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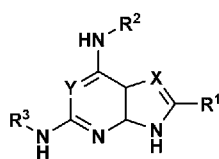
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(54) Title: HETEROBICYCLIC COMPOUNDS USEFUL AS MODULATORS OF IL-12, IL-23 AND/OR IFN ALPHA RESPONSES



(1)

(57) Abstract: Compounds having the following formula (I), or a stereoisomer or pharmaceutically-acceptable salt thereof, where all substituents are as defined herein, are useful in the modulation of IL-12, IL-23 and/or IFN α , by acting on Tyk-2 to cause signal transduction inhibition.



HETEROBICYCLIC COMPOUNDS USEFUL AS MODULATORS OF
IL-12, IL-23 AND/OR IFN ALPHA RESPONSES

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional Application No. 62/414,158 filed October 28, 2016, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

10 This invention relates to compounds useful in the modulation of IL-12, IL-23 and/or IFN α by acting on Tyk-2 to cause signal transduction inhibition. Provided herein are substituted heterobicyclic compounds, compositions comprising such compounds, and methods of their use. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention that are useful for the
15 treatment of conditions related to the modulation of IL-12, IL-23 and/or IFN α in a mammal.

BACKGROUND OF THE INVENTION

The heterodimeric cytokines interleukin IL-12 and IL-23, which share a common
20 p40 subunit, are produced by activated antigen-presenting cells and are critical in the differentiation and proliferation of Th1 and Th17 cells, two effector T cell lineages which play key roles in autoimmunity. IL-23 is composed of the p40 subunit along with a unique p19 subunit. IL-23, acting through a heterodimeric receptor composed of IL-23R and IL-12R β 1, is essential for the survival and expansion of Th17 cells which produce
25 pro-inflammatory cytokines such as IL-17A, IL-17F, IL-6 and TNF- α (McGeachy, M.J. et al., "The link between IL-23 and Th17 cell-mediated immune pathologies", *Semin. Immunol.*, 19:372-376 (2007)). These cytokines are critical in mediating the pathobiology of a number of autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and lupus. IL-12, in addition to the p40
30 subunit in common with IL-23, contains a p35 subunit and acts through a heterodimeric receptor composed of IL-12R β 1 and IL-12R β 2. IL-12 is essential for Th1 cell development and secretion of IFN γ , a cytokine which plays a critical role in immunity by

stimulating MHC expression, class switching of B cells to IgG subclasses, and the activation of macrophages (Gracie, J.A. et al., "Interleukin-12 induces interferon-gamma-dependent switching of IgG alloantibody subclass", *Eur. J. Immunol.*, 26:1217-1221 (1996); Schroder, K. et al., "Interferon-gamma: an overview of signals, mechanisms and functions", *J. Leukoc. Biol.*, 75(2):163-189 (2004)).

The importance of the p40-containing cytokines in autoimmunity is demonstrated by the discovery that mice deficient in either p40, p19, or IL-23R are protected from disease in models of multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, lupus and psoriasis, among others (Kytтары, V.C. et al., "Cutting edge: IL-23 receptor deficiency prevents the development of lupus nephritis in C57BL/6-lpr/lpr mice", *J. Immunol.*, 184:4605-4609 (2010); Hong, K. et al., "IL-12, independently of IFN-gamma, plays a crucial role in the pathogenesis of a murine psoriasis like skin disorder", *J. Immunol.*, 162:7480-7491 (1999); Hue, S. et al., "Interleukin-23 drives innate and T cell-mediated intestinal inflammation", *J. Exp. Med.*, 203:2473-2483 (2006); Cua, D.J. et al., "Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain", *Nature*, 421:744-748 (2003); Murphy, C.A. et al., "Divergent pro- and anti-inflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation", *J. Exp. Med.*, 198:1951-1957 (2003)).

In human disease, high expression of p40 and p19 has been measured in psoriatic lesions, and Th17 cells have been identified in active lesions in the brain from MS patients and in the gut mucosa of patients with active Crohn's disease (Lee, E. et al., "Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris", *J. Exp. Med.*, 199:125-130 (2004); Tzartos, J.S. et al., "Interleukin-17 production in central nervous system infiltrating T cells and glial cells is associated with active disease in multiple sclerosis", *Am. J. Pathol.*, 172:146-155 (2008)). The mRNA levels of p19, p40, and p35 in active SLE patients were also shown to be significantly higher compared with those in inactive SLE patients (Huang, X. et al., "Dysregulated expression of interleukin-23 and interleukin-12 subunits in systemic lupus erythematosus patients", *Mod. Rheumatol.*, 17:220-223 (2007)), and T cells from lupus patients have a predominant Th1 phenotype (Tucci, M. et al., "Overexpression of interleukin-12 and T helper 1 predominance in lupus nephritis", *Clin. Exp. Immunol.*, 154:247-254 (2008)).

Moreover, genome-wide association studies have identified a number of loci associated with chronic inflammatory and autoimmune diseases that encode factors that function in the IL-23 and IL-12 pathways. These genes include IL23A, IL12A, IL12B, IL12RB1, IL12RB2, IL23R, JAK2, TYK2, STAT3, and STAT4 (Lees, C.W. et al., "New
5 IBD genetics: common pathways with other diseases", *Gut*, 60:1739-1753 (2011); Tao, J.H. et al., "Meta-analysis of TYK2 gene polymorphisms association with susceptibility to autoimmune and inflammatory diseases", *Mol. Biol. Rep.*, 38:4663-4672 (2011); Cho, J.H. et al., "Recent insights into the genetics of inflammatory bowel disease", *Gastroenterology*, 140:1704-1712 (2011)).

10 Indeed, anti-p40 treatment, which inhibits both IL-12 and IL-23, as well as IL-23-specific anti-p19 therapies have been shown to be efficacious in the treatment of autoimmunity in diseases including psoriasis, Crohn's Disease and psoriatic arthritis (Leonardi, C.L. et al., "PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis:
15 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1)", *Lancet*, 371:1665-1674 (2008); Sandborn, W.J. et al., "Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease", *Gastroenterology*, 135:1130-1141 (2008); Gottlieb, A. et al., "Ustekinumab, a human interleukin 12/23
20 monoclonal antibody, for psoriatic arthritis: randomized, double-blind, placebo-controlled, crossover trial", *Lancet*, 373:633-640 (2009)). Therefore, agents which inhibit the action of IL-12 and IL-23 may be expected to have therapeutic benefit in human autoimmune disorders.

The Type I group of interferons (IFNs), which include the IFN α members as well
25 as IFN β , IFN ϵ , IFN κ and IFN ω , act through a heterodimer IFN α/β receptor (IFNAR). Type I IFNs have multiple effects in both the innate and adaptive immune systems including activation of both the cellular and humoral immune responses as well as enhancing the expression and release of autoantigens (Hall, J.C. et al., "Type I interferons: crucial participants in disease amplification in autoimmunity", *Nat. Rev. Rheumatol.*, 6:40-49 (2010)).
30

In patients with systemic lupus erythematosus (SLE), a potentially fatal autoimmune disease, increased serum levels of interferon (IFN) α (a type I interferon) or

increased expression of type I IFN-regulated genes (a so-called IFN α signature) in peripheral blood mononuclear cells and in affected organs has been demonstrated in a majority of patients (Bennett, L. et al., "Interferon and granulopoiesis signatures in systemic lupus erythematosus blood", *J. Exp. Med.*, 197:711-723 (2003); Peterson, K.S. et al., "Characterization of heterogeneity in the molecular pathogenesis of lupus nephritis from transcriptional profiles of laser-captured glomeruli", *J. Clin. Invest.*, 113:1722-1733 (2004)), and several studies have shown that serum IFN α levels correlate with both disease activity and severity (Bengtsson, A.A. et al., "Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies", *Lupus*, 9:664-671 (2000)). A direct role for IFN α in the pathobiology of lupus is evidenced by the observation that the administration of IFN α to patients with malignant or viral diseases can induce a lupus-like syndrome. Moreover, the deletion of the IFNAR in lupus-prone mice provides high protection from autoimmunity, disease severity and mortality (Santiago-Raber, M.L. et al., "Type-I interferon receptor deficiency reduces lupus-like disease in NZB mice", *J. Exp. Med.*, 197:777-788 (2003)), and genome-wide association studies have identified loci associated with lupus that encode factors that function in the type I interferon pathway, including IRF5, IKBKE, TYK2, and STAT4 (Deng, Y. et al., "Genetic susceptibility to systemic lupus erythematosus in the genomic era", *Nat. Rev. Rheumatol.*, 6:683-692 (2010); Sandling, J.K. et al., "A candidate gene study of the type I interferon pathway implicates IKBKE and IL8 as risk loci for SLE", *Eur. J. Hum. Genet.*, 19:479-484 (2011)). In addition to lupus, there is evidence that aberrant activation of type I interferon-mediated pathways are important in the pathobiology of other autoimmune diseases such as Sjögren's syndrome and scleroderma (Båve, U. et al., "Activation of the type I interferon system in primary Sjögren's syndrome: a possible etiopathogenic mechanism", *Arthritis Rheum.*, 52:1185-1195 (2005); Kim, D. et al., "Induction of interferon-alpha by scleroderma sera containing autoantibodies to topoisomerase I: association of higher interferon-alpha activity with lung fibrosis", *Arthritis Rheum.*, 58:2163-2173 (2008)). Therefore, agents which inhibit the action of type I interferon responses may be expected to have therapeutic benefit in human autoimmune disorders.

Tyrosine kinase 2 (Tyk2) is a member of the Janus kinase (JAK) family of nonreceptor tyrosine kinases and has been shown to be critical in regulating the signal

transduction cascade downstream of receptors for IL-12, IL-23 and type I interferons in both mice (Ishizaki, M. et al., "Involvement of Tyrosine Kinase-2 in Both the IL-12/Th1 and IL-23/Th17 Axes *In vivo*", *J. Immunol.*, 187:181-189 (2011); Prchal-Murphy, M. et al., "TYK2 kinase activity is required for functional type I interferon responses *in vivo*", *PLoS One*, 7:e39141 (2012)) and humans (Minegishi, Y. et al., "Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity", *Immunity*, 25:745-755 (2006)). Tyk2 mediates the receptor-induced phosphorylation of members of the STAT family of transcription factors, an essential signal that leads to the dimerization of STAT proteins and the transcription of STAT-dependent pro-inflammatory genes. Tyk2-deficient mice are resistant to experimental models of colitis, psoriasis and multiple sclerosis, demonstrating the importance of Tyk2-mediated signaling in autoimmunity and related disorders (Ishizaki, M. et al., "Involvement of Tyrosine Kinase-2 in Both the IL-12/Th1 and IL-23/Th17 Axes *In vivo*", *J. Immunol.*, 187:181-189 (2011); Oyamada, A. et al., "Tyrosine kinase 2 plays critical roles in the pathogenic CD4 T cell responses for the development of experimental autoimmune encephalomyelitis", *J. Immunol.*, 183:7539-7546 (2009)).

In humans, individuals expressing an inactive variant of Tyk2 are protected from multiple sclerosis and possibly other autoimmune disorders (Couturier, N. et al., "Tyrosine kinase 2 variant influences T lymphocyte polarization and multiple sclerosis susceptibility", *Brain*, 134:693-703 (2011)). Genome-wide association studies have shown other variants of Tyk2 to be associated with autoimmune disorders such as Crohn's Disease, psoriasis, systemic lupus erythematosus, and rheumatoid arthritis, further demonstrating the importance of Tyk2 in autoimmunity (Ellinghaus, D. et al., "Combined Analysis of Genome-wide Association Studies for Crohn Disease and Psoriasis Identifies Seven Shared Susceptibility Loci", *Am. J. Hum. Genet.*, 90:636-647 (2012); Graham, D. et al., "Association of polymorphisms across the tyrosine kinase gene, TYK2 in UK SLE families", *Rheumatology (Oxford)*, 46:927-930 (2007); Eyre, S. et al., "High-density genetic mapping identifies new susceptibility loci for rheumatoid arthritis", *Nat. Genet.*, 44:1336-1340 (2012)).

In view of the conditions that may benefit by treatment involving the modulation of cytokines and/or interferons, new compounds capable of modulating cytokines and/or

interferons, such as IL-12, IL-23 and/or IFN α , and methods of using these compounds may provide substantial therapeutic benefits to a wide variety of patients in need thereof.

SUMMARY OF THE INVENTION

5 The invention is directed to compounds of Formula I which are useful as modulators of IL-12, IL-23 and/or IFN α by inhibiting Tyk2-mediated signal transduction.

The present invention also provides processes and intermediates for making the compounds of the present invention.

10 The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention.

15 The present invention also provides a method for the modulation of IL-12, IL-23 and/or IFN α by inhibiting Tyk-2-mediated signal transduction comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention.

The present invention also provides a method for treating proliferative, metabolic, allergic, autoimmune and inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention.

20 One embodiment is a method for treating inflammatory and autoimmune diseases or diseases. For the purposes of this invention, an inflammatory and autoimmune disease or disorder includes any disease having an inflammatory or autoimmune component.

Another embodiment is a method for treating metabolic diseases, including type 2 diabetes and atherosclerosis.

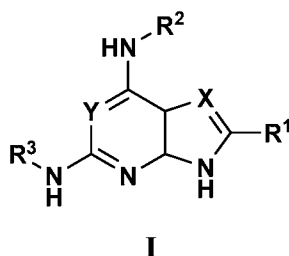
25 The present invention also provides the use of the compounds of the present invention for the manufacture of a medicament for the treatment of cancers.

The present invention also provides the compounds of the present invention for use in therapy.

30 DETAILED DESCRIPTION OF THE INVENTION

In a first aspect of the present invention, there is provided a compound of formula

(I)



wherein:

- X is -N- or -CH-;
- 5 Y is -N- or -CH-;
- R¹ is hydrogen, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;
- R² is C₅₋₈ aryl or C₅₋₈ heteroaryl, substituted with 0-4 R^{2a};
- R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4
- 10 heteroatoms selected from N, O, and S substituted with 0-2 R^b;
- R^{2b} is hydrogen or C₁₋₄ alkyl;
- R^{2c} is hydrogen or C₁₋₄ alkyl;
- R^{2d} is hydrogen or C₁₋₄ alkyl;
- R^b is hydrogen or C₁₋₄ alkyl;
- 15 R³ is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a};
- R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, C(O)- 5-7 membered heterocycle containing 1-4
- 20 heteroatoms selected from N, O, and S or 2-pyrrolidone;
- R^{3b} is hydrogen or C₁₋₄ alkyl;
- R^{3c} is hydrogen or C₁₋₄ alkyl;
- or a stereoisomer or pharmaceutically-acceptable salt thereof.

25 In a second aspect of the invention, there are provided compounds of formula II,



(II)

wherein:

- R^1 is hydrogen, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;
- 5 R^2 is C₅₋₈ aryl or C₅₋₈ heteroaryl, substituted with 0-4 R^{2a} ;
- R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;
- R^{2b} is hydrogen or C₁₋₄ alkyl;
- 10 R^{2c} is hydrogen or C₁₋₄ alkyl;
- R^{2d} is hydrogen or C₁₋₄ alkyl;
- R^b is hydrogen or C₁₋₄ alkyl;
- R^3 is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a} ;
- 15 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S;
- R^{3b} is hydrogen or C₁₋₄ alkyl;
- 20 R^{3c} is hydrogen or C₁₋₄ alkyl;
- or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a third aspect of the invention, there are provided compounds of formula II, wherein:

- 25 R^1 is hydrogen, C₁₋₄ alkyl or C₃₋₆ cycloalkyl;
- R^2 is C₅₋₈ aryl or C₅₋₈ heteroaryl, substituted with 0-3 R^{2a} ;
- R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;
- 30 R^{2b} is hydrogen or C₁₋₄ alkyl;
- R^{2c} is hydrogen or C₁₋₄ alkyl;
- R^{2d} is hydrogen or C₁₋₄ alkyl;

R^b is hydrogen or C₁₋₄ alkyl;

R³ is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a};

R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂,
5 CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4
heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing
1-4 heteroatoms selected from N, O, and S;

R^{3b} is hydrogen or C₁₋₄ alkyl;

R^{3c} is hydrogen or C₁₋₄ alkyl;

10 or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a fourth aspect of the invention, there are provided compounds of formula II,
wherein:

R¹ is hydrogen or C₁₋₄ alkyl;

15 R² is phenyl or pyridyl, substituted with 0-2 R^{2a};

R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆
alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4
heteroatoms selected from N, O, and S substituted with 0-2 R^b;

R^{2b} is hydrogen or C₁₋₄ alkyl;

20 R^{2c} is hydrogen or C₁₋₄ alkyl;

R^{2d} is hydrogen or C₁₋₄ alkyl;

R^b is hydrogen or C₁₋₄ alkyl;

R³ is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing
1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a};

25 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂,
CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4
heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing
1-4 heteroatoms selected from N, O, and S;

R^{3b} is hydrogen or C₁₋₄ alkyl;

30 R^{3c} is hydrogen or C₁₋₄ alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a fifth aspect of the invention, there are provided compounds of formula II, wherein:

R¹ is C₁₋₄ alkyl;

R² is phenyl or pyridyl, substituted with 0-2 R^{2a};

5 R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;

R^{2b} is hydrogen or C₁₋₄ alkyl;

R^{2c} is hydrogen or C₁₋₄ alkyl;

10 R^{2d} is hydrogen or C₁₋₄ alkyl;

R^b is hydrogen or C₁₋₄ alkyl;

R³ is C(O)-C₃₋₆ cycloalkyl, phenyl, pyridyl, pyrimidinyl, piperazinyl or pyridazinyl, substituted with 0-4 R^{3a};

15 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S;

R^{3b} is hydrogen or C₁₋₄ alkyl;

R^{3c} is hydrogen or C₁₋₄ alkyl;

20 or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a sixth aspect of the invention, there are provided compounds of formula II, wherein:

R¹ is C₁₋₄ alkyl;

25 R² is phenyl or pyridyl, substituted with 0-2 R^{2a};

R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂ C₁₋₄ alkyl, C(O)NH₂ or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;

R^b is hydrogen or C₁₋₄ alkyl;

30 R³ is C(O)-C₃₋₆ cycloalkyl, phenyl, pyrazolyl, pyridyl, pyrimidinyl, piperazinyl or pyridazinyl, substituted with 0-4 R^{3a};

R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S;

- 5 R^{3b} is hydrogen or C₁₋₄ alkyl;
R^{3c} is hydrogen or C₁₋₄ alkyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a seventh aspect of the invention, there are provided compounds of formula II,
10 wherein:

- R¹ is C₁₋₄ alkyl;
R² is phenyl or pyridyl, substituted with 0-2 R^{2a};
R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂
C₁₋₄ alkyl, C(O)NH₂ or a 5-7 membered heterocycle containing 1-4 heteroatoms selected
15 from N, O, and S substituted with 0-2 R^b;
R^b is hydrogen or C₁₋₄ alkyl;
R³ is C(O)-C₃₋₆ cycloalkyl, phenyl, pyrazolyl, pyridyl, pyrimidinyl, piperazinyl or
pyridazinyl, substituted with 0-2 R^{3a};
R^{3a} is independently, at each occurrence, hydrogen, halo, OH, CF₃, CN, C₁₋₃ alkyl,
20 C₁₋₃ alkoxy, -C(O)NH₂, morpholinyl, or C(O)- morpholinyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In an eighth aspect of the invention, there are provided compounds of formula II,
wherein

- 25 R¹ is C₁₋₄ alkyl;
R² is phenyl or pyridyl, substituted with 0-2 R^{2a};
R^{2a} is independently, at each occurrence, hydrogen, CH₃, OCH₃, -S(O)₂ CH₃, or
C(O)NH₂;
R³ is C(O)-C₃₋₆ cycloalkyl, phenyl, pyrazolyl, pyridyl, pyrimidinyl, piperazinyl or
30 pyridazinyl, substituted with 0-2 R^{3a};
R^{3a} is independently, at each occurrence, hydrogen, halo, OH, CF₃, CN, C₁₋₃ alkyl,
C₁₋₃ alkoxy, -C(O)NH₂, morpholinyl, or C(O)- morpholinyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, there is provided a compound selected from the exemplified examples within the scope of the first aspect, or a pharmaceutically acceptable salt,
5 tautomer or stereoisomer thereof.

In another aspect, there is provided a compound selected from any subset list of compounds within the scope of any of the above aspects.

In another embodiment, there is provided a pharmaceutical composition comprising one or more compounds of formula I and a pharmaceutically acceptable
10 carrier or diluent.

The present invention is also directed to pharmaceutical compositions useful in treating diseases associated with the modulation of IL-12, IL-23 and/or IFN α by acting on Tyk-2 to cause signal transduction inhibition, comprising compounds of formula I, or pharmaceutically-acceptable salts thereof, and pharmaceutically-acceptable carriers or
15 diluents.

The invention further relates to methods of treating diseases associated with the modulation of IL-12, IL-23, and/or IFN α , comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound according to formula I.

The present invention also provides a method for treating proliferative, metabolic,
20 allergic, autoimmune and inflammatory diseases (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention.

The present invention also provides a method of treating an inflammatory or
25 autoimmune disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases) comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula I.

The present invention also provides a method for treating a disease (or use of the
30 compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula I, wherein the

disease is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), lupus nephritis, cutaneous lupus, inflammatory bowel disease, psoriasis, Crohn's Disease, psoriatic arthritis, Sjögren's syndrome, systemic scleroderma, ulcerative colitis, Graves' disease, discoid lupus erythematosus, adult onset Stills, systemic onset juvenile idiopathic arthritis, gout, gouty arthritis, type 1 diabetes, insulin dependent diabetes mellitus, sepsis, septic shock, Shigellosis, pancreatitis (acute or chronic), glomerulonephritis, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, myasthenia gravis, pancreatitis (acute or chronic), ankylosing spondylitis, pemphigus vulgaris, Goodpasture's disease, antiphospholipid syndrome, idiopathic thrombocytopenia, ANCA-associated vasculitis, pemphigus, Kawasaki disease, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), dermatomyositis, polymyositis, uveitis, Guillain-Barre syndrome, autoimmune pulmonary inflammation, autoimmune thyroiditis, autoimmune inflammatory eye disease, and chronic demyelinating polyneuropathy.

15 The present invention also provides a method of treating an inflammatory or autoimmune disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of said diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula I, wherein the disease is selected from systemic lupus erythematosus (SLE), lupus nephritis, cutaneous lupus, Crohn's Disease, ulcerative colitis, type 1 diabetes, psoriasis, rheumatoid arthritis, systemic onset juvenile idiopathic arthritis, ankylosing spondylitis, and multiple sclerosis.

 The present invention also provides a method for treating a rheumatoid arthritis (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of rheumatoid arthritis, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula I.

 In addition, the present invention also provides a method of treating a condition (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these conditions) comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula I, wherein the condition is selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, solid tumors,

ocular neovascularization, and infantile haemangiomas, B cell lymphoma, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, Type I diabetes, membranous nephritis, inflammatory
5 bowel disease, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evans syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjögren's syndrome, peripheral neuropathies, pemphigus vulgaris and asthma.

The present invention also provides a method of treating a IL-12, IL-23, and/or
10 IFN α mediated disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I.

The present invention also provides a method of treating a IL-12, IL-23 and/or
15 IFN α mediated disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I, wherein the IL-12, IL-23 and/or IFN α mediated disease is a disease modulated by IL-12, IL-23 and/or IFN α .

20 The present invention also provides a method of treating diseases, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula I in combination with other therapeutic agents.

The present invention also provides the compounds of the present invention for use in therapy.

25 In another embodiment, compounds of formula I are selected from exemplified compounds or combinations of exemplified compounds or other embodiments herein.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects and/or embodiments of the invention noted herein. It is understood that any
30 and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own

independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

5

DEFINITIONS

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group,
10 unless otherwise indicated.


Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and
15 all such stable isomers are contemplated in the present invention. *Cis*- and *trans*-geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting
20 materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (*e.g.*, R³) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every
25 other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R³, then said group may optionally be substituted with up to two R³ groups and R³ at each occurrence is selected independently from the definition of R³. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring,
30 then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

A dash "-" that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula I (*e.g.*, an optionally substituted heteroaryl group) refers to a moiety having 0, 1, 2, or more substituents. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

As used herein, the term "at least one chemical entity" is interchangeable with the term "a compound".

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C₁₋₁₀ alkyl" (or alkylene), is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkyl groups. Additionally, for example, "C₁₋₆ alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), and the like.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may

occur in any stable point along the chain. For example, "C₂₋₆ alkenyl" (or alkenylene), is intended to include C₂, C₃, C₄, C₅, and C₆ alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C₂₋₆ alkynyl" (or alkynylene), is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

One skilled in the field will understand that, when the designation "CO₂" is used herein, this is intended to refer to the group $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$.

When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C₀₋₄)alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C₀)alkyl. The term "heteroarylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is a heteroaryl.

When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

The term "alkoxy" refers to an oxygen atom substituted by alkyl or substituted alkyl, as defined herein. For example, the term "alkoxy" includes the group -O-C₁₋₆alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, *tert*-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

It should be understood that the selections for all groups, including for example, alkoxy, thioalkyl, and aminoalkyl, will be made by one skilled in the field to provide stable compounds.

The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo, or keto, (*i.e.*, =O) then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

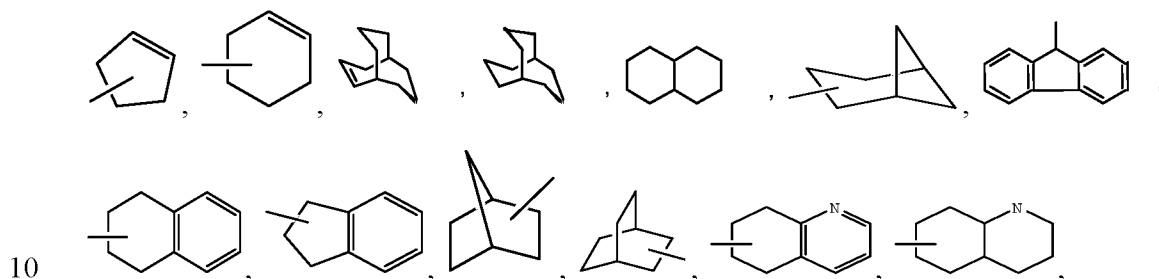
Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture to a useful degree of purity, and subsequent formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, S(O)₂H, or S(O)H group.

The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or polycyclic ring systems. C₃₋₇ cycloalkyl is intended to include C₃, C₄, C₅, C₆, and C₇ cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a


bridge always converts a monocyclic ring into a bicyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which
5 may be substituted.

Accordingly, in compounds of formula I, the term "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclooctyl, etc., as well as the following ring systems:



and the like, which optionally may be substituted at any available atoms of the ring(s).

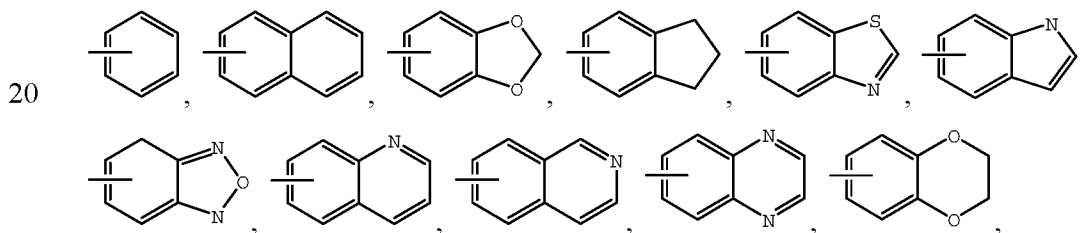
Preferred cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, and .

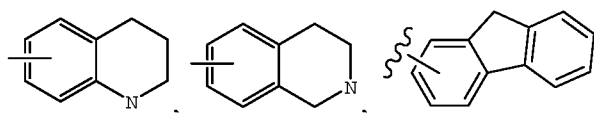
15 The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF₃.

Thus, examples of aryl groups include:



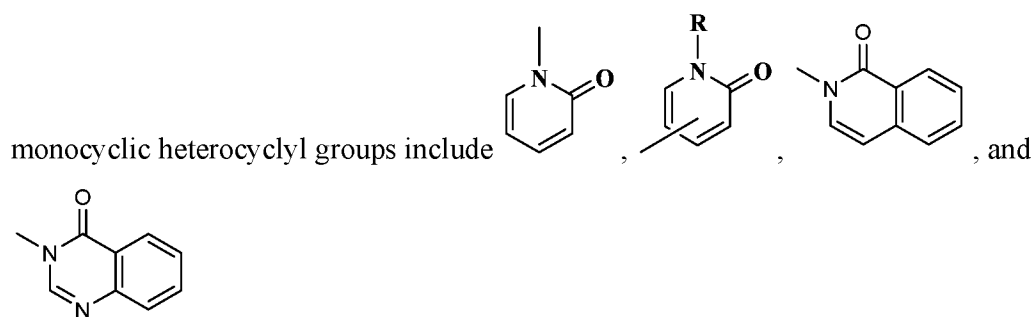


(fluorenyl) and the like, which

optionally may be substituted at any available carbon or nitrogen atom. A preferred aryl group is optionally-substituted phenyl.

5 The terms "heterocycle", "heterocycloalkyl", "heterocyclo", "heterocyclic", or "heterocyclyl" may be used interchangeably and refer to substituted and unsubstituted 3- to 7-membered monocyclic groups, 7- to 11-membered bicyclic groups, and 10- to 15-membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1, 2, or 3 heteroatoms
 10 selected from O, S, and N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The
 15 fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or fully unsaturated. The heterocyclo group may be attached at any available nitrogen or carbon atom. As used herein the terms "heterocycle", "heterocycloalkyl", "heterocyclo", "heterocyclic", and "heterocyclyl" include "heteroaryl" groups, as defined below.

20 In addition to the heteroaryl groups described below, exemplary monocyclic heterocyclyl groups include azetidiny, pyrrolidiny, oxetany, imidazoliny, oxazolidiny, isoxazoliny, thiazolidiny, isothiazolidiny, tetrahydrofurany, piperidyl, piperaziny, 2-oxopiperaziny, 2-oxopiperidyl, 2-oxopyrrolodiny, 2-oxoazepiny, azepiny, 1-pyridony, 4-piperidony, tetrahydropyrany, morpholiny, thiamorpholiny, thiamorpholiny
 25 sulfoxide, thiamorpholiny sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothiényl and the like. Exemplary bicyclic heterocyclo groups include quinuclidiny. Additional



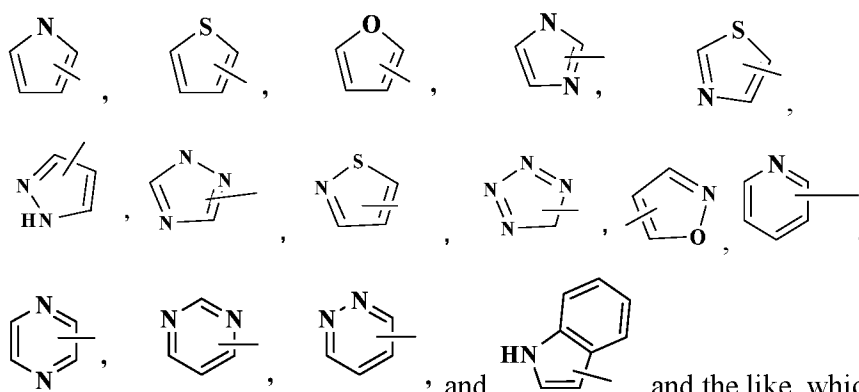
The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-
 5 membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-
 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one
 of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms
 selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can
 contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms
 provided that the total number of heteroatoms in each ring is four or less and each ring
 10 has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups
 may contain only carbon atoms and may be saturated, partially saturated, or unsaturated.
 The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may
 optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include
 at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-
 15 aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom
 of any ring. As valence allows, if said further ring is cycloalkyl or heterocyclo it is
 additionally optionally substituted with =O (oxo).

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl,
 imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl,
 20 oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl,
 benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl,
 isoquinolinyl, benzimidazolyl, benzopyranyl, indoliziny, benzofuranyl, chromonyl,
 coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl,
 25 furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl,
 phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

In compounds of formula I, preferred heteroaryl groups include:



and the like, which optionally may be substituted at any available carbon or nitrogen atom.

5

Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl, piperidinyl, and morpholinyl) or heteroaryl (*e.g.*, tetrazolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, and furyl) the reference is intended to include rings having 0 to 3, preferably 0 to 2, substituents selected from those recited above for the aryl, cycloalkyl, heterocyclo and/or heteroaryl groups, as appropriate.

10

The term "carbocyclyl" or "carbocyclic" refers to a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of mono- and bicyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl and naphthyl. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

15

20

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

25

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful

as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

The compounds of formula I may exist in a free form (with no ionization) or can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to the free form and to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s)" may include zwitterions (inner salts), *e.g.*, when a compound of formula I, contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of the formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-
5 β -phenethylamine, 1-phenamine, *N,N'*-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates
10 (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. Preferred salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate salts.

The phrase "pharmaceutically acceptable" is employed herein to refer to those
15 compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically-acceptable salts" refer to derivatives of the
20 disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically-acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically-acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent
25 compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic,
30 benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically-acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Easton, PA (1990), the disclosure of which is hereby incorporated by reference.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. Stereoisomers may include compounds which are optical isomers through possession of one or more chiral atoms, as well as compounds which are optical isomers by virtue of limited rotation about one or more bonds (atropisomers). The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C . Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the

formula I, and/or a salt and/or solvate thereof. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, the compound for formula I) is a prodrug within the scope and spirit of the invention. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C₁₋₆alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆alkanoyloxy-C₁₋₆alkyl, *e.g.*, acetoxymethyl, pivaloyloxyethyl or propionyloxyethyl, C₁₋₆alkoxycarbonyloxy-C₁₋₆alkyl, *e.g.*, methoxycarbonyloxyethyl or ethoxycarbonyloxyethyl, glycyloxyethyl, phenylglycyloxyethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);
 - b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", Krosgaard-Larsen, P. et al., eds., *A Textbook of Drug Design and Development*, pp. 113-191, Harwood Academic Publishers (1991); and
 - c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992),
- each of which is incorporated herein by reference.

Compounds of the formula I and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have *trans*- and *cis*-isomers.

It should further be understood that solvates (*e.g.*, hydrates) of the compounds of Formula I are also with the scope of the present invention. Methods of solvation are generally known in the art.

5

UTILITY

The compounds of the invention modulate IL-23-stimulated and IFN α -stimulated cellular functions, including gene transcription. Other types of cellular functions that may be modulated by the compounds of the instant invention include, but are not limited to, IL-12-stimulated responses.

10

Accordingly, compounds of formula I have utility in treating conditions associated with the modulation of the function of IL-23 or IFN α , and particularly the selective inhibition of function of IL-23, IL-12 and/or IFN α , by acting on Tyk2 to mediate signal transduction. Such conditions include IL-23-, IL-12-, or IFN α -associated diseases in which pathogenic mechanisms are mediated by these cytokines.

15

As used herein, the terms "treating" or "treatment" encompass the treatment of a disease state in a mammal, particularly in a human, and include: (a) preventing or delaying the occurrence of the disease state in a mammal, in particular, when such mammal is predisposed to the disease state but has not yet been diagnosed as having it; (b) inhibiting the disease state, *i.e.*, arresting its development; and/or (c) achieving a full or partial reduction of the symptoms or disease state, and/or alleviating, ameliorating, lessening, or curing the disease or disorder and/or its symptoms.

20

In view of their activity as modulators of IL-23-, IL-12 and IFN α -stimulated cellular responses, compounds of Formula I are useful in treating IL-23-, IL-12- or IFN α -associated diseases including, but not limited to, inflammatory diseases such as Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, cutaneous lupus, lupus nephritis, discoid lupus erythematosus, psoriasis; auto-inflammatory diseases including CAPS, TRAPS, FMF, adult onset stills, systemic onset juvenile idiopathic arthritis, gout, gouty arthritis;

25

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metabolic diseases including type 2 diabetes, atherosclerosis, myocardial infarction; destructive bone disorders such as bone resorption disease, osteoarthritis, osteoporosis, multiple myeloma-related bone disorder; proliferative disorders such as acute

myelogenous leukemia, chronic myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury, oncologic and viral diseases such as metastatic melanoma, Kaposi's sarcoma, multiple myeloma, and HIV infection and CMV retinitis, AIDS, respectively.

More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, cutaneous lupus, lupus nephritis, discoid lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β -cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, keloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hypoxia [should this be hypoxia], vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet

aggregation, endotoxemia and/or toxic shock syndrome, conditions associated with prostaglandin endoperoxidase synthase-2, and pemphigus vulgaris. Preferred methods of treatment are those wherein the condition is selected from Crohn's disease, ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris. Alternatively preferred methods of treatment are those wherein the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusion injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction. Another preferred method of treatment is one in which the condition is multiple myeloma.

10 When the terms "IL-23-, IL-12- and/or IFN α -associated condition" or "IL-23-, IL-12- and/or IFN α -associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified above as if repeated at length, as well as any other condition that is affected by IL-23, IL-12 and/or IFN α .

 The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof a therapeutically-effective amount of at least one compound of Formula I or a salt thereof. "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit IL-23, IL-12 and/or IFN α function and/or treat diseases.

20 The methods of treating IL-23-, IL-12 and/or IFN α -associated conditions may comprise administering compounds of Formula I alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Accordingly, "therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit IL-23, IL-12 and/or IFN α function and/or treat diseases associated with IL-23, IL-12 and/or IFN α .

 Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, PROGRAF®); anti-malarials such as

hydroxychloroquine; cytotoxic drugs such as azathioprine and cyclophosphamide; TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or RAPAMUNE®) or derivatives thereof.

5 The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the *Physicians' Desk Reference* (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds. The present invention also provides
10 pharmaceutical compositions capable of treating IL-23-, IL-12- or IFN α -associated conditions by inhibiting Tyk2-mediated signal transduction, including IL-23-, IL-12- and/or IFN α -mediated diseases, as described above.

FORMULATIONS/PHARMACEUTICAL COMPOSITIONS

15 The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (*e.g.*, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical
20 formulation.

Accordingly, the present invention further includes compositions comprising one or more compounds of Formula I and a pharmaceutically acceptable carrier.

A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals.

25 Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include without limitation the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable
30 carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in

the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical*
5 *Sciences*, 17th Edition (1985), which is incorporated herein by reference in its entirety.

The compounds of Formula I may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous
10 conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques
15 (*e.g.*, as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release.
20 Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

25 Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium
30 stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, *e.g.*, with molded,

compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

10 Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

20 Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The therapeutically-effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 1000 mg/kg; 1-1000 mg/kg; 1-50 mg/kg; 5-250 mg/kg; 250-1000 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and

diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used
5 herein, this term is intended to include all subjects, most preferably mammalian species that are affected by modulation of IL-23, IL-12 and/or IFN α -mediated functions.

METHODS OF PREPARATION

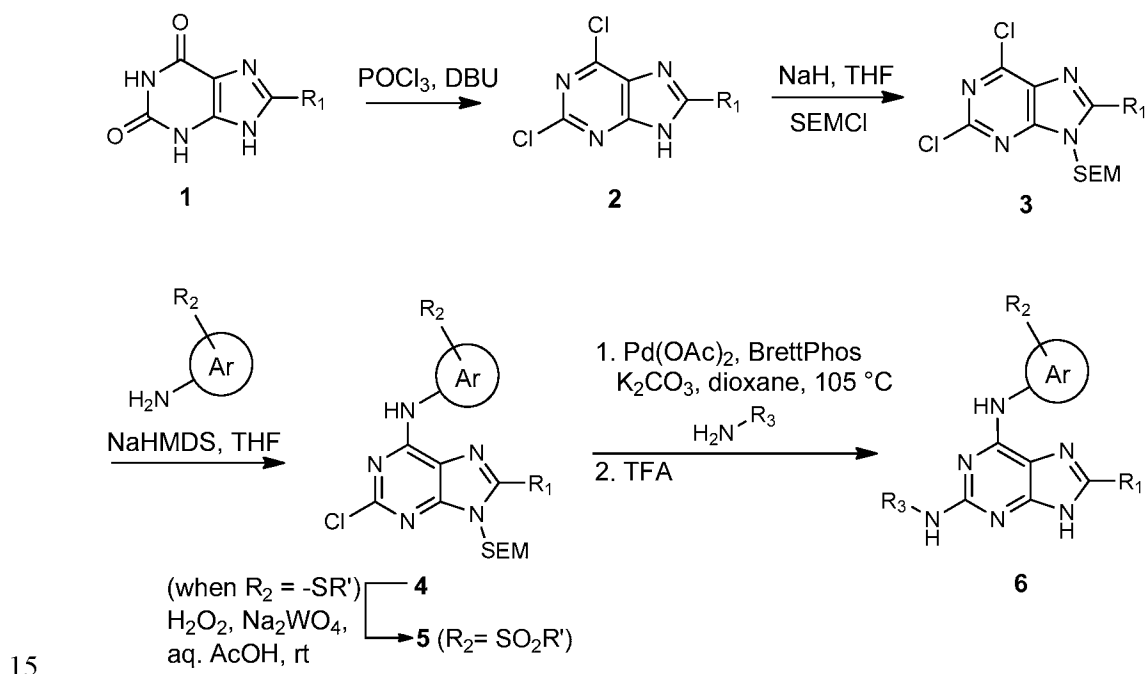
The compounds of the present invention may be synthesized by many methods
10 available to those skilled in the art of organic chemistry. General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art.
15 Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds. Examples of compounds of the present invention prepared by methods described in the general schemes are given in the preparations and examples section set out hereinafter. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example,
20 homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products.

The reactions and techniques described in this section are performed in solvents appropriate to the reagents and materials employed and are suitable for the
25 transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in
30 the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily

apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, Third Edition, Wiley and Sons (1999)).

Substituents used in the schemes do not necessarily correspond to those used in the claims.

SCHEME 1

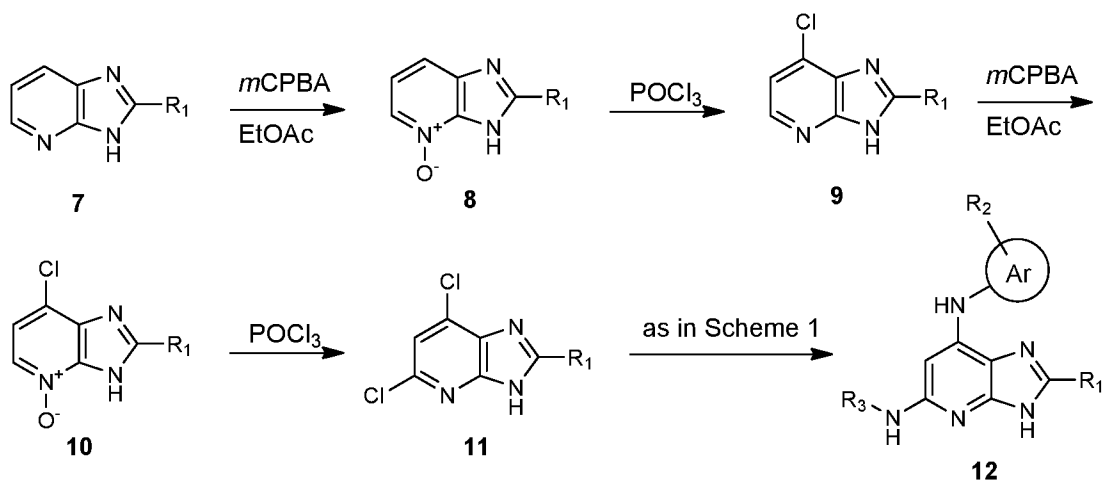


Scheme 1 illustrates a general synthesis of 8-substituted 2,6-diamino-9H-purines of the general structure **6**. Starting with 8-substituted 1H-purine-2,6(3H,9H)-dione (**1**) and reacting with phosphorus oxychloride in the presence of a suitable base such as 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) under heating affords the 2,6-dichloropurine **2**.

Protection of **2** using a suitable protecting group reagent such as 2-trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in the presence of a base such as sodium hydride affords the suitably protected intermediate **3**. Subsequent coupling of an arylamino group (R_2ArNH_2) can be performed using an appropriate base such as sodium bis(trimethylsilyl)amide (NaHMDS) in a suitable solvent such as THF to afford the monochloro intermediate **4**. Finally, this intermediate can be reacted with an amine (R_3NH_2) in the presence of a suitable catalyst such as palladium acetate, a ligand such as BrettPhos, and a base such as potassium carbonate in a solvent such as dioxane at elevated temperature to afford the desired product **6**. Alternatively, when intermediate **4** is substituted with $R_2 = SR'$, reaction of **4** under suitable oxidation conditions such as hydrogen peroxide in the presence of a catalyst such as sodium tungstate in acetic acid affords intermediate **5** where $R_2 = -SO_2R'$. Intermediate **5** can then be converted to the final product **6** as previously described.

15

SCHEME 2



Scheme 2 illustrates a general synthesis of 2-substituted-3H-imidazo[4,5-b]pyridine-5,7-diamines of the general structure **12**. Starting with the appropriate 2-substituted 3H-imidazo[4,5-b]pyridine **7** and reacting with a suitable oxidizing agent such as *meta*-chloroperbenzoic acid (*m*CPBA) in a solvent such as ethyl acetate affords the *N*-oxide intermediate **8**. Reaction of **8** with phosphorus oxychloride (POCl₃) provides the chloride **9** which can be subjected to another similar oxidation and chlorination sequence to afford the key dichloride intermediate **11**. Intermediate **11** can then be converted to

25

product 12 similar to the sequence described in Scheme 1 for the conversion of intermediate 3 to 6.

EXAMPLES

5 Preparation of compounds of Formula (I), and intermediates used in the preparation of compounds of Formula (I), can be prepared using procedures shown in the following Examples and related procedures. The methods and conditions used in these examples, and the actual compounds prepared in these Examples, are not meant to be limiting, but are meant to demonstrate how the compounds of Formula (I) can be prepared. Starting materials and reagents used in these examples, when not prepared by a procedure described herein, are generally either commercially available, or are reported in the chemical literature, or may be prepared by using procedures described in the chemical literature.

15 In the Examples given, the phrase "dried and concentrated" generally refers to drying of a solution in an organic solvent over either sodium sulfate or magnesium sulfate, followed by filtration and removal of the solvent from the filtrate (generally under reduced pressure and at a temperature suitable to the stability of the material being prepared). Column chromatography was performed with pre-packed silica gel cartridges using a medium pressure chromatography apparatus (Teledyne Corporation), eluting with the solvent or solvent mixture indicated. Preparative high performance liquid chromatography (HPLC) was performed using a reverse phase column (Waters Sunfire C₁₈, Waters Xbridge C₁₈, PHENOMENEX® Axia C₁₈, YMC S5 ODS or the like) of a size appropriate to the quantity of material being separated, generally eluting with a gradient of increasing concentration of methanol or acetonitrile in water, also containing 25 0.05% or 0.1% trifluoroacetic acid or 10 mM ammonium acetate, at a rate of elution suitable to the column size and separation to be achieved. Chemical names were determined using ChemDraw Ultra, version 9.0.5 (CambridgeSoft). The following abbreviations are used:

30 NaHCO₃ = sodium bicarbonate
brine = saturated aqueous sodium chloride
DCM = dichloromethane

DIEA = *N,N*-diisopropylethylamine

DMAP = 4-(*N,N*-dimethylamino)pyridine

DMF = *N,N*-dimethylformamide

DMSO = dimethyl sulfoxide

5 EtOAc = ethyl acetate

rt = ambient room temperature (generally about 20-25 °C)

TEA = triethylamine

TFA = trifluoroacetic acid

THF = tetrahydrofuran

10

Analytical LC/MS Methods Employed in Characterization of Examples:

Method A:

Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm particles

15 Mobile Phase: (A) 5:95 acetonitrile:water; (B) 95:5 acetonitrile:water

Buffer: 10 mM ammonium acetate

Gradient Range: 0-100% B

Gradient Time: 3 min

Flow Rate: 1.11 mL/min

20 Temp = 50 C

Analysis Time: 4 min

Detection:

Detector 1: UV at 220 nm

Detector 2: MS (ESI+)

25 Detector 3: ELSD

Method B:

Column = Waters Acquity BEH C18 1.7 µm 2.0 x 50 mm

Start % B = 0

30 Final % B = 100

Gradient Time = 1.5 min

Flow Rate = 1 mL/min

Temp = 40 C

Inj volume = 1 uL

Wavelength = 220 nm

Detection = MS (ESI+)

5 Solvent A = 90% water - 10% acetonitrile – 0.1% TFA

Solvent B = 10% water - 90% acetonitrile – 0.1% TFA

Method C:

Column: (LCMS) BEH C18, 2.1 x 50 mm, 1.7 μm particles

Mobile Phase: (A) water; (B) acetonitrile

Buffer: 0.05% TFA

Gradient Range: 2%-98% B (0 to 1 min) 98%B (to 1.5 min) 98%-2% B (to 1.6 min)

Gradient Time: 1.6 min

Flow Rate: 0.8 mL/min

Analysis Time: 2.2 min

Detection:

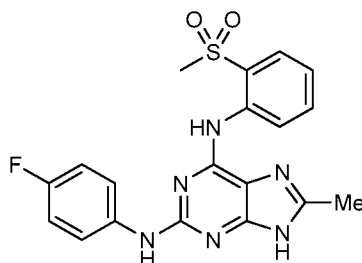
Detector 1: UV at 254 nm

Detector 2: MS (ESI+)

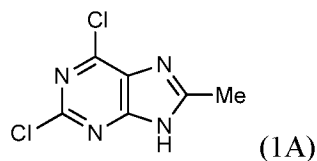
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EXAMPLE 1

N2-(4-fluorophenyl)-8-methyl-N6-(2-(methylsulfonyl)phenyl)-9H-purine-2,6-diamine



Intermediate 1A: 2,6-dichloro-8-methyl-9H-purine

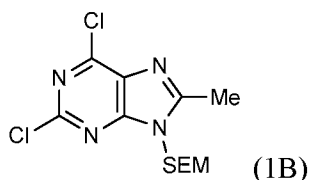


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8-Methyl-1H-purine-2,6(3H,9H)-dione (2.8 g, 16.8 mmol) was slurried in POCl₃ (15.7 mL, 169 mmol) and warmed to ~ 50°C, then slowly added DBU (15 mL, 100

mmol) dropwise via syringe over ~ 3 min causing the solution to warm to near refluxing. After the addition was complete, the oil bath temp. was increased to allow the resulting heterogeneous reaction mixture to continue refluxing for a total of 6 h followed by cooling to rt giving a thick viscous oil which was slowly poured in several portions into a well-stirred mixture of saturated aqueous sodium bicarbonate (~ 300 mL) and crushed ice (~300 mL). Precautions were taken to not overflow the flask due to vigorous CO₂ evolution during neutralization. After all of the reaction mixture had been added and the gas evolution had subsided, DCM (~ 300 mL) was added and the mixture was stirred vigorously for ~ 1.5 h while warming to rt. The layers were separated and the aqueous portion was extracted with additional DCM (2 x 200 mL) and the combined extracts were washed with brine (~ 150 mL), dried over anhyd. sodium sulfate, decanted and concentrated in vacuo to give an oil which afforded ~ 3.6 g of a yellow-orange semi-solid as the crude product. This semi-solid was dissolved in DCM (~ 35 mL) and the mixture was sonicated which caused a yellow solid to precipitate from solution. The solid was collected by vacuum filtration, rinsed w/ additional DCM then was air dried in the funnel to afford 1.32 g (39%) of a tan solid as the pure product which was used directly in the next transformation. LC/MS (M+H): 203.1.

Intermediate 1B: 2,6-dichloro-8-methyl-9-((2-(trimethylsilyl)ethoxy)methyl)-9H-purine



To a mixture of 2,6-dichloro-8-methyl-9H-purine (1.3 g, 6.40 mmol) in DMF (20 mL) at 0 °C was added 60% sodium hydride dispersion in mineral oil (0.512 g, 12.81 mmol) and the resulting dark brown mixture was stirred at this temperature for 15 min. followed by adding (2-(chloromethoxy)ethyl)trimethylsilane (1.36 mL, 7.68 mmol). The resulting mixture was then allowed to warm to rt and stir for ~ 3 h, LCMS indicated the complete consumption of the starting material to afford a less polar major product consistent with the expected product (observed MH+ 333/335). The reaction mixture was cooled in an ice bath and water was slowly added dropwise initially to quench, then the contents were diluted with additional water to a total volume of ~ 80 mL. The dark brown mixture was extracted with EtOAc (3 x 50 mL) and the combined extracts were

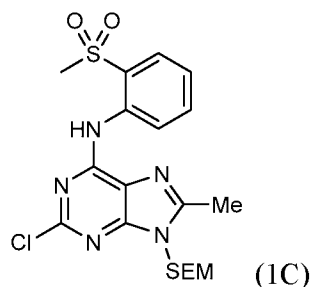
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diluted with one volume of hexanes and washed with water (4 x 40 mL), then brine before drying over anhyd. sodium sulfate. Decanting the dried extracts and concentration under vacuum afforded ~2.7 g of a dark red-brown oil as the crude product mixture. The crude product was subjected to silica gel chromatography using a 40 g cartridge and loading the crude product dissolved in a minimal amount of dichloromethane. The column was then eluted under a standard linear gradient of solvent A (Hexanes) and solvent B (EtOAc). Fractions containing the major product were combined and concentrated to afford 445 mg (21%) of a dark red/brown oil as the desired product. LC/MS (M+H): 334.0.

10

Intermediate 1C: 2-chloro-8-methyl-N-(2-(methylsulfonyl)phenyl)-9-((2-(trimethylsilyl)ethoxy)-methyl)-9H-purin-6-amine



15 To a -78 °C solution of 2-(methylsulfonyl)aniline (56.5 mg, 0.330 mmol) in THF (1 mL) was added NaHMDS (1 M in THF) (0.330 mL, 0.330 mmol) and the resulting yellow solution was allowed to stir ~15 min whereupon a solution of 2,6-dichloro-8-methyl-9-((2-(trimethylsilyl)ethoxy)methyl)-9H-purine (100 mg, 0.300 mmol) in THF (0.5 mL) was added dropwise at -78 °C. After the addition was complete, the resulting dark amber colored solution was allowed to stir at -78 °C for ~ 3 min. then warm to 0°C and stir for ~ 15 min. The reaction was quenched at this time by adding MeOH (~ 1 mL) and the mixture was concentrated to yield a red/brown oil as the crude product. The crude product was dissolved in a minimal amount of DCM and was loaded onto a 4 g silica gel cartridge. The column was then eluted using a linear gradient of solvent A (hexanes) to solvent B (ethyl acetate). Fractions containing the desired product were concentrated in vacuo to afford 36 mg (26%) of the product as a pale yellow oil. LC/MS (M+H): 468.3.

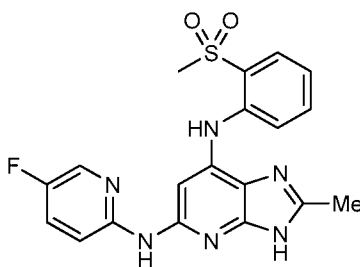
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Example 1:

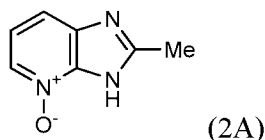
2-chloro-8-methyl-N-(2-(methylsulfonyl)phenyl)-9-((2-(trimethylsilyl)ethoxy)methyl)-9H-purin-6-amine (36 mg, 0.077 mmol), 4-fluoroaniline (11 mg, 0.10 mmol), K_2CO_3 (21.3 mg, 0.15 mmol) and BrettPhos (6.2 mg, 0.012 mmol) were added to a reaction vial with magnetic stir bar and the contents was flushed with nitrogen. Dioxane (0.3 mL) was then added and the resulting mixture was sparged with nitrogen for a few minutes before finally adding $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and heating to 115 °C in a preheated heating block. After 3 h at this temperature, the reaction was cooled and diluted with EtOAc and the organic solution was pipetted away from the insoluble inorganics and the solution was concentrated under vacuum. This residue was dissolved in TFA (1.5 mL) and was stirred for 30 min. The mixture was then warmed to 50 °C for 1 h. The mixture was concentrated under vacuum and the resulting residue was purified by preparative LC/MS under the following conditions: Column: Waters XBridge C18, 19 x 250 mm, 5- μ m particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5- μ m particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 5-100% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford 1.2 mg (4%) of the desired product. LC/MS (M+H): 413.2; LC retention time: 1.34 min (analytical HPLC Method A); 1H NMR (500 MHz, $DMSO-d_6$): δ 12.73 (s, 1H), 9.73 - 9.69 (m, 1H), 9.66 (s, 1H), 9.15 - 9.10 (m, 1H), 8.36 - 8.23 (m, 2H), 7.89 (dd, $J=7.9, 1.5$ Hz, 1H), 7.80 - 7.65 (m, 2H), 7.30 (t, $J=7.7$ Hz, 1H), 3.27 (s, 3H), 2.46 (s, 3H).

EXAMPLE 2

N5-(5-fluoropyridin-2-yl)-2-methyl-N7-(2-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine-5,7-diamine

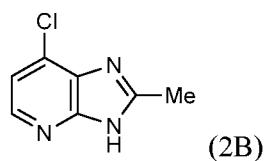


Intermediate 2A: 2-methyl-3H-imidazo[4,5-b]pyridine 4-oxide



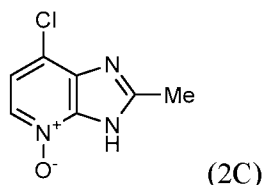
2-methyl-3H-imidazo[4,5-b]pyridine (10.8 g, 81 mmol) was mixed in EtOAc (500 mL) to give a partial suspension and mCPBA (18.66 g, 81 mmol) was added in portions
 5 over 15 minutes. The resulting mixture was stirred at rt for ~ 1.5 h. LCMS analysis indicated reaction was only ~ 85% complete, therefore an addition amount of mCPBA (2.2 g) was added. After stirring an additional 30 min at rt., the resulting precipitate which had formed was collected by filtration, rinsed with additional cold EtOAc (50 mL x 3) and dried under vacuum to afford 12 g (99%) of the desired product as a tan solid.
 10 ¹H NMR (400 MHz, METHANOL-d₄): δ 8.24 (dd, *J*=6.4, 0.7 Hz, 1H), 7.74 (d, *J*=7.9 Hz, 1H), 7.31 (dd, *J*=8.1, 6.4 Hz, 1H), 2.67 (s, 3H).

Intermediate 2B: 7-chloro-2-methyl-3H-imidazo[4,5-b]pyridine



Intermediate 2A (12 g, 80 mmol) in POCl₃ (60.0 mL, 644 mmol) was heated gradually in a oil bath to 80°C causing some effervescence. The reaction was held at this temperature for 15 min, then brought temperature to 120 °C gradually. After 3h at 120 °C, the reaction was cooled to rt and the POCl₃ was removed under reduced pressure to give an oil which was dissolved in DCM (50 mL) and was reconcentrated and repeating
 20 to afford a tan semi-solid. The mixture was cooled in an ice bath and cold water (75 mL) was added to make clear solution which was transferred to 1 L flask. With stirring the mixture was slowly neutralized by a dropwise addition of aq sat sodium bicarbonate until a pH of ~ 7 was obtained. The cooling bath was removed and the mixture was stirred at rt for 30 min. then was extracted with EtOAc (200 mL x 4) and the combined organic
 25 extracts were dried over anhydrous sodium sulfate, filtered and concentrated to afford 12.4 g (92%) of a cream solid as the desired product. ¹H NMR (400MHz, METHANOL-d₄): δ 8.24 (d, *J*=4.0 Hz, 1H), 7.34 (d, *J*=5.3 Hz, 1H), 2.67 (s, 3H).

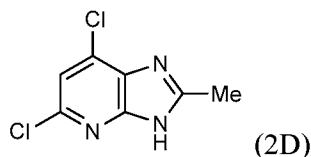
Intermediate 2C: 7-chloro-2-methyl-3H-imidazo[4,5-b]pyridine 4-oxide



To a partial suspension of intermediate 2B (10.5 g, 62.7 mmol) in ethyl acetate (500 mL) was added mCPBA (15.86 g, 68.9 mmol) portion wise over 15 min. After stirring at rt for ~ 30 min, the mixture became a clear solution followed by precipitation of a light tan solid. After stirring at rt for an additional 2h, the mixture was cooled in an ice bath for 30 min., then the precipitated solid was collected by vacuum filtration and was rinsed with additional ice-cold EtOAc (~ 10 mL x 3) followed by drying the resulting solid under vacuum to afford 8.5 g (74%) of a cream-colored solid as the desired product.

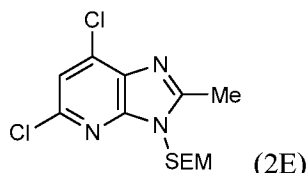
LC/MS (M+H): 184.1/186.1 (3:1). LC retention time: 0.41 min (analytical HPLC Method A).

Intermediate 2D: 5,7-dichloro-2-methyl-3H-imidazo[4,5-b]pyridine



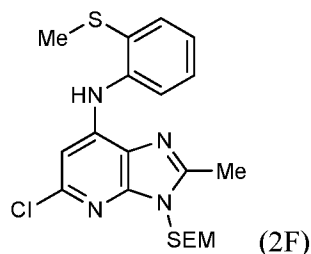
Intermediate 2C (8.5 g, 46.5 mmol) was slurried in DMF (70 mL) and heated to 50 °C whereupon methanesulfonyl chloride (4.71 mL, 60.4 mmol) was added dropwise and the resulting solution was then heated to 80 °C. After 2h, additional methanesulfonyl chloride (4.71 mL, 60.4 mmol) was added and heated to 95°C for 1.5h. LCMS analysis indicated reaction was complete. The reaction was cooled in an ice bath whereupon cold water added (250 mL) to make cloudy solution, followed by a dropwise addition of 6 N aq sodium hydroxide, until pH of solution was ~ 8 causing the mixture to become cloudy. After sonicating briefly and stirring in an ice bath for ~ 1h, the resulting precipitated solid was collected by vacuum filtration, rinsed with water, and was dried on the funnel then under vacuum to afford 6.49 g (69%) of a tan solid as the desired product. LC/MS (M+H): 202/204/206. ¹H NMR (400MHz, METHANOL-d₄): δ 7.35 (s, 1H), 3.31 (s, 3H).

Intermediate 2E: 5,7-dichloro-2-methyl-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridine



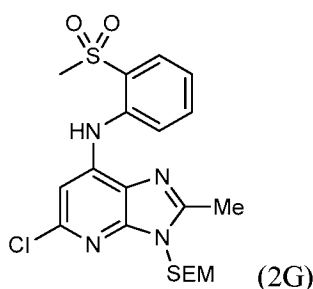
To a partial suspension of Intermediate 2D (6.50 g, 32.2 mmol) in DMF (80 mL) at 0 °C was added 60% mineral oil dispersion of sodium hydride (2.57 g, 64.3 mmol) in portions over 15 min and the resulting mixture was allowed to warm to rt and stir for 15 minutes whereupon SEM-Cl (8.56 mL, 48.3 mmol) was added dropwise via syringe. During addition, an exothermic reaction was observed, so a cold water bath was used for latter part of the addition. After the addition was complete, the reaction was allowed to stir at rt for 2h at which time LCMS analysis indicated that the reaction was complete. The reaction was cooled in an ice bath and slowly diluted with water (~ 140 mL) and extracted with ethyl acetate (3 x 200 mL). The combined extracts were diluted with ~ 1/2 volume of hexanes (~ 200 mL) and were washed with water (3 x 150 mL) then brine before drying over anhydrous sodium sulfate. Decanting and concentration under vacuum afforded a yellow brown oil as the crude product (12.7g). This material was dissolved in a minimal amount of DCM and was loaded onto a 220 g silica gel cartridge and was eluted with a linear gradient of ethyl acetate in hexanes. The major product began eluting near 40% EtOAc in hexanes and the fractions containing this product were concentrated under vacuum to afford 4.75 g (44%) of a tan oil as the desired product which solidified on standing to a tan solid. LC/MS (M+H): 332.0; ¹H NMR (400MHz, METHANOL-d₄): δ 7.48 (s, 1H), 5.71 (s, 2H), 3.78 - 3.54 (m, 2H), 2.75 (s, 3H), 1.09 - 0.82 (m, 2H), -0.01 (s, 9H).

Intermediate 2F: 5-chloro-2-methyl-N-(2-(methylthio)phenyl)-3-((2-(trimethylsilyl)ethoxy)-methyl)-3H-imidazo[4,5-b]pyridin-7-amine



To a solution of intermediate 2E (1.00 g, 3.01 mmol) and 2-(methylthio)aniline (0.45 mL, 3.6 mmol) in THF (10 mL) at 0 °C was slowly added NaHMDS (1 M in THF) (9.03 mL, 9.03 mmol) dropwise via syringe giving a dark amber colored solution. LCMS analysis after 30 min at 0 °C indicated complete conversion to product near 4.27 min (observed MH⁺ 435/437). After cooling in an ice bath, the reaction was quenched with 10 mL of MeOH and the reaction mixture was concentrated and the resulting residue was partitioned between 30 mL of water and 200 mL of ethyl acetate. The layers were separated and the aqueous portion was extracted twice with additional ethyl acetate (100 mL each). The combined extracts were dried over anhyd. sodium sulfate, decanted and concentrated to afford tan oil which was purified via preparative chromatography (Hexanes/EtOAc; 40g column). Fractions containing the major product were concentrated under vacuum to afford a yellow oil which was dried further under vacuum to afford 0.76 g (58%) of a tan solid as the final product. LC/MS (M+H): 435.3. ¹H NMR (400MHz, METHANOL-d₄): δ 7.55 - 7.49 (m, 1H), 7.46 - 7.41 (m, 1H), 7.39 - 7.29 (m, 2H), 6.51 - 6.37 (m, 1H), 5.65 (s, 2H), 3.77 - 3.58 (m, 2H), 2.70 (s, 3H), 2.47 (s, 3H), 1.05 - 0.84 (m, 2H), 0.00 (s, 9H).

Intermediate 2G: 5-chloro-2-methyl-N-(2-(methylsulfonyl)phenyl)-3-((2-(trimethylsilyl)ethoxy)-methyl)-3H-imidazo[4,5-b]pyridin-7-amine



To a solution of Intermediate 2F (0.83 g, 1.9 mmol) and sodium tungstate

dihydrate (0.13 g, 0.38 mmol) in acetic acid (10 mL) at rt was added an aqueous solution of H₂O₂ (2.92 mL, 29 mmol) dropwise using a cooling bath to keep reaction mixture cool during the exothermic addition. After the addition was complete, the cooling bath was removed and the resulting solution was stirred at rt for 2h. The reaction was cooled in an ice bath and 25% aqueous sodium thiosulfate solution (~ 20 mL) was slowly added via pipette causing a solid to eventually precipitate from solution. Water (50 mL) was added and the resulting clear solution was neutralized by slowly adding saturated aqueous sodium bicarbonate until pH ~ 7. The resulting solid was collected by vacuum filtration and was rinsed with water and dried in the funnel to afford a tan solid which was purified by preparative chromatography using a 40 g silica gel cartridge and ethyl acetate/hexanes mixtures as the eluent. Fractions containing the major uv active product were collected and concentrated to afford 0.54 g (61%) of a tan solid as the desired product. LC/MS (M+H): 467/469 (~3:1). ¹H NMR (400MHz, METHANOL-d₄) δ 8.12 - 8.02 (m, 1H), 7.85 - 7.76 (m, 2H), 7.43 (ddd, *J*=8.1, 5.9, 2.3 Hz, 1H), 7.04 (s, 1H), 5.67 (s, 2H), 3.77 - 3.59 (m, 2H), 3.14 (s, 3H), 2.70 (s, 3H), 1.04 - 0.87 (m, 2H), 0.00 (s, 9H).

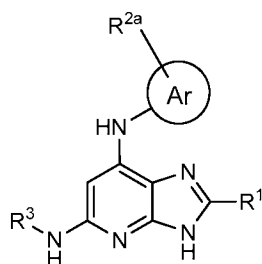
Example 2:

A vial was charged with intermediate 2G (60 mg, 0.128 mmol), 5-fluoropyridin-2-amine (17.3 mg, 0.154 mmol), BrettPhos (8.27 mg, 0.015 mmol) and Pd₂(dba)₃ (11.76 mg, 0.013 mmol) in dioxane (0.6 mL) and the resulting mixture was sparged with nitrogen for a few minutes. After sparging, a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 0.283 mL, 0.283 mmol) was then added dropwise giving a dark amber colored solution which was heated in a preheated heating block at 110 °C. After heating for 1 h at 110 °C, the mixture was cooled to rt and was concentrated under vacuum. This crude material was dissolved in DCM (0.2 mL) and treated with TFA (1.5 mL) at rt for 30min, followed by reconcentration under vacuum to afford the crude product. This material was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 19 x 150 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-100% B over 15 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford 34.9 mg (65%) of the desired product. LC/MS

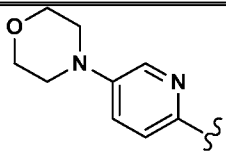
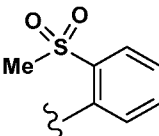
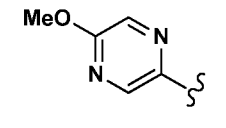
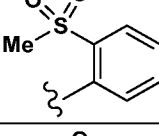
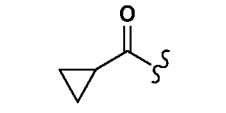
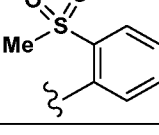
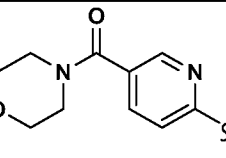
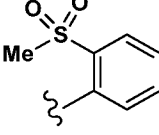
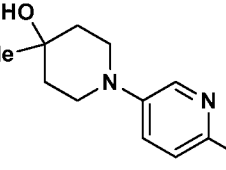
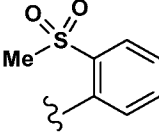
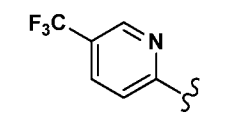
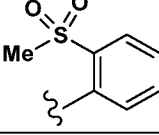
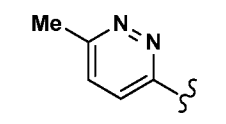
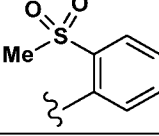
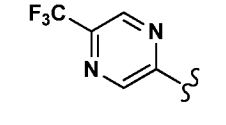
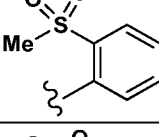
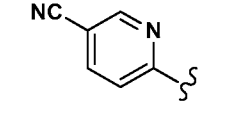
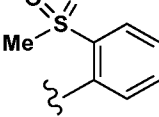
(M+H): 413.2; LC retention time: 1.38 min (analytical HPLC Method A); $^1\text{H NMR}$ (400MHz, METHANOL- d_4): δ 8.14 - 8.06 (m, 2H), 8.02 - 7.86 (m, 2H), 7.79 (t, $J=7.8$ Hz, 1H), 7.53 (ddd, $J=9.2, 8.0, 3.1$ Hz, 1H), 7.42 - 7.35 (m, 1H), 7.24 (s, 1H), 3.22 (s, 3H), 2.65 (s, 3H).

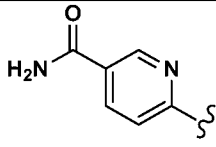
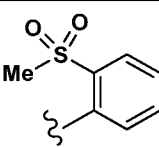
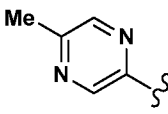
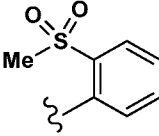
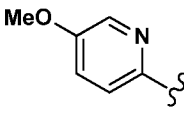
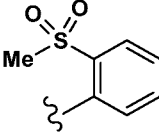
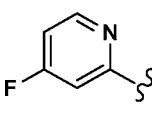
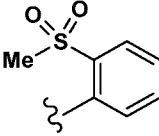
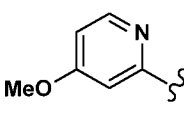
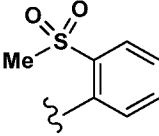
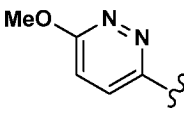
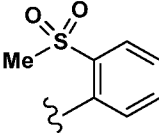
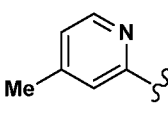
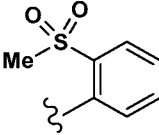
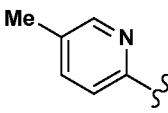
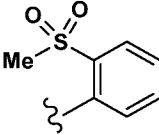
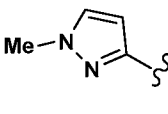
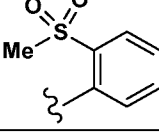
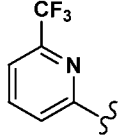
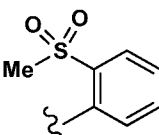
5

Examples 3 - 52 were prepared using similar methods as previously described for the preparation of Example 2. Examples 32 - 34 were prepared using commercially available 2-aminobenzamide in place of 2-(methylthio)aniline in Example 2. Examples 35-38 were prepared using commercially available 2-methoxyaniline in place of 2-(methylthio)aniline in Example 2. Examples 39 and 40 were prepared using 2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)aniline (prepared as described in *WO 2015069310*) in place of 2-(methylthio)aniline in Example 2. Examples 41 - 50 were prepared using commercially available 2-amino-3-(thiomethyl)pyridine in place of 2-(thiomethyl)aniline in Example 2. Examples 51 - 52 were prepared from 2-ethyl-3H-imidazo[4,5-b]pyridine (*Tet. Lett.* **2006**, 47, 2883 - 2886) using similar procedures as described in the preparation of Example 2.



Example No.	R ³	-Ar-R ^{2a}	R ¹	Rt (min) [Method]	<i>m/z</i> [M+H] ⁺
3			Me	0.63 [C]	420.3
4			Me	1.15 [B]	424.2

Example No.	R ³	-Ar-R ^{2a}	R ¹	Rt (min) [Method]	m/z [M+H] ⁺
5			Me	1.23 [A]	480.2
6			Me	1.29 [A]	426.1
7			Me	1.16 [A]	386.1
8			Me	1.13 [A]	508.2
9			Me	1.19 [A]	508.2
10			Me	1.56 [A]	463.1
11			Me	1.10 [A]	410.1
12			Me	1.49 [A]	464.1
13			Me	1.30 [A]	420.1

Example No.	R ³	-Ar-R ^{2a}	R ¹	Rt (min) [Method]	<i>m/z</i> [M+H] ⁺
14			Me	1.02 [A]	438.1
15			Me	1.20 [A]	410.1
16			Me	1.28 [A]	425.1
17			Me	1.35 [A]	413.1
18			Me	1.25 [A]	425.1
19			Me	1.18 [A]	426.1
20			Me	1.20 [A]	409.1
21			Me	1.39 [A]	409.1
22			Me	1.05 [A]	398.2
23			Me	1.58 [A]	463.1

Example No.	R ³	-Ar-R ^{2a}	R ¹	Rt (min) [Method]	<i>m/z</i> [M+H] ⁺
24			Me	1.21 [A]	478.2
25			Me	1.40 [A]	434.1
26			Me	1.20 [A]	412.2
27			Me	1.20 [A]	435.1
28			Me	1.47 [A]	448.2
29			Me	1.34 [A]	409.1
30			Me	1.33 [A]	426.2
31			Me	1.48 [A]	427.1
32			Me	0.61 [C]	378.2
33			Me	0.91 [A]	389.2

Example No.	R ³	-Ar-R ^{2a}	R ¹	Rt (min) [Method]	<i>m/z</i> [M+H] ⁺
34			Me	0.97 [A]	445.2
35			Me	1.25 [A]	338.2
36			Me	1.23 [A]	376.2
37			Me	1.32 [A]	432.2
38			Me	1.45 [A]	365.2
39			Me	0.97 [A]	419.2
40			Me	1.14 [A]	446.2
41			Me	0.91 [B]	414.2
42			Me	0.90 [B]	426.2

Example No.	R ³	-Ar-R ^{2a}	R ¹	Rt (min) [Method]	<i>m/z</i> [M+H] ⁺
43			Me	0.92 [B]	414.3
45			Me	1.06 [A]	427.2
46			Me	1.16 [A]	410.2
47			Me	1.20 [A]	387.3
48			Me	1.10 [A]	410.9
49			Me	1.26 [A]	410.2
50			Me	1.20 [A]	481.1
51			Et	1.39 [A]	427.1
52			Et	1.13 [A]	438.2

The following table lists the IUPAC names for the compounds of examples 3-52.

Example No.	IUPAC Name
3	2-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)pyridine-4-carbonitrile
4	5-N-(2,6-dimethylpyrimidin-4-yl)-7-N-(2-methanesulfonylphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
5	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-[5-(morpholin-4-yl)pyridin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
6	7-N-(2-methanesulfonylphenyl)-5-N-(5-methoxy pyrazin-2-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
7	N-{7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} cyclopropanecarboxamide
8	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-[5-(morpholine-4-carbonyl)pyridin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
9	1-[6-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)pyridin-3-yl]-4-methylpiperidin-4-ol
10	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-[5-(trifluoromethyl)pyridin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
11	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-(6-methylpyridazin-3-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
12	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-[5-(trifluoromethyl)pyrazin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
13	6-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)pyridine-3-carbonitrile
14	6-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)pyridine-3-carboxamide
15	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-(5-methylpyrazin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
16	7-N-(2-methanesulfonylphenyl)-5-N-(5-methoxy pyridin-2-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine

Example No.	IUPAC Name
17	5-N-(4-fluoropyridin-2-yl)-7-N-(2-methanesulfonylphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
18	7-N-(2-methanesulfonylphenyl)-5-N-(4-methoxy pyridin-2-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
19	7-N-(2-methanesulfonylphenyl)-5-N-(6-methoxy pyridazin-3-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
20	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-(4-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
21	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-(5-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
22	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-(1-methyl-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
23	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-[6-(trifluoromethyl)pyridin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
24	1-[6-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)pyridin-3-yl]pyrrolidin-2-one
25	6-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)-2-methylpyridine-3-carbonitrile
26	5-N-(1,5-dimethyl-1H-pyrazol-3-yl)-7-N-(2-methanesulfonylphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
27	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-{pyrazolo[1,5-a]pyrimidin-5-yl}-3H-imidazo[4,5-b]pyridine-5,7-diamine
28	6-({7-[(2-methanesulfonylphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} amino)-2,4-dimethylpyridine-3-carbonitrile
29	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-(6-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
30	7-N-(2-methanesulfonylphenyl)-2-methyl-5-N-[1-(propan-2-yl)-1H-pyrazol-3-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
31	5-N-(5-fluoro-4-methylpyridin-2-yl)-7-N-(2-methanesulfonylphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine

Example No.	IUPAC Name
32	2-({5-[(5-fluoropyridin-2-yl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-7-yl} amino)benzamide
33	2-({5-[(2,6-dimethylpyrimidin-4-yl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-7-yl} amino)benzamide
34	2-[(2-methyl-5-{[5-(morpholin-4-yl)pyridin-2-yl]amino}-3H-imidazo[4,5-b]pyridin-7-yl)amino]benzamide
35	N-{7-[(2-methoxyphenyl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} cyclopropanecarboxamide
36	5-N-(2,6-dimethylpyrimidin-4-yl)-7-N-(2-methoxyphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
37	7-N-(2-methoxyphenyl)-2-methyl-5-N-[5-(morpholin-4-yl)pyridin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
38	5-N-(5-fluoropyridin-2-yl)-7-N-(2-methoxyphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
39	N-(7-{[2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl]amino}-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl)cyclopropanecarboxamide
40	5-N-(5-fluoropyridin-2-yl)-7-N-[2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl]-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
41	5-N-(5-fluoropyridin-2-yl)-7-N-(3-methanesulfonylpyridin-2-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
42	7-N-(3-methanesulfonylpyridin-2-yl)-5-N-(5-methoxy pyridin-2-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
43	5-N-(4-fluoropyridin-2-yl)-7-N-(3-methanesulfonylpyridin-2-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
45	7-N-(3-methanesulfonylpyridin-2-yl)-5-N-(6-methoxy pyridazin-3-yl)-2-methyl-3H-imidazo[4,5-b]pyridine-5,7-diamine
46	7-N-(3-methanesulfonylpyridin-2-yl)-2-methyl-5-N-(4-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
47	N-{7-[(3-methanesulfonylpyridin-2-yl)amino]-2-methyl-3H-imidazo[4,5-b]pyridin-5-yl} cyclopropanecarboxamide

Example No.	IUPAC Name
48	7-N-(3-methanesulfonylpyridin-2-yl)-2-methyl-5-N-(5-methylpyrazin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
49	7-N-(3-methanesulfonylpyridin-2-yl)-2-methyl-5-N-(6-methylpyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
50	7-N-(3-methanesulfonylpyridin-2-yl)-2-methyl-5-N-[5-(morpholin-4-yl)pyridin-2-yl]-3H-imidazo[4,5-b]pyridine-5,7-diamine
51	2-ethyl-5-N-(5-fluoropyridin-2-yl)-7-N-(2-methanesulfonylphenyl)-3H-imidazo[4,5-b]pyridine-5,7-diamine
52	5-N-(2,6-dimethylpyrimidin-4-yl)-2-ethyl-7-N-(2-methanesulfonylphenyl)-3H-imidazo[4,5-b]pyridine-5,7-diamine

5

BIOLOGICAL ASSAYS

Probe Displacement Assay (SPA format)

The probe displacement assay is conducted as follows: In a 385 well plate, test compounds along with recombinantly expressed His-tagged protein corresponding to amino acids 575-869 of human Tyk2 (sequence shown below) at 2.5 nM, 40 nM ((*R*)-*N*-(1-(3-(8-methyl-5-

10 (methylamino)-8*H*-imidazo[4,5-d]thiazolo[5,4-b]pyridin-2-yl)phenyl)ethyl)-2-([³H]methylsulfonyl)benzamide) (preparation described below) and 80 µg/mL Copper His-Tag scintillation proximity assay beads (Perkin Elmer, Catalog #RPNQ0095) in 50 mM HEPES, pH 7.5, containing 100 µg/mL bovine serum albumin and 5% DMSO were incubated for 30 minutes at room temperature. The amount of radiolabeled probe

15 (preparation described below) bound to Tyk2 was then quantified by scintillation counting, and the inhibition by the test compound calculated by comparison to wells either with no inhibitor (0% inhibition) or without Tyk2 (100% inhibition). The EC₅₀ value is defined as the concentration of test compound required to inhibit radiolabeled probe binding by 50%.

20 **Probe Displacement Assay (HTRF format)**

To 10 μ L 26 nM fluorescein labeled probe plus 0.2 nM anti-6xHis-terbium labeled antibody (Medarex, labeled by Cisbio) in assay buffer (20 mM Hepes pH 7.5, 150 mM NaCl, 10 mM MgCl₂, 2 mM DTT, 50 μ g/mL BSA, and 0.015% Brij 35) was added 10 μ L recombinant human His-tagged Tyk2 pseudokinase domain (His-TVMV-Tyk2, 575-869) to a final concentration of 0.5 nM. After 1 h at room temperature, the HTRF signal (ratio of fluorescence intensities at emission wavelengths for fluorescein acceptor at 520 nm and terbium donor at 495 nm) was measured on an Envision Plate Reader. Percent inhibition was calculated by comparison to a control without inhibitor and a control without protein. Dose response curves were generated to determine the concentration required for inhibiting 50% of the HTRF signal (EC₅₀).

Protein Sequence of recombinant His-tagged Tyk2 (575-869):

MGSSHHHHHH SSGETVRFQG HMNLSQLSFH RVDQKEITQL SHLGQGTRTN
 VYEGRLRVEG SGDPEEGKMDDDEDPLVPGRD RGQELRVVLK VLDPSHHDIA
 LAFYETASLM SQVSHTHLAF VHGV CVRGPE NIMVTEYVEHGPLDVWLRRR
 15 RGHVPMWKM VVAQQLASAL SYLENKNLVH GNVCGRNILL ARLGLAEGTS
 PFIKLSDPGVGLGALSREER VERIPWLAPE CLPGGANLSL TAMDKWGFGA
 TLLEICFDGE APLQSRSPSE KEHFYQRQHRLPEPSCPQLA TLTSQCLTYE
 PTQRPSFRTI LRDTRL. (SEQ ID NO: 1).

20 The preparation of radiolabeled probe, (*R*)-*N*-(1-(3-(8-methyl-5-(methylamino)-8*H*-imidazo[4,5-*d*]thiazolo[5,4-*b*]pyridin-2-yl)phenyl)ethyl)-2-([³H]methylsulfonyl)benzamide, was performed as described below:

2-([³H]methylsulfonyl)benzoic acid: 2-Mercaptobenzoic acid (2.3 mg, 0.015 mmol) and cesium carbonate (2 mg, 0.006 mmol) were added to a 5 mL round-bottomed flask. The flask was attached to a ported glass vacuum line and anhydrous DMF (0.5 mL) was introduced with magnetic stirring. An ampoule of tritiated methyl iodide (200 mCi, Perkin-Elmer lot 3643419) was added to the reaction flask and stirring was maintained at rt for 3h. In-process HPLC analysis with radiometric detection indicated 80% conversion to the desired product by comparison with authentic standard. Without purification, the crude product was reacted with mCPBA (10 mg, 0.058 mmol) pre-dissolved in CH₂Cl₂ (1 mL) at room temperature with stirring. The reaction was stirred for 7h and additional mCPBA (10 mg, 0.058 mmol) was added. The reaction was stirred for approximately

24h and HPLC analysis indicated 35-40% conversion to the desired sulfonate product. The crude product was purified by semi-preparative HPLC (Luna 5um C18 (10X250 cm); A: MeOH/H₂O=15/85(0.1%TFA); B: MeOH; 270nm; 0-8min 0%B 1ml/min; 8-10min 0%B 1-3ml/min; 10-55min 0%B 3ml/min; 55-65min 0-10%B 3ml/min; 65-75min 10-50%B 3ml/min; 75-80min 50-100%B 3ml/min) to give 81 mCi (40% radiochemical yield) of 2-([³H]methylsulfonyl)benzoic acid product identified by its HPLC co-elution with an authentic standard. The radiochemical purity was measured by HPLC to be 99% (Luna 5u C18 (4.6X150 cm); A: H₂O (0.1%TFA); B: MeOH; 1.2ml/min; 270nm; 0-10min 20%B; 10-15min 20-100%B; 15-25min 100%B). The product was dissolved in anhydrous acetonitrile to give a final solution activity of 5.8 mCi/mL.

(*R*)-*N*-(1-(3-(8-methyl-5-(methylamino)-8*H*-imidazo[4,5-*d*]thiazolo[5,4-*b*]pyridin-2-yl)phenyl)ethyl)-2-([³H]methylsulfonyl)benzamide: A solution of 2-([³H]methylsulfonyl)benzoic acid (23.2 mCi) in acetonitrile was added to a 5 mL round-bottomed flask which was then attached to a vacuum line and carefully evaporated to dryness. (*R*)-2-(3-(1-aminoethyl)phenyl)-*N*,8-dimethyl-8*H*-imidazo[4,5-*d*]thiazolo[5,4-*b*]pyridin-5-amine (prepared as described in WO 2004/106293 and Dyckman et al., *Bioorganic and Medicinal Chemistry Letters*, 383-386 (2011)) (1.1 mg, 0.0033 mmol) and PyBOP (2 mg, 0.0053 mmol) dissolved in anhydrous DMF (1.5 mL) were added to the flask followed by *N,N*-diisopropylethylamine (0.010 mL). The resulting clear solution was stirred at room temperature for 18h. HPLC analysis (Luna 5u C18 (4.6X150 cm); A: H₂O(0.1%TFA); B: MeOH; 1.2ml/min; 335nm; 0-20min 50% B; 20-25min 50-100% B; 25-30min 100%B) indicated approximately a 20% conversion to the desired product by retention time comparison to a sample of non-radiolabeled (*R*)-*N*-(1-(3-(8-methyl-5-(methylamino)-8*H*-imidazo[4,5-*d*]thiazolo[5,4-*b*]pyridin-2-yl)phenyl)ethyl)-2-([³H]methylsulfonyl)benzamide. The crude reaction mixture was purified by semi-preparative HPLC (Luna 5u C18 (10X250 cm); A: MeOH/H₂O=50/50(0.1%TFA); B: MeOH; 335nm; 0-40min 0%B 3ml/min; 40-45min 0-100%B 3ml/min). The purification routine was performed a second time to yield a total of 1.7 mCi (7% radiochemical yield) of the desired product in 99.9% radiochemical purity. Mass spectral analysis of the tritiated product (*m/z* M+H 527.33) was used to establish the specific activity at 80.6 Ci/mmol.

Probe Displacement Data

(using SPA assay format unless otherwise noted)

Example No.	Probe Displacement (EC ₅₀ , μ M)
1	0.270
2	0.013
3	0.012
4	0.012
5	0.011
6	0.037
7	0.014
8	0.021
9	0.017
10	0.013
11	0.010
12	0.030
13	0.009
14	0.011
15	0.031
16	0.014
17	0.015
18	0.240
19	0.019
20	0.053
21	0.027
22	N/A
23	0.005
24	0.015
25	0.007
26	0.015
27	0.004

Example No.	Probe Displacement (EC ₅₀ , μM)
28	0.009
29	0.006
30	0.058
31	0.012
32	0.167
33	N/A
34	N/A.
35	0.814
36	0.291
37	0.432
38	0.509
39	0.017
40	0.038
41	0.0004 (HTRF)
42	0.0006 (HTRF)
43	0.0008 (HTRF)
45	0.0012 (HTRF)
46	0.0018 (HTRF)
47	0.0004 (HTRF)
48	0.0006 (HTRF)
49	0.0007 (HTRF)
50	0.0011 (HTRF)
51	0.158
52	0.107

Kit225 T Cell Assay

Kit225 T cells with a stably-integrated STAT-dependent luciferase reporter were plated in RPMI (Gibco) containing 10% heat-inactivated FBS (Gibco) and 100 U/mL PenStrep (Gibco). The cells were then stimulated with either 20 ng/mL human recombinant IL-23 or 200 U/mL human recombinant IFN α (PBL InterferonSource) for 5-

6 hours. Luciferase expression was measured using the STEADY-GLO® Luciferase Assay System (Promega) according to the manufacturer's instructions. Inhibition data were calculated by comparison to no inhibitor control wells for 0% inhibition and non-stimulated control wells for 100% inhibition. Dose response curves were generated to
 5 determine the concentration required to inhibit 50% of cellular response (IC₅₀) as derived by non-linear regression analysis.

Kit225 T Cell Inhibition Data

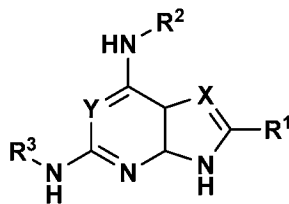
Example No.	IL-23 Kit225 Reporter (IC ₅₀ , μM)	IFN α Kit225 Reporter (IC ₅₀ , μM)
1	1.410	4.256
2	0.162	0.088
3	0.275	0.190
4	0.347	0.196
5	0.190	0.161
6	0.447	0.371
7	0.718	0.285
8	1.948	1.471
9	0.854	0.564
10	0.143	0.190
11	0.875	0.463
12	0.357	0.818
13	0.185	0.190
14	7.857	6.085
15	0.183	0.207
16	0.090	0.128
17	0.104	0.128
18	2.401	3.625
19	0.480	0.732
20	0.407	0.401
21	0.261	0.201

Example No.	IL-23 Kit225 Reporter (IC ₅₀ , μM)	IFN α Kit225 Reporter (IC ₅₀ , μM)
22	0.370	0.264
23	0.081	0.044
24	1.231	0.636
25	0.205	0.126
26	0.140	0.119
27	0.327	0.123
28	0.070	0.053
29	0.021	0.035
30	0.579	0.503
31	0.235	0.105
32	3.313	1.157
33	1.955	1.219
34	4.377	5.120
35	3.145	5.134
36	0.824	1.521
37	3.882	1.035
38	8.066	5.176
39	3.010	2.719
40	0.738	1.238
41	0.028	0.068
42	0.075	0.067
43	0.053	0.045
45	0.462	0.288
46	2.980	0.323
47	0.698	0.403
48	0.742	0.307
49	0.107	0.098
50	0.367	0.267
51	1.474	1.420

Example No.	IL-23 Kit225 Reporter (IC ₅₀ , μM)	IFN α Kit225 Reporter (IC ₅₀ , μM)
52	1.410	4.256

WHAT IS CLAIMED IS:

1. A compound having the following formula I:



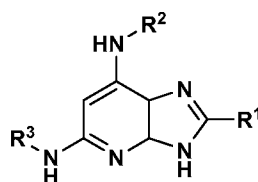
I

5

wherein:

- X is -N- or -CH-;
- Y is -N- or -CH-;
- C₁₋₆ alkyl or C₃₋₈ cycloalkyl;
- 10 R² is C₅₋₈ aryl or C₅₋₈ heteroaryl, substituted with 0-4 R^{2a};
- R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;
- R^{2b} is hydrogen or C₁₋₄ alkyl;
- 15 R^{2c} is hydrogen or C₁₋₄ alkyl;
- R^{2d} is hydrogen or C₁₋₄ alkyl;
- R^b is hydrogen or C₁₋₄ alkyl;
- R³ is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a};
- 20 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, C(O)- 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S or 2-pyrrolidone;
- R^{3b} is hydrogen or C₁₋₄ alkyl;
- 25 R^{3c} is hydrogen or C₁₋₄ alkyl;
- or a stereoisomer or pharmaceutically-acceptable salt thereof.

2. The compound according to claim 1, of the formula



wherein:

- 5 R^1 is hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;
 R^2 is C_{5-8} aryl or C_{5-8} heteroaryl, substituted with 0-4 R^{2a} ;
 R^{2a} is independently, at each occurrence, hydrogen, C_{1-6} alkyl, C_{1-6}
 alkoxy, $-S(O)_2R^{2b}$, $C(O)NR^{2c}R^{2d}$ or a 5-7 membered heterocycle containing 1-4
 heteroatoms selected from N, O, and S substituted with 0-2 R^b ;
 R^{2b} is hydrogen or C_{1-4} alkyl;
 10 R^{2c} is hydrogen or C_{1-4} alkyl;
 R^{2d} is hydrogen or C_{1-4} alkyl;
 R^b is hydrogen or C_{1-4} alkyl;
 R^3 is $C(O)-C_{3-10}$ cycloalkyl, C_{6-10} aryl or a 5-10 membered heterocyclyl containing
 1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a} ;
 15 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF_3 , CF_3 , CHF_2 ,
 CN, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)NR^{3b}R^{3c}$, 5-7 membered heterocycle containing 1-4
 heteroatoms selected from N, O, and S, or $C(O)-$ 5-7 membered heterocycle containing
 1-4 heteroatoms selected from N, O, and S;
 R^{3b} is hydrogen or C_{1-4} alkyl;
 20 R^{3c} is hydrogen or C_{1-4} alkyl;
 or a stereoisomer or pharmaceutically-acceptable salt thereof.

3. The compound according to claim 2

wherein:

- 25 R^1 is hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl;
 R^2 is C_{5-8} aryl or C_{5-8} heteroaryl, substituted with 0-3 R^{2a} ;
 R^{2a} is independently, at each occurrence, hydrogen, C_{1-6} alkyl, C_{1-6}
 alkoxy, $-S(O)_2R^{2b}$, $C(O)NR^{2c}R^{2d}$ or a 5-7 membered heterocycle containing 1-4
 heteroatoms selected from N, O, and S substituted with 0-2 R^b ;
 30 R^{2b} is hydrogen or C_{1-4} alkyl;

- R^{2c} is hydrogen or C₁₋₄ alkyl;
 R^{2d} is hydrogen or C₁₋₄ alkyl;
 R^b is hydrogen or C₁₋₄ alkyl;
 R^3 is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing
5 1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a};
 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂,
CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4
heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing
1-4 heteroatoms selected from N, O, and S;
10 R^{3b} is hydrogen or C₁₋₄ alkyl;
 R^{3c} is hydrogen or C₁₋₄ alkyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.
4. The compound according to claim 3
- 15 wherein:
- R^1 is hydrogen or C₁₋₄ alkyl;
 R^2 is phenyl or pyridyl, substituted with 0-2 R^{2a};
 R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆
alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4
20 heteroatoms selected from N, O, and S substituted with 0-2 R^b;
 R^{2b} is hydrogen or C₁₋₄ alkyl;
 R^{2c} is hydrogen or C₁₋₄ alkyl;
 R^{2d} is hydrogen or C₁₋₄ alkyl;
 R^b is hydrogen or C₁₋₄ alkyl;
25 R^3 is C(O)-C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl or a 5-10 membered heterocyclyl containing
1-4 heteroatoms selected from N, O, and S, each group substituted with 0-4 R^{3a};
 R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂,
CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4
heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing
30 1-4 heteroatoms selected from N, O, and S;
 R^{3b} is hydrogen or C₁₋₄ alkyl;
 R^{3c} is hydrogen or C₁₋₄ alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

5. The compound according to claim 4

wherein:

5 R¹ is C₁₋₄ alkyl;

R² is phenyl or pyridyl, substituted with 0-2 R^{2a};

R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂R^{2b}, C(O)NR^{2c}R^{2d} or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;

10 R^{2b} is hydrogen or C₁₋₄ alkyl;

R^{2c} is hydrogen or C₁₋₄ alkyl;

R^{2d} is hydrogen or C₁₋₄ alkyl;

R^b is hydrogen or C₁₋₄ alkyl;

15 R³ is C(O)-C₃₋₆ cycloalkyl, phenyl, pyridyl, pyrimidinyl, piperazinyl or pyridazinyl, substituted with 0-4 R^{3a};

R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S;

20 R^{3b} is hydrogen or C₁₋₄ alkyl;

R^{3c} is hydrogen or C₁₋₄ alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

6. The compound according to claim 5

25 wherein:

R¹ is C₁₋₄ alkyl;

R² is phenyl or pyridyl, substituted with 0-2 R^{2a};

R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂ C₁₋₄ alkyl, C(O)NH₂ or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b;

30 R^b is hydrogen or C₁₋₄ alkyl;

R^3 is C(O)-C₃₋₆ cycloalkyl, phenyl, pyrazolyl, pyridyl, pyrimidinyl, piperazinyl or pyridazinyl, substituted with 0-4 R^{3a} ;

R^{3a} is independently, at each occurrence, hydrogen, halo, OH, OCF₃, CF₃, CHF₂, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy, -C(O)NR^{3b}R^{3c}, 5-7 membered heterocycle containing 1-4
5 heteroatoms selected from N, O, and S, or C(O)- 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S;

R^{3b} is hydrogen or C₁₋₄ alkyl;

R^{3c} is hydrogen or C₁₋₄ alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

10

7. The compound according to claim 6,

wherein:

R^1 is C₁₋₄ alkyl;

R^2 is phenyl or pyridyl, substituted with 0-2 R^{2a} ;

R^{2a} is independently, at each occurrence, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, -S(O)₂
15 C₁₋₄ alkyl, C(O)NH₂ or a 5-7 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S substituted with 0-2 R^b ;

R^b is hydrogen or C₁₋₄ alkyl;

R^3 is C(O)-C₃₋₆ cycloalkyl, phenyl, pyrazolyl, pyridyl, pyrimidinyl, piperazinyl or
20 pyridazinyl, substituted with 0-2 R^{3a} ;

R^{3a} is independently, at each occurrence, hydrogen, halo, OH, CF₃, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, -C(O)NH₂, morpholinyl, or C(O)- morpholinyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

25

8. The compound according to claim 7,

wherein

R^1 is C₁₋₄ alkyl;

R^2 is phenyl or pyridyl, substituted with 0-2 R^{2a} ;

R^{2a} is independently, at each occurrence, hydrogen, CH₃, OCH₃, -S(O)₂ CH₃, or
30 C(O)NH₂;

R^3 is C(O)-C₃₋₆ cycloalkyl, phenyl, pyrazolyl, pyridyl, pyrimidinyl, piperazinyl or pyridazinyl, substituted with 0-2 R^{3a} ;

R^{3a} is independently, at each occurrence, hydrogen, halo, OH, CF₃, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, -C(O)NH₂, morpholinyl, or C(O)- morpholinyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.

5 9. A pharmaceutical composition comprising one or more compounds
according to any one of claims 1-8 and a pharmaceutically acceptable carrier or diluent.

10 10. A method of treating a disease, comprising administering to a patient in
need of such treatment a therapeutically-effective amount of a compound according to
any one of claims 1-8, wherein the disease is an inflammatory or autoimmune disease.

11. The method of claim 10 wherein the autoimmune disease is rheumatoid
arthritis, multiple sclerosis, inflammatory bowel disease, or lupus.

15

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/058645

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/131687 A2 (PORTOLA PHARM INC [US]; SONG YONGHONG [US]; XU QING [US]; BAUER SHAWN) 29 October 2009 (2009-10-29) compounds of claim 37; compunds of claim 50; paragraph [0008]; paragraph [0328]; -----	1-11
X	WO 2009/126515 A1 (IRM LLC [US]; NOVARTIS AG [CH]; CHEN BEI [US]; JIANG TAO [US]; MARSILJ) 15 October 2009 (2009-10-15) claim 5, compounds of formula (3C); examples 70-72 on pages 101-102; paragraf [0070]; -----	1-6,9,10
X	WO 2008/135232 A1 (CORTESE RICCARDO [IT]; MUSACCHIO ANDREA [IT]) 13 November 2008 (2008-11-13) compound (XV) on page 87; claim 1; claim 8, compound (XV); -----	1-6,9,10
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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

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

Date of the actual completion of the international search 29 November 2017	Date of mailing of the international search report 14/12/2017
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 Wolf, Claudia

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/058645

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MICHELLYS PIERRE-YVES ET AL: "Design and synthesis of novel selective anaplastic lymphoma kinase inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 26, no. 3, 17 November 2015 (2015-11-17), pages 1090-1096, XP029391884, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2015.11.049 compounds 16a and 16b on page 1092; page 1090 2nd paragraph "inflammatory myofibroblastic tumors"; -----</p>	1-6,9,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/058645

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