber using two platinum rods (Goodfellow). hERG currents are evoked using an activating pulse to +40 mV for 1000 ms followed by a tail current pulse to −50 mV for 2000 ms, holding potential was -80 mV. Pulses are applied every 20s and all experiments are performed at room temperature.
4.4.2 Data Analysis

[00428] IC_{50} and IC_{20} values are calculated for each compound tested. The fold difference between the IC_{50} and the unbound C_{max} concentrations of the test compound obtained at relevant therapeutic doses as determined by results obtained from the rat CIA model is calculated.

[00429] For the concentration response curves, peak tail current amplitude is measured during the voltage step to -50 mV. Curve-fitting of concentration-response data is performed using the equation:

\[ y = a + \left\{ \frac{b - a}{1 + 10^{(\log c - x) d}} \right\} \]

[00430] where a is minimum response, b is maximum response and d is Hill slope, this equation can be used to calculate both IC_{50} (where y = 50 and c is the IC_{50} value) and IC_{20} (where y = 20 and c is the IC_{20} value). GraphPad® Prism® (Graphpad® Software Inc.) software was used for all curve fitting.

[00431] A difference of 100 fold or greater indicates a low potential for QT prolongation.

Example 4.5 Microsomal stability

[00432] A 10 mM stock solution of compound in DMSO was diluted 1000 fold in a 182 mM phosphate buffer pH 7.4 in a 96 deep well plate (Greiner, Cat no. 780285) and pre-incubated at 37°C.

[00433] 40μL of deionised water was added to a well of a polypropylene Matrix 2D barcode labelled storage tube (Thermo Scientific) and pre-incubated at 37°C.

[00434] A Glucose-6-phosphate-dehydrogenase (G6PDH) working stock solution was prepared in 182 mM phosphate buffer pH 7.4 and placed on ice before use. A co-factor containing MgCl\(_2\), glucose-6-phosphate and NADP\(^+\) was prepared in deionised water and placed on ice before use.

[00435] A final working solution containing liver microsomes (Xenotech) of a species of interest (human, mouse, rat, dog), previously described G6PDH and co-factors was prepared and this mix was incubated for no longer than 20 minutes at room temperature.

[00436] 30μL of the pre-heated compound dilution was added to 40μL of pre-heated water in the Matrix tubes and 30μL of the microsomal mix was added. Final reaction concentrations were 3μM compound, 1mg microsomes, 0.4U/mL GDPDH, 3.3 mM MgCl\(_2\), 3.3 mM glucose-6-phosphate and 1.3 mM NADP\(^+\).

[00437] To measure percentage remaining of compound at time zero MeOH or ACN was added (1:1) to the well before adding the microsomal mix. The plates were sealed with Matrix Sepra sealSTM (Matrix, Cat. No. 4464) and shaken for a few seconds ensure complete mixing of all components.

[00438] The samples which were not stopped are incubated at 37°C, 300rpm and after 1 hour of incubation the reaction was stopped with MeOH or ACN (1:1).

[00439] After stopping the reaction the samples were mixed and placed on ice for 30min to precipitate the proteins. The plates were then centrifuged 30 min at 1200rcf at 4°C and the supernatant was transferred to a 96 v-bottom PP plate (Greiner, 651201) for analysis on LCMS.
These plates were sealed with sealing mats (MA96RD-04S) of www.kinesis.co.uk and samples were measured at room temperature on LCMS (ZQ 1525 from Waters) under optimized conditions using Quanoptimize to determine the appropriate mass of the parent molecule.

The samples were analyzed on LCMS with a flow rate of 1mL/min. Solvent A was 15mM ammonia and solvent B was methanol or acetonitrile, depending on the stop solution used. The samples were run under positive ion spray on an XBridge C18 3.5μM (2.1 x 30mm) column, from Waters. The solvent gradient had a total run time of 2 minutes and ranges from 5% B to 95% B.

Peak area from the parent compound at time 0 was considered to be 100% remaining. The percentage remaining after 1 hour incubation was calculated from time 0 and was calculated as the percentage remaining. The solubility of the compound in the final test concentration in buffer is inspected by microscope and results are reported.

The data on microsomal stability are expressed as a percentage of the total amount of compound remaining after 60 minutes.

* 0-25
** 26-50
*** 51-75
**** 76-100
N/A – not available

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<td>86</td>
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</table>
Example 4.6  Caco2 Permeability

[00444]  Bi-directional Caco-2 assays were performed as described below. Caco-2 cells were obtained from European Collection of Cell Cultures (ECACC, cat 86010202) and used after a 21 day cell culture in 24-well Transwell plates (Fisher TKT-545-020B).

[00445]  2x10^5 cells/well were seeded in plating medium consisting of DMEM + GlutaMAXI + 1% NEAA + 10% FBS (FetalClone II) + 1% Pen/Strep. The medium was changed every 2 – 3 days.

[00446]  Test and reference compounds (propranolol and rhodamine123 or vinblastine, all purchased from Sigma) were prepared in Hanks’ Balanced Salt Solution containing 25 mM HEPES (pH7.4) and added to either the apical (125μL) or basolateral (600μL) chambers of the Transwell plate assembly at a concentration of 10 μM with a final DMSO concentration of 0.25%.

[00447]  50μM Lucifer Yellow (Sigma) was added to the donor buffer in all wells to assess integrity of the cell layers by monitoring Lucifer Yellow permeation. As Lucifer Yellow (LY) cannot freely permeate lipophilic barriers, a high degree of LY transport indicates poor integrity of the cell layer.

[00448]  After a 1 hour incubation at 37°C while shaking at an orbital shaker at 150rpm, 70μL aliquots were taken from both apical (A) and basal (B) chambers and added to 100μL 50:50 acetonitrile:water solution containing analytical internal standard (0.5μM carbamazepine) in a 96 well plate.

[00449]  Lucifer yellow was measured with a Spectramax Gemini XS (Ex 426nm and Em 538nm) in a clean 96 well plate containing 150μL of liquid from basolateral and apical side.

[00450]  Concentrations of compound in the samples were measured by high performance liquid-chromatography/mass spectrometry (LC-MS/MS).

[00451]  Apparent permeability (P_{app}) values were calculated from the relationship:

\[
P_{app} = \frac{[\text{compound}]_{\text{acceptor final}} \times V_{\text{acceptor}}}{([\text{compound}]_{\text{donor initial}} \times V_{\text{donor}}) / T_{\text{inc}} \times V_{\text{donor}} / \text{surface area} \times 60 \times 10^6 \text{ cm/s}}
\]

\[V = \text{chamber volume}\]

\[T_{\text{inc}} = \text{incubation time}\]

\[\text{surface area} = 0.33\text{cm}^2\]

[00452]  The Efflux ratios, as an indication of active efflux from the apical cell surface, were calculated using the ratio of P_{app} B>A/ P_{app} A>B.

[00453]  The following assay acceptance criteria were used:

- Propranolol: P_{app} (A>B) value ≥ 20(×10^6 cm/s)
- Rhodamine 123 or Vinblastine: P_{app} (A>B) value < 5 (×10^6 cm/s) with Efflux ratio ≥5.
- Lucifer yellow permeability: ≤100 nm/s

Table X – Caco2 Efflux rate
<table>
<thead>
<tr>
<th>Compound #</th>
<th>Papp (A2B)cm x 10-6/sec-1</th>
<th>Efflux ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>68.58</td>
<td>0.57</td>
</tr>
<tr>
<td>8</td>
<td>13.29</td>
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<tr>
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<td>12.75</td>
<td>2</td>
</tr>
<tr>
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<td>2.5</td>
<td>16</td>
</tr>
<tr>
<td>23</td>
<td>17.5</td>
<td>2</td>
</tr>
<tr>
<td>25</td>
<td>32.7</td>
<td>1</td>
</tr>
<tr>
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<td>18</td>
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<td>11.1</td>
</tr>
<tr>
<td>85</td>
<td>8.28</td>
<td>6.11</td>
</tr>
</tbody>
</table>

**Example 4.7  Pharmacokinetic study in rodents**

4.7.1  **Pharmacokinetic study**

[00454] Compounds are formulated in PEG200/physiological saline or PEG400/DMSO/physiological saline mixtures for the intravenous route and in 0.5% methylcellulose or 10-30% hydroxypropyl-β-cyclodextrine pH3 or pH7.4 for the oral route. Test compounds are orally dosed as a single esophageal gavage at 5-10 mg/kg and intravenously dosed as a bolus via the caudal vein at 1 mg/kg. Each group consists of 3 rats. Blood samples are collected either via the jugular vein using cannulated rats or at the retro-orbital sinus with lithium heparin as anti-coagulant at the time points in the following range: 0.05 to 8 hours (intravenous route), and 0.25 to 6 or 24 hours (oral route). Whole blood samples are centrifuged at 5000 rpm for 10 min and the resulting plasma samples are stored at -20°C pending analysis.

4.7.2  **Quantification of compound levels in plasma**

[00455] Plasma concentrations of each test compound are determined by an LC-MS/MS method in which the mass spectrometer is operated in positive electrospray mode.

4.7.3  **Determination of pharmacokinetic parameters**

[00456] Pharmacokinetic parameters are calculated using Winnonlin® (Pharsight®, United
Example 4.8  7-Day rat toxicity study

[00457] A 7-day oral toxicity study with test compounds is performed in Sprague-Dawley male rats to assess their toxic potential and toxicokinetics, at daily doses of 100, 300 and 500 mg/kg/day, by gavage, at the constant dosage-volume of 5 mL/kg/day.

[00458] The test compounds are formulated in 30% (v/v) HPβCD in purified water. Each group includes 5 principal male rats as well as 3 satellite animals for toxicokinetics. A fourth group is given 30% (v/v) HPβCD in water only, at the same frequency, dosage volume and by the same route of administration, and acts as the vehicle control group.

[00459] The goal of the study is to determine the lowest dose that results in no adverse events being identified (no observable adverse effect level - NOAEL).

[00460] It will be appreciated by those skilled in the art that the foregoing descriptions are exemplary and explanatory in nature, an as induced intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognise apparent modifications and variations that may be made without departing from the spirit of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

[00461] REFERENCES


Oste L et al., ECTC Montreal 2007: A high throughput method of measuring bone architectural disturbance in a murine CIA model by micro-CT morphometry


Osteoarthritis - an untreatable disease?

Wirtz et al. (2007) Mouse Models of Inflammatory Bowel Disease, Advanced Drug Delivery Reviews, 2007, 1073-1083:


Constantinescu et al., 2007, Trends in Biochemical Sciences 33(3): 122-131


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 were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

From the foregoing description, various modifications and changes in the compositions and methods of this invention will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

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 \textit{in vitro} biochemical and cellular assays.

At least some of the chemical names of compounds 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 Lexicem 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.

Chemical structures shown herein were prepared using either ChemDraw\textsuperscript{®} or ISIS\textsuperscript{®} /DRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.
WHAT IS CLAIMED IS:

1. A compound according to Formula I below:

\[
\begin{align*}
&\text{Cy1} \\
&(R^{3b})_{m2} L_1 (CR^{4b}R^{4c})_{m1} R^{3b} \\
&(R^{1})_{m1} \begin{array}{c}
N \\
\end{array} \begin{array}{c}
\text{NH} \\
\end{array}
\end{align*}
\]

wherein

each \( R^1 \) is independently selected from \( C_1-C_6 \) alkyl, substituted \( C_1-C_6 \) alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted \( C_1-C_6 \) alkoxy, substituted or unsubstituted amido, substituted or unsubstituted amino, substituted sulfanyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano, substituted or unsubstituted \( C_3-C_7 \) cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, and hydroxyl;

\( R^{2a} \) is selected from substituted or unsubstituted \( C_1-C_6 \) alkyl or \( C_3-C_7 \) cycloalkyl;

\( \text{Cy1} \) is selected from aryl and heteroaryl;

\( L_1 \) is selected from a single bond, -O-, -N(R^{3b})-, -C(=O)-, -CON(R^{4b})-, -(SO_2)-, -SO_2N(R^{4c})-, -N(R^{4c})CO-, or -N(R^{4b})SO_2-; -CR^{3b}=CR^{4c}.

each \( R^{3a} \) is independently selected from \( C_1-C_6 \) alkyl, substituted \( C_1-C_6 \) alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted \( C_1-C_6 \) alkoxy, substituted or unsubstituted amido, alkoxy carbonyl, substituted alkoxy carbonyl, arylalkyloxy, substituted arylalkyloxy, substituted or unsubstituted amino, aryl, substituted aryl, arylalkyl, substituted sulfanyl, substituted sultfinyl, substitued sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, substituted or unsubstituted \( C_3-C_7 \) cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, substituted or unsubstituted heteroaryl, hydroxyl, nitro, and thiol;

\( R^{3b} \) is H, substituted or unsubstituted \( C_1-C_6 \) alkyl, substituted or unsubstituted \( C_3-C_7 \) cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted \( C_1-C_6 \) alkoxy, substituted or unsubstituted amino, substituted or unsubstituted acylamino, cyano or -O-aryl;

\( R^{4a}, R^{4b}, R^{4c} \) are independently selected from H, \( C_1-C_6 \) alkyl, substituted or unsubstituted acyl;

\( m1 \) is 0, 1, or 2; \( m2 \) is 0, 1, 2, or 3; and \( n1 \) is 0, 1, 2, or 3;
provided that

when \( L^1 \) is \(-N(R^{4b})\), \(-CON(R^{4b})\), or \(-SO_2N(R^{4b})\), and \( R^{2c} \) is other than \( H \), \( C_1-C_6 \) alkyl, \( C_3-C_7 \) cycloalkyl, aryl or heteroaryl, then \( m_1 \) is 1, 2, 3, or 4;
or pharmaceutically acceptable salts thereof.

2. The compound according to claim 1, wherein

each \( R^1 \) is independently selected from unsubstituted \( C_1-C_6 \) alkyl, unsubstituted acyl, unsubstituted acylamino, unsubstituted \( C_1-C_6 \) alkoxy, unsubstituted amido, unsubstituted amino, unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano, unsubstituted \( C_3-C_7 \) cycloalkyl, unsubstituted 4-7 membered heterocycloalkyl, halo, and hydroxy;
\( R^{2a} \) is selected from unsubstituted \( C_1-C_6 \) alkyl or unsubstituted \( C_3-C_7 \) cycloalkyl;
\( Cy^1 \) is selected from aryl and heteroaryl;
\( L^1 \) is selected from a single bond, \(-O-\), \(-N(R^{4b})\), \(-C(=O)-\), \(-CON(R^{4b})-\), \(-SO_2-\), \(-SO_2N(R^{4b})-\), \(-N(R^{4b})CO-\), or \(-N(R^{4b})SO_2-\); \(-CR^{3b}=CR^{3b}\).

each \( R^{3a} \) is independently selected from unsubstituted \( C_1-C_6 \) alkyl, unsubstituted acyl, unsubstituted acylamino, unsubstituted \( C_1-C_6 \) alkoxy, unsubstituted amido, unsubstituted alkoxy carbonyl, unsubstituted arylalkoxy, unsubstituted amino, unsubstituted aryl, unsubstituted sulfanyl, unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, unsubstituted \( C_3-C_7 \) cycloalkyl, unsubstituted 4-7 membered heterocycloalkyl, halo, unsubstituted heteroaryl, hydroxyl, nitro, and thiol;
\( R^{3b} \) is \( H \), \( C_1-C_6 \) alkyl (which \( C_1-C_6 \) alkyl may be substituted with cyano), \( C_3-C_7 \) cycloalkyl (which \( C_3-C_7 \) cycloalkyl may be substituted with unsubstituted \( C_1-C_4 \) alkyl), 4-7 membered heterocycloalkyl (which 4-7 membered heterocycloalkyl may be substituted with unsubstituted \( C_1-C_4 \) alkyl, cyano, OH), aryl (which aryl may be substituted with unsubstituted \( C_1-C_4 \) alkyl, cyano), heteroaryl (which heteroaryl may be substituted with unsubstituted \( C_1-C_4 \) alkyl, unsubstituted \( C_1-C_4 \) alkoxy, cyano, halo, OH, unsubstituted aryl), \( C_1-C_6 \) alkoxy (which \( C_1-C_6 \) alkoxy may be substituted with cyano), amino (which amino may be substituted with unsubstituted aryl), substituted or unsubstituted acylamino (which acylamino may be substituted with unsubstituted \( C_1-C_4 \) alkyl, cyano or unsubstituted \(-O\)-aryl);
\( R^{4a} \), \( R^{4b} \), \( R^{4c} \) are independently selected from \( H \), unsubstituted \( C_1-C_6 \) alkyl, acyl (which acyl may be substituted with unsubstituted \( C_1-C_4 \) alkyl)

\( m_1 \) is 0, 1, or 2; \( m_2 \) is 0, 1, 2, or 3; and \( n_1 \) is 0, 1, 2, or 3;

provided that

when \( L^1 \) is \(-N(R^{4b})\), \(-CON(R^{4b})\), or \(-SO_2N(R^{4b})\), and \( R^{2c} \) is other than \( H \), \( C_1-C_6 \) alkyl, \( C_3-C_7 \) cycloalkyl, aryl or heteroaryl, then \( n_1 \) is 1, 2, 3, or 4;
or pharmaceutically acceptable salts thereof.
3. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein R₂ is substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

4. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein R₂ is cyclopropyl.

5. The compound or pharmaceutically acceptable salt according to any one of claims 1-4 wherein each R is independently halo, C₁-C₆ alkyl or C₁-C₆ haloalkyl.

6. The compound or pharmaceutically acceptable salt according to any one of claims 1-5 wherein m₁ is 0.

7. The compound or pharmaceutically acceptable salt according to any one of claims 1-6 wherein Cyl is aryl.

8. The compound or pharmaceutically acceptable salt according to claim 7 wherein Cyl is phenyl.

9. The compound or pharmaceutically acceptable salt according to any one of claims 1-6 wherein Cyl is heteroaryl.

10. The compound or pharmaceutically acceptable salt according to claim 9 wherein Cyl is pyridyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzodioxany1, dihydroindolyl, dihydroisoindolyl, isoindolone, phthalimide, benzooxazolyl, quinolinyl and isoquinolinyl.

11. The compound or pharmaceutically acceptable salt according to any one of claims 1-10 wherein each R₂ is selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo, C₁-C₆ alkoxy, -O-aryl, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted amido, carboxy, substituted or unsubstituted acylamino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, and m₂ is 0, 1, 2 or 3.

12. The compound or pharmaceutically acceptable salt according to any one of claims 1-10 wherein each R₂ is selected from Me, Et, CF₃, Cl, F, OMe, OEt, O-Pr, O-Pr, -OCF₃, -CO₂H, -NHAc, -Ph or -OH and m₂ is 0, 1, 2 or 3.

13. The compound or pharmaceutically acceptable salt according to claim 1 or 2, wherein the compound is according to Formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, II or IIj:
wherein $R^{3e}$ is as in claim 12; and $R^{3b}$, $R^{4b}$, $R^{4c}$, and $n1$ are as in claim 1 or 2
14. The compound or pharmaceutically acceptable salt according to claim 12 or 13 wherein R^{1b} is selected from H, Me, Et, i-Pr, OMe, CF₃, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, cyano, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy, substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, substituted or unsubstituted azepinyl, substituted or unsubstituted diazepinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted tetrahydroquinolinyl, substituted or unsubstituted tetrahydroisoquinolinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyrroloxyln, substituted or unsubstituted oxazolyl, substituted or unsubstituted imidazolyl, and substituted or unsubstituted oxadiazolyl.

15. The compound or pharmaceutically acceptable salt according to claim 14 wherein R^{1b} is selected from phenyl, phenoxy, pyridinyl, pyrrolyl, pyrazolyl, oxazolyl, imidazolyl, and oxadiazolyl unsubstituted or substituted with one or more groups selected from Me, Cl, F, CF₃, substituted or unsubstituted acyl, substituted or unsubstituted benzyl, and substituted or unsubstituted phenyl.

16. The compound or pharmaceutically acceptable salt according to claim 13 wherein the compound is according to Formula IIa, IIb, IIc, IId, IIf, III, IIm or IIIi; m₁ is 0; and R^{3b} is selected from substituted or unsubstituted pyrrolidin-1-yl, piperidin-1-yl, piperizin-1-yl, 1,4-diazepan-1-yl, morpholin-1-yl and tetrahydroquinolin-1-yl.

17. The compound or pharmaceutically acceptable salt according to claim 13 wherein the compound is according to Formula IIa, IIb, IIc, IId, IIf, III, IIm or IIIi; m₁ is 0; and R^{3b} is selected from pyrrolidin-1-yl, piperidin-1-yl, piperizin-1-yl, 1,4-diazepan-1-yl, morpholin-1-yl, and tetrahydroquinolin-1-yl substituted with one or more groups selected from Me, Cl, F, CF₃, substituted or unsubstituted acyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzoyl, and substituted or unsubstituted phenyl.

18. The compound or pharmaceutically acceptable salt according to claim 1 or 2, wherein the compound is according to Formula IIIa, IIIb, IIIc, IId, IIIe, IIIf, IIIg, IIIh, or IIIi.
wherein n1 is 0, 1, 2 or 3; R^{3i} is as in claim 12; each R^{5i} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, amino, acylamino, cyano, C_{1-6} alkoxy and C_{1-6} haloalkyl-O-; and m3 is 0, 1, 2, 3, 4 or 5.
19. The compound or pharmaceutically acceptable salt according to claim 18 wherein m₃ is 1 or 2; and each R⁵ₐ is independently Me, CF₃, OMe, NH₂, NHAc, OCF₃, Cl, or F.

20. The compound or pharmaceutically acceptable salt according to claim 18 or 19 wherein n₁ is 0 or 1.

21. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula IVa, IVb, IVc, IVd, IVe or IVf:

![Chemical Structures](image)

and wherein n₁ is 0, 1, 2 or 3; R⁴ is as in claim 11; and m₃ is 0, 1, 2, 3, 4 or 5.; L is –O–, –NH–, or –CONH–; each R⁵ₐ is independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, Ph, benzyl and halo; n₁ is 0, 1, 2, 3 or 4; and m₃ is 0, 1, 2, 3 or 4.

22. The compound or pharmaceutically acceptable salt according to claim 21 wherein L is –O–.

23. The compound or pharmaceutically acceptable salt according to claim 21 wherein L is –NH–.

24. The compound or pharmaceutically acceptable salt according to claim 21 wherein L is –CONH–.

25. The compound or pharmaceutically acceptable salt according to any one of claims 21-24 wherein n₁ is 0, 1, or 2.
26. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula Va:

![Chemical Structure Diagram]

and wherein \( R^{3a} \) is as in claim 12; \( n1 \) is 1 or 2; each \( R^{5a} \) is independently selected from \( C_1-C_6 \) alkyl, \( C_1-C_6 \) haloalkyl and halo; \( R^{6i}, R^{6c} \) are as in claim 1 or 2; \( R^{4d} \) is selected from \( C_1-C_6 \) alkyl; and \( m3 \) is 0, 1, 2, 3, 4 or 5.

27. The compound or pharmaceutically acceptable salt according to claim 26 wherein \( R^{4d} \) is Me.

28. The compound or pharmaceutically acceptable salt according to any one of claims 21-27 wherein \( m3 \) is 1 or 2; and each \( R^{5a} \) is independently selected from Me, Cl, F and CF₃.

29. The compound or pharmaceutically acceptable salt according to any one of claims 1-28 wherein \( R^{5b}, R^{6c} \) are independently selected from H and Me.

30. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula Vla, Vlb, Vlc, Vld, Vle, Vlf, Vlg or Vlh:
and wherein R\(^{3a}\) is as in claim 12.

31. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula VIIa, VIIb, VIIc, VIId, VIIe, or VIIf:
and wherein R^3 is as in claim 12.

32. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula VIIa, VIIb or VIIc:
and wherein $R^{3a}$ is as in claim 12.

33. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula IXa, IXb, or IXc:

![Chemical Structures IXa, IXb, IXc]

and wherein $R^{3a}$ is as in claim 12.

34. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is according to Formula Xa, Xb, or Xc:

![Chemical Structures Xa, Xb, Xc]

and wherein $R^{3a}$ is as in claim 12.

35. The compound or pharmaceutically acceptable salt according to any one of claims 12-34 wherein $R^{3z}$ is selected from H, Me, Cl, F and CF₃.

36. The compound or pharmaceutically acceptable salt according to any one of claims 12-34 wherein $R^{3z}$ is H.

37. The compound or pharmaceutically acceptable salt according to claim 1 or 2 wherein the compound is selected from compounds listed in Table 1.

38. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt according to any one of claims 1-37.

39. The pharmaceutical composition of claim 38, wherein the carrier is a parenteral carrier.
40. The pharmaceutical composition of claim 38, wherein the carrier is an oral carrier.

41. The pharmaceutical composition of claim 38, wherein the carrier is a topical carrier.

42. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 37 for use in medicine.

43. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 37 for use in the treatment or prophylaxis of a disease involving cartilage degradation, bone and/or joint degradation, for example osteoarthritis; and/or conditions involving inflammation or immune responses, such as Crohn's disease, rheumatoid arthritis, psoriasis, allergic airways disease (e.g. asthma, rhinitis), juvenile idiopathic arthritis, colitis, inflammatory bowel diseases, endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), diseases involving impairment of cartilage turnover (e.g. diseases involving the anabolic stimulation of chondrocytes), congenital cartilage malformations, diseases associated with hypersecretion of IL6, transplantation rejection (e.g. organ transplant rejection) or proliferative diseases.

44. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 37 for use in the treatment or prophylaxis of rheumatoid arthritis.

45. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 37, for use in the treatment or prophylaxis of a condition or a disease involving inflammation.

46. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 37, for use in the treatment or prophylaxis of a condition or a disease characterized by abnormal JAK1 activity.
WHAT IS CLAIMED IS:

1. A compound according to Formula I below:

![Chemical Structure](image)

wherein

each R¹ is independently selected from C₁-C₆ alkyl, substituted C₁-C₆ alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted C₁-C₆ alkoxy, substituted or unsubstituted amido, substituted or unsubstituted amino, substituted sulfanyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, carboxy, cyano, substituted or unsubstituted C₅-C₇ cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, and hydroxyl;

R²a is selected from substituted or unsubstituted C₁-C₆ alkyl or C₅-C₇ cycloalkyl;

Cy₁ is selected from aryl and heteroaryl;

L₁ is selected from a single bond, -O-, -N(R⁴₅)-, -C(=O)-, -CON(R⁴₅)-, -(SO₂)-, -SO₂N(R⁴₅)-, -N(R⁴₅)CO₂-, or -N(R⁴₅)SO₂-, -CR⁴₅=CR⁴₆.

each R³a is independently selected from C₁-C₆ alkyl, substituted C₁-C₆ alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted C₁-C₆ alkoxy, -O-aryl, substituted or unsubstituted amido, alkoxy carbonyl, substituted alkoxy carbonyl, arylalkyloxy, substituted arylalkyloxy, substituted or unsubstituted amino, aryl, substituted aryl, arylalkyl, substituted sulfanyl, substituted sulfanyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, substituted or unsubstituted C₅-C₇ cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, substituted or unsubstituted heteroaryl, hydroxyl, nitro, and thiol;

R³b is H, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₅-C₇ cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C₁-C₆ alkoxy, substituted or unsubstituted amino, substituted or unsubstituted acylamino, cyano or -O-aryl;

R⁴a, R⁴b, R⁴c are independently selected from H, and C₁-C₆ alkyl;

m₁ is 0, 1, or 2; m₂ is 0, 1, 2, or 3; and n₁ is 0, 1, 2, or 3;

provided that

AMENDED SHEET (ARTICLE 19)
when L1 is $-\text{O-}$, $-\text{N(R^{4b})-}$, $-\text{CON(R^{4b})-}$, or $-\text{SO}_{2}\text{N(R^{4b})-}$, and $R^{3b}$ is other than cycloalkyl, aryl or 5-10 membered heteroaryl, then n1 is 1, 2 or 3;

or pharmaceutically acceptable salts thereof.

2. The compound or pharmaceutically acceptable salt according to claim 1, wherein each $R^{3a}$ is independently selected from $C_1$-$C_6$ alkyl, substituted $C_1$-$C_6$ alkyl, acyl, substituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted $C_1$-$C_6$ alkoxy, substituted or unsubstituted amido, alkoxy carbonyl, substituted alkoxy carbonyl, arylalkyloxy, substituted arylalkyloxy, substituted or unsubstituted amino, aryl, substituted aryl, arylalkyl, substituted sulfanyl, substituted sulfynil, substituted sulfonil, substituted or unsubstituted aminosulfonil, sulfonic acid, sulfonic acid ester, azido, carboxy, cyano, substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, halo, substituted or unsubstituted heteroaryl, hydroxyl, nitro, and thiol.

3. The compound or pharmaceutically acceptable salt according to claim 1, wherein each $R^{3b}$ is substituted or unsubstituted $C_1$-$C_6$ alkyl, substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted $C_1$-$C_6$ alkoxy, substituted or unsubstituted amino, substituted or unsubstituted acylamino, cyano or $-\text{O-aryl}$.

4. The compound or pharmaceutically acceptable salt according to claim 1 wherein $R^{2a}$ is substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

5. The compound or pharmaceutically acceptable salt according to claim 1 wherein $R^{2a}$ is cyclopropyl.

6. The compound or pharmaceutically acceptable salt according to any one of claims 1-5 wherein each $R^1$ is independently halo, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ haloalkyl.

7. The compound or pharmaceutically acceptable salt according to any one of claims 1-6 wherein n1 is 0.

8. The compound or pharmaceutically acceptable salt according to any one of claims 1-7 wherein Cy1 is aryl.

9. The compound or pharmaceutically acceptable salt according to claim 8 wherein Cy1 is phenyl.

10. The compound or pharmaceutically acceptable salt according to any one of claims 1-7 wherein Cy1 is heteroaryl.

11. The compound or pharmaceutically acceptable salt according to claim 10 wherein Cy1 is pyridyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzodioxanly, quinolinyl and isoquinolinyl.

12. The compound or pharmaceutically acceptable salt according to any one of claims 1 or 4-11 wherein each $R^{3b}$ is selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, halo, $C_1$-$C_6$ alkoxy, $-\text{O-aryl}$, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted amido, carboxy,
substituted or unsubstituted acylamino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C3-C7 cycloalkyl, substituted or unsubstituted 4-7 membered heterocycloalkyl, and m2 is 0, 1, 2 or 3.

13. The compound or pharmaceutically acceptable salt according to any one of claims 1-11 wherein each Rb is selected from Me, Et, CF3, Cl, F, OMe, OEt, O-iPr, O-nPr, -OCF3, -CO2H, -NHAc, -Ph or -OH and m2 is 0, 1, 2 or 3.

14. The compound or pharmaceutically acceptable salt according to claim 1, 2 or 3, wherein the compound is according to Formula Iia, Iib, Iic, Iid, Iie, IIf, Iig, Ih or IIi:
wherein $R^{3a}$ is as in claim 13; and $R^{3b}$, $R^{4h}$, $R^{5o}$, and $n1$ are as in claim 1.

15. The compound or pharmaceutically acceptable salt according to claim 14 wherein $R^{3b}$ is selected from Me, Et, i-Pr, OMe, CF$_3$, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, cyano, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy, substituted or unsubstituted piperidinyl, substituted or unsubstituted piperazinyl, substituted or
unsubstituted azepinyl, substituted or unsubstituted diazepinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted tetrahydroquinolinyl, substituted or unsubstituted tetrahydroisoquinolinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted imidazolyl, and substituted or unsubstituted oxadiazolyl.

16. The compound or pharmaceutically acceptable salt according to claim 15 wherein R² is selected from phenyl, phenoxy, pyridinyl, pyrrolyl, pyrazolyl, oxazolyl, imidazolyl, and oxadiazolyl unsubstituted or substituted with one or more groups selected from Me, Cl, F, CF₃, substituted or unsubstituted acyl, substituted or unsubstituted benzyl, and substituted or unsubstituted phenyl.

17. The compound or pharmaceutically acceptable salt according to claim 14 wherein the compound is according to Formula IIa, IIc, IIe, III or III; m₁ is 0; and R³ is selected from substituted or unsubstituted pyrrolidin-1-yl, piperidin-1-yl, piperizin-1-yl, 1,4-diazepan-1-yl, morpholin-1-yl and tetrahydroquinolin-1-yl.

18. The compound or pharmaceutically acceptable salt according to claim 14 wherein the compound is according to Formula IIa, IIc, IIe, III or III; m₁ is 0; and R³ is selected from pyrrolidin-1-yl, piperidin-1-yl, piperizin-1-yl, 1,4-diazepan-1-yl, morpholin-1-yl, and tetrahydroquinolin-1-yl substituted with one or more groups selected from Me, Cl, F, CF₃, substituted or unsubstituted acyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzoyl, and substituted or unsubstituted phenyl.

19. The compound or pharmaceutically acceptable salt according to claim 1, wherein the compound is according to Formula IIIa, IIIb, IIIc, IID, IIIe, IIIf, IIIg, IIIh, or IIIi:
wherein n₁ is 0, 1, 2 or 3; R³₈ is as in claim 13; each R³₈ is independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo, amino, acylamino, cyano, C₁-C₆ alkoxy and C₁-C₆ haloalkyl-O⁻; and m₃ is 0, 1, 2, 3, 4 or 5.

20. The compound or pharmaceutically acceptable salt according to claim 19 wherein m₃ is 1 or 2; and each R³₈ is independently Me, CF₃, OMe, NH₂, NHAc, OCF₃, Cl, or F.

AMENDED SHEET (ARTICLE 19)
21. The compound or pharmaceutically acceptable salt according to claim 19 or 20 wherein n1 is 0, 1, 2, or 3.

22. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is according to Formula IVa, IVb, IVc, IVd, IVe or IVf:

IVa

IVb

IVc

IVd

IVe

IVf

and wherein n1 is 0, 1, 2 or 3; R₃ is as in claim 12; and m3 is 0, 1, 2, 3, 4 or 5; L is –O–, –NH–, or –CONH–; each R₅ is independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, Ph, benzyl and halo; n1 is 0, 1, 2, 3 or 4; and m3 is 0, 1, 2, 3 or 4.

23. The compound or pharmaceutically acceptable salt according to claim 22 wherein L is –O–.

24. The compound or pharmaceutically acceptable salt according to claim 22 wherein L is –NH–.

25. The compound or pharmaceutically acceptable salt according to claim 22 wherein L is –CONH–.

26. The compound or pharmaceutically acceptable salt according to any one of claims 22-25 wherein n1 is 0, 1, or 2.

27. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is according to Formula Va:
and wherein $R^{3a}$ is as in claim 13; $n1$ is 1 or 2; each $R^{3a}$ is independently selected from C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl and halo; $R^{d}$, $R^{e}$ are as in claim 1; $R^{4d}$ is selected from C$_1$-C$_6$ alkyl; and $m3$ is 0, 1, 2, 3, 4 or 5.

28. The compound or pharmaceutically acceptable salt according to claim 27 wherein $R^{4d}$ is Me.

29. The compound or pharmaceutically acceptable salt according to any one of claims 22-28 wherein $m3$ is 1 or 2; and each $R^{3a}$ is independently selected from Me, Cl, F and CF$_3$.

30. The compound or pharmaceutically acceptable salt according to any one of claims 1-29 wherein $R^{4b}$, $R^{4e}$ are independently selected from H and Me.

31. The compound or pharmaceutically acceptable salt according to claim 1, 2 or 3 wherein the compound is according to Formula VIa, VIb, VIc, VId, VIe, VIf, VIg or Vlh.
and wherein $R^{3a}$ is as in claim 13.

32. The compound or pharmaceutically acceptable salt according to claim 1, 2 or 3 wherein the compound is according to Formula VIIa, VIIb, VIIc, VIId, or VIIe:
and wherein $R^{3a}$ is as in claim 13.

33. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is according to Formula VIIa, VIIb or VIIc:
and wherein $R^{3a}$ is as in claim 12.

34. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is according to Formula IXa, IXb, or IXc:

![Formula IXa, IXb, IXc]

and wherein $R^{3a}$ is as in claim 13.

35. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is according to Formula Xa, Xb, or Xc:

![Formula Xa, Xb, Xc]

and wherein $R^{3a}$ is as in claim 13.

36. The compound or pharmaceutically acceptable salt according to any one of claims 13-35 wherein $R^{3a}$ is selected from H, Me, Cl, F and CF$_3$.

37. The compound or pharmaceutically acceptable salt according to any one of claims 13-35 wherein $R^{3a}$ is H.

38. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is selected from:
39. The compound or pharmaceutically acceptable salt according to claim 1 wherein the compound is selected from:

- N-(8-(1-benzyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
- N-(8-(1-pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
- N-(8-(2-benzylisoindolin-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
- N-(8-(4-(4-benzyl-4-hydroxypiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
- N-(8-(4-(3,3-dimethylpiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
- 4-(2-(cyclopropanecarboxamido)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)-N-(2-(1-phenyl-1H-pyrazol-4-yl)ethyl)benzamide
N-(8-(1-(3-phenylpropyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(cyanomethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(pyridin-2-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((1,5-dimethyl-1H-pyrazol-3-yl)methyl(dimethyl-1H-pyrazol-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(1-(2-phenoxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(3-methylpiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(2-(1H-pyrazol-1-yl)ethyl-1H-pyrazol-1-yl)ethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(1-cyanethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(3-(cyanomethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(2-hydroxypyridin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(1H-indol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(1H-indazol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-methoxypyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-methoxypyridin-3-yl)ethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-hydroxy-3,5-dimethylphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(benzyl/oxo)-3-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(3-fluoro-4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-oxo-1,6-dihydropyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide

AMENDED SHEET (ARTICLE 19)
N-[8-(1-phenethyl-1H-pyrazol-4-yl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
(E)-N-[8-(4-(2-cyanovinyl)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(butylsulfonyl)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(benzoxoxy)-3-methoxyphenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(pyridin-2-ylmethylsulfonyl)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(pyridin-3-ylmethylsulfonyl)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(4-isopropylpiperazine-1-carbonyl)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(5-cyanopyridin-2-yl)methoxy)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(3,5-dimethyl-4-(pyridin-3-ylmethoxy)phenyl)-triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-(1-cyanoethoxy)-3,5-dimethylphenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(3,5-dimethyl-4-((1-methyl-1H-pyrazol-3-yl)methylmethyl-1H-pyrazol-3-yl)methoxy)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(3,5-dimethyl-4-(pyridin-2-ylmethoxy)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl)-triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(2-(pyridin-3-ylmethoxy)pyridin-4-yl)-triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(1-(pyridin-3-ylmethyl)indolin-5-yl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(1,3-dioxo-2-(pyridin-3-ylmethyl)isoindolin-5-yl)-triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-[8-(4-((6-methylpyridin-3-yl)methoxy)phenyl)triazolo[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide
N-(8-(2-phenylbenzoxazol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((phenylamino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(4-cyanopiperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((5-methylisoxazol-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((5-methylpyridin-2-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(morpholinomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-propoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(1-(4-cyanobenzyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-chloropyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(2-cyanoethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(pyridin-3-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(1-(4-cyanobenzyl)-1H-pyrrol-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)propan-2-yl)oxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-methoxypyridin-2-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-methylpyridin-2-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-((6-cyanopyridin-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide
N-(8-(4-Benzylxoy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide
Cyclopropanecarboxylic acid [8-(2-benzyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]amide
Cyclopropanecarboxylic acid \{8-[4-(1-methyl-1H-[1,2,4]triazol-3-ylmethoxy)-
phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl\}-amide

N-(8-(4-(2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl)oxy)phenyl)-
[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide

N-(8-(4-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)phenyl)-[1,2,4]triazolo[1,5-
a]pyridin-2-yl)cyclopropanecarboxamide

N-(8-(4-(2-(5-methyl-1,2,4-oxadiazol-3-yl)ethoxy)phenyl)-[1,2,4]triazolo[1,5-
a]pyridin-2-yl)cyclopropanecarboxamide

Cyclopropanecarboxylic acid \{8-(4-acetylamino-phenyl)-[1,2,4]triazolo[1,5-
a]pyridin-2-yl\}-amide

Cyclopropanecarboxylic acid \{8-[4-(acetyl-pyridin-2-ylmethyl-amino)-phenyl]-
[1,2,4]triazolo[1,5-a]pyridin-2-yl\}-amide

Cyclopropanecarboxylic acid \{8-[4-(6-cyano-pyridin-3-yl)-phenyl]-
[1,2,4]triazolo[1,5-a]pyridin-2-yl\}-amide

N-(8-(4-(2,6-dimethylmorpholine-4-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-
yl)cyclopropanecarboxamide

Cyclopropanecarboxylic acid \{8-[4-(1,1-dioxo-1lambda*6*-chimorpholine-4-
carbonyl)-phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl\}-amide

N-(8-(4-(4-hydroxyperidine-1-carbonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-
yl)cyclopropanecarboxamide

N-(8-(4-(2,2,2-trifluoroacetamido)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-
yl)cyclopropanecarboxamide

N-(8-(4-(2,6-dimethylmorpholine-4-carbonyl)-3-fluorophenyl)-[1,2,4]triazolo[1,5-
a]pyridin-2-yl)cyclopropanecarboxamide

Cyclopropanecarboxylic acid \{8-[4-(3,3-dimethyl-azetidine-1-carbonyl)-phenyl]-
[1,2,4]triazolo[1,5-a]pyridin-2-yl\}-amide

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a
pharmaceutically effective amount of a compound or pharmaceutically acceptable salt
according to any one of claims 1-39.

40. The pharmaceutical composition of claim 40, wherein the carrier is a parenteral carrier.

41. The pharmaceutical composition of claim 40, wherein the carrier is an oral carrier.

42. The pharmaceutical composition of claim 40, wherein the carrier is a topical carrier.

43. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 39 for
use in medicine.

44. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 39 for
use in the treatment or prophylaxis of a disease involving cartilage degradation, bone and/or
joint degradation.
46. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 39 for use in the treatment or prophylaxis of rheumatoid arthritis.

47. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 39, for use in the treatment or prophylaxis of a condition or a disease involving inflammation.

48. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 39, for use in the treatment or prophylaxis of a condition or a disease characterized by abnormal JAK1 activity.

49. A method of treatment or prophylaxis of a disease involving degradation of cartilage, comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 1 to 39, or a pharmaceutical composition according to claims 40-43.

50. A method of treatment or prevention of osteoarthritis, comprising administering to a subject, a therapeutically effective amount of a compound according to any one of claims 1 to 39, or a pharmaceutical composition according to claims 40-43.

51. A method of treatment or prevention of a condition or a disease involving inflammation, comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 1 to 39, or a pharmaceutical composition according to claims 40-43.

52. Use of a compound according to any one of claim 1 to 39 in the manufacture of a medicament for the treatment or prevention of a disease involving degradation of cartilage.

53. Use of a compound according to any one of claim 1 to 39 in the manufacture of a medicament for the treatment or prevention of osteoarthritis.

54. Use of a compound according to any one of claim 1 to 39 in the manufacture of a medicament for the treatment or prevention of a condition or a disease involving inflammation.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 A61K31/437 A61P19/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
4 September 2009

Date of mailing of the international search report
21/09/2009

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL -2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax (+31-70) 340-3016

Authorized officer
Sarakinos, Georgios

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See patent family annex.
### INTERNATIONAL SEARCH REPORT

**PCT/EP2009/059598**

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