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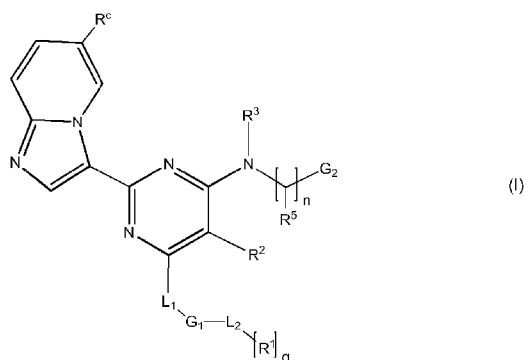
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(54) Title: IMIDAZOLOPYRIMIDIN-2-YL DERIVATIVES AS JAK INHIBITORS



(57) Abstract: New imidazopyrimidin-2-yl derivatives are disclosed; as well as process for their preparation, pharmaceutical compositions comprising them and their use as inhibitors of Janus Kinases (JAK) for the treatment of myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases.

IMIDAZOLOPYRIMIDIN-2-YL DERIVATIVES AS JAK INHIBITORS

Cytokines have critical functions in regulating many aspects of immunity and inflammation, ranging from the development and differentiation of immune cells to the suppression of immune responses. Type I and type II cytokine receptors lack intrinsic enzymatic activity capable of mediating signal transduction, and thus require association with tyrosine kinases for this purpose. The JAK family of kinases comprises four different members, namely JAK1, JAK2, JAK3 and TYK2, which bind to type I and type II cytokine receptors for controlling signal transduction (Murray PJ, (2007). The JAK-STAT signalling pathway: input and output integration. *J Immunol*, 178: 2623). Each of the JAK kinases is selective for the receptors of certain cytokines. In this regard, JAK-deficient cell lines and mice have validated the essential role of each JAK protein in receptor signalling: JAK1 in class II cytokine receptors (IFN and IL-10 family), those sharing the gp130 chain (IL-6 family) and the common gamma chain (IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21) (Rodig et al. (1998). Disruption of the JAK1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biological response. *Cell*, 93:373; Guschin et al. (1995). A major role for the protein tyrosine kinase JAK1 in the JAK/STAT signal transduction pathway in response to interleukin-6. *EMBO J.* 14: 1421; Briscoe et al. (1996). Kinase-negative mutants of JAK1 can sustain interferon-gamma-inducible gene expression but not an antiviral state. *EMBO J.* 15:799; JAK2 in hematopoietic factors (Epo, Tpo, GM-CSF, IL-3, IL-5) and type II IFNs (Parganas et al., (1998). JAK2 is essential for signalling through a variety of cytokine receptors. *Cell*, 93:385; JAK3 in receptors sharing the common gamma chain (IL-2 family) (Park et al., (1995). Developmental defects of lymphoid cells in JAK3 kinase-deficient mice. *Immunity*, 3:771; Thomis et al., (1995). Defects in B lymphocyte maturation and T lymphocyte activation in mice lacking JAK3. *Science*, 270:794; Russell et al., (1995). Mutation of JAK3 in a patient with SCID: Essential role of JAK3 in lymphoid development. *Science*, 270:797; and Tyk2 in the receptors of IL-12, IL-23, IL-13 and type I IFNs (Karaghiosoff et al., (2000). Partial impairment of cytokine responses in Tyk2-deficient mice. *Immunity*, 13:549; Shimoda et al., (2000). Tyk2 plays a restricted role in IFN γ signaling, although it is required for IL-12-mediated T cell function. *Immunity*, 13:561; Minegishi et al., (2006). Human Tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity*, 25:745).

Receptor stimulation leads sequentially to JAK activation by phosphorylation, receptor phosphorylation, STAT protein recruitment and STAT activation and dimerization. The

STAT dimer then functions as a transcription factor, translocating to the nucleus and activating the transcription of multiple response genes. There are seven STAT proteins identified: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. Each particular cytokine receptor associates preferentially with a particular STAT protein.

- 5 Some associations are independent of cell type (ex: IFNg- STAT1) while others may be cell type dependent (Murray PJ, (2007). The JAK-STAT signaling pathway: input and output integration. *J Immunol*, 178: 2623).

- The phenotype of deficient mice has provided insights on the function of each JAK and the cytokine receptors signaling through them. JAK3 associates exclusively with the common gamma chain of the receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokines. By virtue of this exclusive association, JAK3 knock out mice and common gamma chain deficient mice have an identical phenotype (Thomis et al., (1995). Defects in B lymphocyte maturation and T lymphocyte activation in mice lacking JAK3. *Science*, 270:794; DiSanto et al., (1995). Lymphoid development in mice with a targeted deletion of the interleukin 2 receptor gamma chain. *PNAS*, 92:377). Moreover, this phenotype is shared to a great extent with SCID patients that hold mutations/defects in the common gamma chain or JAK3 genes (O'Shea et al., (2004). JAK3 and the pathogenesis of severe combined immunodeficiency. *Mol Immunol*, 41: 727). JAK3-deficient mice are viable but display abnormal lymphopoiesis which leads to a reduced thymus size (10-100 fold smaller than wild type). JAK3-deficient peripheral T cells are unresponsive and have an activated/memory cell phenotype (Baird et al., (1998). T cell development and activation in JAK3-deficient mice. *J. Leuk. Biol.* 63: 669). The thymic defect in these mice strongly resembles that seen in IL-7 and IL-7 receptor knockout mice, suggesting that the absence of IL-7 signaling accounts for this defect in JAK3 $-/-$ mice (von Freeden-Jeffry et al., (1995). Lymphopenia in Interleukin (IL)-7 Gene-deleted Mice Identifies IL-7 as a non-redundant Cytokine. *J Exp Med*, 181:1519; Peschon et al, (1994). Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. *J Exp Med*, 180: 1955). These mice, like SCID humans, have no NK cells, probably due to the absence of IL-15 signaling, a survival factor for these cells. JAK3 knockout mice, unlike SCID patients, show deficient B cell lymphopoiesis while in human patients, B cells are present in circulation but are not responsive leading to hypoglobulinemia (O'Shea et al., (2004). JAK3 and the pathogenesis of severe combined immunodeficiency. *Mol Immunol*, 41: 727). This is explained by species-specific differences in IL-7 function in B and T cell development in mice and humans. On the other hand, Grossman et al. (1999. Dysregulated myelopoiesis in mice lacking JAK3. *Blood*, 94:932:939) have shown that the loss of

JAK3 in the T-cell compartment drives the expansion of the myeloid lineages leading to dysregulated myelopoiesis.

JAK2-deficient mice are embryonically lethal, due to the absence of definitive erythropoiesis. Myeloid progenitors fail to respond to Epo, Tpo, IL-3 or GM-CSF, while G-CSF and IL-6 signaling are not affected. JAK2 is not required for the generation, amplification or functional differentiation of lymphoid progenitors (Parganas et al., (1998). JAK2 is essential for signaling through a variety of cytokine receptors. *Cell*, 93:385).

JAK1-deficient mice die perinatally due to a nursing defect. JAK1 binds exclusively to the gp130 chain shared by the IL-6 cytokine family (i.e. LIF, CNTF, OSM, CT-1) and along with JAK3, is an essential component of the receptors sharing the common gamma chain, by binding to the non-shared receptor subunit. In this regard, JAK1-deficient mice show similar hematopoiesis defects as JAK3-deficient mice. In addition, they show defective responses to neurotrophic factors and to all interferons (class II cytokine receptors) (Rodig et al., (1998). Disruption of the JAK1 gene demonstrates obligatory and non-redundant roles of the JAKs in cytokine-induced biological response. *Cell*, 93:373).

Finally, Tyk2-deficient mice show an impaired response to IL-12 and IL-23 and only partially impaired to IFN-alpha (Karaghiosoff et al., (2000). Partial impairment of cytokine responses in Tyk2-deficient mice. *Immunity*, 13:549; Shimoda et al., (2000). Tyk2 plays a restricted role in IFNg signaling, although it is required for IL-12-mediated T cell function. *Immunity*, 13:561). However, human Tyk2 deficiency demonstrates that Tyk2 is involved in the signaling from IFN- α , IL-6, IL-10, IL-12 and IL-23 (Minegishi et al., (2006). Human Tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity*, 25:745).

The role of JAK kinases in transducing the signal from a myriad of cytokines makes them potential targets for the treatment of diseases in which cytokines have a pathogenic role, such as inflammatory diseases, including but not limited to allergies and asthma, chronic obstructive pulmonary disease (COPD), psoriasis, autoimmune diseases such as rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis, uveitis, transplant rejection, as well as in solid and hematologic malignancies such as myeloproliferative disorders, leukemia and lymphomas.

Inhibition of JAK kinases, especially JAK1 and JAK3, could give rise to potent immunosuppression which could be used therapeutically to prevent transplant rejection. In this regard, the JAK inhibitor CP-690,550 (tofacitinib, formerly tasocitinib)

has shown efficacy in several animal models of transplantation (heterotopic heart transplantation in mice, cardiac allografts implanted in the ear of mice, renal allotransplantation in cynomolgous monkeys, aorta and tracheal transplantation in rats) by prolonging the mean survival time of grafts (West K (2009). CP-690,550, a JAK3 inhibitor as an immunosuppressant for the treatment of rheumatoid arthritis, transplant rejection, psoriasis and other immune-mediated disorders. *Curr. Op. Invest. Drugs* 10: 491).

In rheumatoid joints, an imbalance between pro and anti-inflammatory cytokine activities favours the induction of autoimmunity, followed by chronic inflammation and tissue destruction. In this regard, the pathogenic role of IL-6 in rheumatoid arthritis (RA) has been validated clinically by the use of the anti-IL-6R antibody tocilizumab. IL-6 activates the transcription factor STAT3, through the use of JAK1 binding to the gp130 receptor chain (Heinrich et al., (2003). Principles of interleukin (IL)-6-type cytokine signaling and its regulation. *Biochem J.* 374: 1). Constitutive STAT3 mediates the abnormal growth and survival properties of RA synoviocytes (Ivashkiv and Hu (2003). The JAK/STAT pathway in rheumatoid arthritis: pathogenic or protective? *Arth & Rheum.* 48:2092). Other cytokines that have been implicated in the pathogenesis of arthritis include IL-12 and IL-23, implicated in Th1 and Th17 cell proliferation, respectively; IL-15, and GM-CSF (McInnes and Schett, (2007). Cytokines in the pathogenesis of rheumatoid arthritis. *Nature Rev Immunol.* 7:429.). The receptors for these cytokines also utilize JAK proteins for signal transduction, making JAK inhibitors potential pleiotropic drugs in this pathology. Consequently, administration of several JAK inhibitors in animal models of murine collagen-induced arthritis and rat adjuvant-induced arthritis has shown to reduce inflammation, and tissue destruction (Milici et al., (2008). Cartilage preservation by inhibition of Janus kinase 3 in two rodent models of rheumatoid arthritis. *Arth. Res.* 10:R14).

Inflammatory bowel disease (IBD) encompasses two major forms of intestinal inflammation: ulcerative colitis and Crohn's disease. Growing evidence has shown that multiple cytokines, including interleukins and interferons, are involved in the pathogenesis of IBD (Strober et al, (2002). The immunology of mucosal models of inflammation. *Annu Rev Immunol.* 20: 495). Activation of the IL-6/STAT3 cascade in lamina propria T cells has been shown to induce prolonged survival of pathogenic T cells (Atreya et al, (2000). Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: Evidence in Crohn's disease and experimental colitis in vivo. *Nature Med.* 6:583). Specifically, STAT3 has been shown

to be constitutively active in intestinal T cells of Crohn's disease patients and a JAK inhibitor has been shown to block the constitutive activation of STAT3 in these cells (Lovato et al, (2003). Constitutive STAT3 activation in intestinal T cells from patients with Crohn's disease. *J Biol Chem.* 278:16777). These observations indicate that the JAK-STAT pathway plays a pathogenic role in IBD and that a JAK inhibitor could be therapeutic in this setting.

Multiple sclerosis is an autoimmune demyelinating disease characterized by the formation of plaques in the white matter. The role of cytokines in the generation of multiple sclerosis has long been known. Potential therapies include blockade of IFN-g, IL-6, IL-12 and IL-23 (Steinman L. (2008). Nuanced roles of cytokines in three major human brain disorders. *J Clin Invest.* 118:3557), cytokines that signal through the JAK-STAT pathways. Use of tyrphostin, a JAK inhibitor, has been shown to inhibit IL-12-induced phosphorylation of STAT3, and to reduce the incidence and severity of active and passive experimental autoimmune encephalitis (EAE) (Bright et al., (1999) Tyrphostin B42 inhibits IL-12-induced tyrosine phosphorylation and activation of Janus kinase-2 and prevents experimental allergic encephalomyelitis. *J Immunol.* 162:6255). Another multikinase inhibitor, CEP701, has been shown to reduce secretion of TNF-alpha, IL-6 and IL-23 as well as the levels of phospho-STAT1, STAT3, and STAT5 in peripheral DCs of mice with EAE, significantly improving the clinical course of EAE in mice (Skarica et al, (2009). Signal transduction inhibition of APCs diminishes Th17 and Th1 responses in experimental autoimmune encephalomyelitis. *J. Immunol.* 182:4192.).

Psoriasis is a skin inflammatory disease which involves a process of immune cell infiltration and activation that culminates in epithelial remodeling. The current theory behind the cause of psoriasis states the existence of a cytokine network that governs the interaction between immune and epithelial cells (Nickoloff BJ. (2007). Cracking the cytokine code in psoriasis, *Nat Med*, 13:242). In this regard, IL-23 produced by dendritic cells is found elevated in psoriatic skin, along with IL-12. IL-23 induces the formation of Th17 cells which in turn produce IL-17 and IL-22, the last one being responsible for epidermis thickening. IL-23 and IL-22 induce the phosphorylation of STAT-3, which is found abundantly in psoriatic skin. JAK inhibitors may thus be therapeutic in this setting. In accordance, a JAK1/3 inhibitor, R348, has been found to attenuate psoriasiform skin inflammation in a spontaneous T cell-dependent mouse model of psoriasis (Chang et al., (2009). JAK3 inhibition significantly attenuates psoriasiform skin inflammation on CD18 mutant PL/J mice. *J Immunol.* 183:2183).

Th2 cytokine-driven diseases such as allergy and asthma could also be a target of JAK inhibitors. IL-4 promotes Th2 differentiation, regulates B-cell function and immunoglobulin class switching, regulates eotaxin production, induces expression of IgE receptor and MHC II on B cells, and stimulates mast cells. Other Th2 cytokines like IL-5 and IL-13 can also contribute to eosinophil recruitment in bronchoalveolar lavage by stimulating eotaxin production. Pharmacological inhibition of JAK has been shown to reduce the expression of IgE receptor and MHCII induced by IL-4 stimulation on B cells (Kudlacz et al., (2008). The JAK3 inhibitor CP-690,550 is a potent anti-inflammatory agent in a murine model of pulmonary eosinophilia. *European J. Pharm.* 582: 154). Furthermore, JAK3-deficient mice display poor eosinophil recruitment and mucus secretion to the airway lumen upon OVA challenge, as compared to wild type mice (Malaviya et al, (2000). Treatment of allergic asthma by targeting Janus kinase 3-dependent leukotriene synthesis in mast cells with 4-(3', 5'- dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline (WHI-P97). *JPET* 295:912.). In this regard, systemic administration of the CP-690,550 JAK inhibitor in mice has been shown to reduce the eosinophil count as well as the levels of eotaxin and IL13 in BAL in a murine model of pulmonary eosinophilia (Kudlacz et al., (2008). The JAK3 inhibitor CP-690,550 is a potent anti-inflammatory agent in a murine model of pulmonary eosinophilia. *European J. Pharm.* 582:154).

There is increasing evidence that cytokines play a pathogenetic role in ocular inflammatory disease such as uveitis or dry eye syndrome. Some cytokines implicated in experimental autoimmune uveitis, such as IL-2, IL-6, IL-12 and IFN γ , would be amenable to JAK inhibition (Vallochi et al, (2007). The role of cytokines in the regulation of ocular autoimmune inflammation. *Cytok Growth Factors Rev.* 18:135). In this regard, drugs or biologicals that interfere with IL-2 signaling such as cyclosporine or anti-IL-2 receptor antibody (daclizumab) have shown efficacy in the treatment of keratoconjunctivitis sicca and refractory uveitis, respectively (Lim et al, (2006). Biologic therapies for inflammatory eye disease. *Clin Exp Opht* 34:365). Similarly, allergic conjunctivitis, a common allergic eye disease characterized by conjunctival congestion, mast cell activation and eosinophil infiltration, could benefit from JAK inhibition. STAT6-deficient mice, showing decreased TH2-mediated immune responses which are normally triggered by IL-4, do not develop the classical early and late phase responses, suggesting that IL-4 pathway abrogation through JAK inhibition may be therapeutic in this setting (Ozaki et al, (2005). The control of allergic conjunctivitis by suppression of cytokine signaling (SOCS)3 and SOCS5 in a murine model. *J Immunol*, 175:5489).

There is growing evidence of the critical role of STAT3 activity in processes involved in tumorigenesis like cell cycle dysregulation, promotion of uncontrolled growth, induction of survival factors and inhibition of apoptosis (Siddiquee et al., (2008). STAT3 as a target for inducing apoptosis in solid and haematological tumors. *Cell Res.* 18: 254).

Antagonism of STAT3 by means of dominant-negative mutants or antisense oligonucleotides has shown to promote apoptosis of cancer cells, inhibition of angiogenesis and up-regulation of host immunocompetence. Inhibition of constitutively active STAT3 in human tumors by means of JAK inhibitors may provide a therapeutic option to the treatment of this disease. In this regard, the use of the JAK inhibitor tyrphostin has been shown to induce apoptosis of malignant cells and inhibit cell proliferation in vitro and in vivo (Meydan et al., (1996). Inhibition of acute lymphoblastic leukemia by a JAK-2 inhibitor. *Nature*, 379:645).

Hematological malignancies with dysregulated JAK-STAT pathways may benefit from JAK inhibition. Recent studies have implicated dysregulation of JAK2 kinase activity by chromosomal translocations and mutations within the pseudokinase domain (such as the JAK2V617F mutation) in a spectrum of myeloproliferative diseases (Ihle and Gililand, 2007), including polycythemia vera, myelofibrosis and essential thrombocythemia. In this regard, several JAK inhibitors that tackle JAK2 potently, such as TG-101209 (Pardanani et al., (2007). TG101209, a small molecular JAK2-selective inhibitor potently inhibits myeloproliferative disorder-associated JAK2V617F and MPLW515L/K mutations *Leukemia*. 21:1658–68), TG101348 (Wernig et al, (2008). Efficacy of TG101348, a selective JAK2 inhibitor, in treatment of a murine model of JAK2V617F-induced polycythemia vera. *Cancer Cell*, 13: 311), CEP701, (Hexner et al, (2008). Lestaurtinib (CEP701) is a JAK2 inhibitor that suppresses JAK2/STAT5 signaling and the proliferation of primary erythroid cells from patients with myeloproliferative disorders. *Blood*, 111: 5663), CP-690,550 (Manshour et al, (2008). The JAK kinase inhibitor CP-690,550 suppresses the growth of human polycythemia vera cells carrying the JAK2V617F mutation. *Cancer Sci*, 99:1265), and CYT387 (Pardanani et al., (2009). CYT387, a selective JAK1/JAK2 inhibitor: invitro assessment of kinase selectivity and preclinical studies using cell lines and primary cells from polycythemia vera patients. *Leukemia*, 23:1441) have been proposed for treating myeloproliferative diseases on the basis of their antiproliferative activity on cells carrying the JAK2V617F mutation. Similarly, T-cell leukemia due to human T-cell leukemia virus (HTLV-1) transformation is associated with JAK3 and STAT5 constitutive activation (Migone et al, (1995). Constitutively activated JAK-STAT

pathway in T cells transformed with HTLV-I. *Science*, 269: 79) and JAK inhibitors may be therapeutic in this setting (Tomita et al, (2006). Inhibition of constitutively active JAK-STAT pathway suppresses cell growth of human T-cell leukemia virus type I-infected T cell lines and primary adult T-cell leukemia cells. *Retrovirology*, 3:22). JAK1-activating mutations have also been identified in adult acute lymphoblastic leukemia of T cell origin (Flex et al, (2008). Somatic acquired *JAK1* mutations in adult acute lymphoblastic leukemia. *J. Exp. Med.* 205:751-8) pointing to this kinase as a target for the development of novel antileukemic drugs.

Conditions in which targeting of the JAK pathway or modulation of the JAK kinases, particularly JAK1, JAK2 and JAK3 kinases, are contemplated to be therapeutically useful for the treatment or prevention of diseases include: neoplastic diseases (e.g. leukemia, lymphomas, solid tumors); transplant rejection, bone marrow transplant applications (e.g., graft- versus-host disease); autoimmune diseases (e.g. diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease); respiratory inflammation diseases (e.g. asthma, chronic obstructive pulmonary disease), inflammation-linked ocular diseases or allergic eye diseases (e.g. dry eye, glaucoma, uveitis, diabetic retinopathy, allergic conjunctivitis or age-related macular degeneration) and skin inflammatory diseases (e.g., atopic dermatitis or psoriasis).

In view of the numerous conditions that are contemplated to benefit by treatment involving modulation of the JAK pathway or of the JAK Kinases it is immediately apparent that new compounds that modulate JAK pathways and use of these compounds should provide substantial therapeutic benefits to a wide variety of patients.

Provided herein are novel pyrimidin-2-yl derivatives for use in the treatment of conditions in which targeting of the JAK pathway or inhibition of JAK kinases can be therapeutically useful.

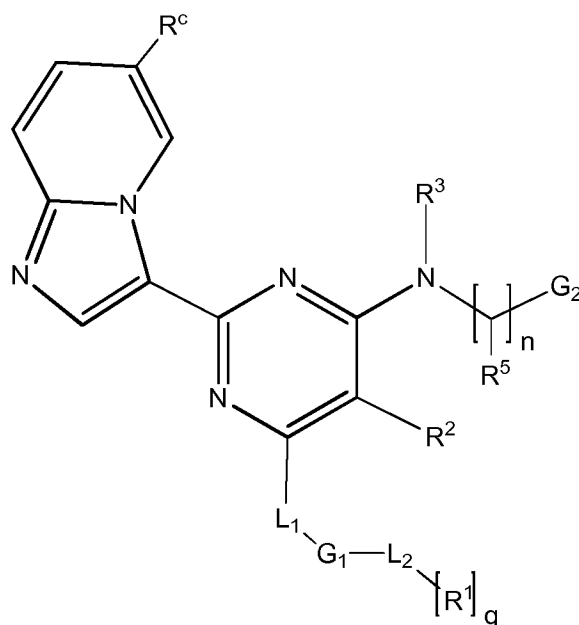
The compounds described in the present invention are simultaneously potent JAK1, JAK2 and JAK3 inhibitors, i.e. pan-JAK inhibitors. This property makes them useful for the treatment or prevention of pathological conditions or diseases such as myeloproliferative disorders (such as polycythemia vera, essential thrombocythemia or myelofibrosis), leukemia, lymphomas and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (such as ulcerative

colitis or Crohn's disease), inflammation-linked ocular diseases or allergic eye diseases (such as dry eye, uveitis, or allergic conjunctivitis), allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), and skin inflammatory diseases (such as atopic dermatitis or psoriasis).

5

It has now been found that certain pyrazolopyrimidin-2-yl derivatives are novel and potent JAK inhibitors and can therefore be used in the treatment or prevention of these diseases.

- 10 Thus the present invention is directed to compounds of formula (I), or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer or deuterated derivative thereof:



Formula (I)

- 15 wherein

G₁ is selected from the group consisting of a linear or branched C₁₋₄ alkyl group, a monocyclic C₅₋₈ aryl group, a monocyclic C₃₋₈ cycloalkyl group, a monocyclic 5- to 8-membered heteroaryl group containing at least one heteroatom selected from O, S and N and a saturated or non-saturated monocyclic 4- to 8- membered heterocyclyl group containing at least one heteroatom selected from O, S and N, wherein the alkyl, aryl, cycloalkyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted with one or more substituents selected from a halogen atom, a hydroxyl group, -CHO group, a C₁₋₂ alkyl group, a C₁₋₂ hydroxyalkyl group, a di (C₁₋₂ alkyl)amino-C₁₋₄ alkyl group, a C₁₋₂ carboxyalkyl group, oxo group, and -NR'-SO₂-R'' group,

25

L_1 is selected from the group consisting of a $-(CH_2)_{(0-1)}-$, $-(CH_2)_{(0-1)}-O-$, $-NR^x-(CH_2)_{(0-1)}-$ group, wherein R^x is selected from the group consisting of a hydrogen atom and a C_{1-2} alkyl group optionally substituted with $-(CH_2)_{(0-2)}NR'R''-$ group,

- 5 L_2 is selected from the group consisting of a $-(CH_2)_p-$, $-(CH_2)-NR-$, $-O-(CH_2)_{(0-2)}$, $-(CH_2)_{(0-1)}-C(O)-(CH_2)_{(0-1)}-O-(CH_2)_{(0-1)}-$, $-C(O)-$, $-S-$ and $-NR-$ group, wherein R represents a hydrogen atom or a C_{1-4} alkyl group optionally substituted with a group selected from $-NR'R''-$ group and a phenyl group wherein said phenyl group is optionally substituted with a hydroxyl group,

10

R^1 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group optionally substituted with a $-NR'R''$ group or with $-OH$ group, a monocyclic C_{5-8} aryl group, a monocyclic C_{3-8} cycloalkyl group, a mono- or bicyclic 5- to 14-

- 15 N and a mono- or bicyclic 5- to 14- membered heterocyclyl group containing at least one heteroatom selected from O, S and N, wherein the aryl, cycloalkyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a linear or branched C_{1-6} alkyl group, a linear or branched C_{1-6} hydroxyalkyl group, a linear or
- 20 branched C_{1-4} alkoxy group, a $-(O)_{(0-1)}(CH_2)_{(0-3)}-NR'R''$ group, a $-CO-O-R^d$ group, a $-CH_2-R^e$ group, a monocyclic 5-to 8-membered heterocyclyl group containing at least one heteroatom selected from O, S and N and a monocyclic 5-to 8-membered heteroaryl group containing at least one heteroatom selected from O, S and N wherein said heterocyclyl and heteroaryl group independently are optionally substituted with
- 25 one or more substituents selected from the group consisting of a C_{1-2} alkyl group and a $-NR'R''$ group;

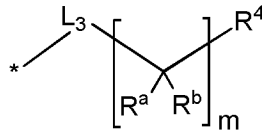
R^2 is selected from the group consisting of a halogen atom and a linear or branched, non-substituted C_{1-4} alkyl group and a NH_2 group,

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R^3 is selected from the group consisting of a hydrogen atom, a C_{1-4} alkyl group and a $-(CH_2)_{(2-4)}NR'R''-$ group,

- G_2 is selected from the group consisting of a monocyclic C_{5-8} aryl group, a mono or a
- 35 bicyclic C_{3-10} cycloalkyl group, a monocyclic 5- to 8- membered heteroaryl group containing at least one heteroatom selected from O, S and N and a monocyclic 5- to 8- membered heterocyclyl group containing at least one heteroatom selected from O, S

and N, wherein the aryl, cycloalkyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from a halogen atom, a hydroxyl group, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a C₁₋₂ hydroxyalkyl group, -NR'R'' group and a group of formula (a):



wherein

L₃ represents a direct bond, -CO- group, -S(O)₂-(CH₂)₍₀₋₁₎- group, or a -C(O)O- group, a -NH-CO- group,

- 10 R⁴ is selected from the group consisting of a hydroxyl group, a -(CH₂)₍₀₋₁₎-CN group, a -CF₃ group, a mono cyclic 3 to 8-membered heterocyclyl group containing at least one heteroatom selected from N, O and S, a monocyclic C₅₋₈ aryl group, a linear or branched C₁₋₄ alkyl group, a linear or branched C₁₋₄ alkoxy group, a linear or branched C₁₋₄ hydroxyalkyl group, a C₁₋₂ haloalkyl and a C₁₋₄ aminoalkyl group wherein the alkyl and the hydroxyalkyl groups are optionally substituted with one or more methyl groups,

- 15 R^a and R^b are independently selected from the group consisting of a hydrogen atom, a hydroxyl, a C₁₋₄ alkyl group or R^a and R^b together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl group or a 3- to 5-membered heterocyclic group containing at least one heteroatom selected from N, O and S,

R⁵ is selected from the group consisting of a hydrogen atom and a linear or branched C₁₋₄ alkyl group,

- 25 R^c is selected from the group consisting of a hydrogen atom, a halogen atom, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a C₅₋₈ aryl group, a 5- to 8- membered heteroaryl group containing at least one heteroatom selected from O, S and N and a -NR'R'' group, wherein the heteroaryl group is optionally substituted with one or more substituents selected from the group consisting of a halogen atom and a C₁₋₄ alkyl group,

- 30 R^d represents a linear or branched C₁₋₄ alkyl group optionally substituted with one or more substituents selected from a phenyl group, a methyl group and a -NR'R'',
R^e is selected from the group consisting of a monocyclic C₅₋₈ aryl group and a
35 monocyclic 5- to 8- membered heteroaryl group containing at least one heteroatom

selected from O, S and N, which cyclic ring are optionally substituted with one or more substituents selected from a hydroxyl group, a linear or branched C₁₋₄ alkyl group and a -CF₃ group,

- 5 R' and R'' independently represents a hydrogen atom, a C₁₋₄ alkyl group or a C₃₋₆ cycloalkyl group, or R' and R'' together with the nitrogen atom to which they are attached form a 4 to 6 membered N-containing heterocyclic group optionally containing one or more additional heteroatom selected from N, S and O, and optionally substituted with a dimethylamino group,

10

n, m and q independently have a value of 0 or 1,

p has a value of 0, 1 or 2,

- 15 with the proviso that the compound is not any one of the following compounds:

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-1-((R)-3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-2,3-dihydroxypropan-1-one,

- 20 (R)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholino-N-(piperidin-3-yl)pyrimidin-4-amine, and

(R)-tert-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidine-1-carboxylate.

- 25 The invention further provides synthetic processes and intermediates described herein, which are useful for preparing said compounds.

The invention is also directed to a compound of the invention as described herein for use in the treatment of the human or animal body by therapy.

30

The invention also provides a pharmaceutical composition comprising the compounds of the invention and a pharmaceutically-acceptable diluent or carrier.

- 35 The invention is also directed to the compounds of the invention as described herein, for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid

malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases; more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

The invention is also directed to use of the compounds of the invention as described herein, in the manufacture of a medicament for treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases; more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis; comprising administering a therapeutically effective amount of the compounds of the invention or a pharmaceutical composition of the invention to a subject in need of such treatment.

In another embodiment of the present invention, the pathological condition or disease is selected from respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated; function disorders and neurological disorders; cardiovascular diseases; viral infection; metabolism/endocrine function disorders; neurological disorders and pain; bone marrow and organ transplant rejection; myelo-dysplastic syndrome; myeloproliferative disorders (MPDs); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors.

In a preferred embodiment, the pathological condition or disease is selected from leukemia, lymphomas and solid tumors, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, autoimmune hemolytic anemia, type I diabetes, cutaneous vasculitis, cutaneous lupus erythematosus, dermatomyositis, blistering diseases including but not limited to pemphigus vulgaris, bullous pemphigoid and epidermolysis bullosa, asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, cough, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

The invention also provides a combination product comprising (i) the compounds of the invention as described herein; and (ii) one or more additional active substances which are known to be useful in the treatment of myeloproliferative disorders (such as polycythemia vera, essential thrombocythemia or myelofibrosis), leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (such as ulcerative colitis or Crohn's disease), dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

As used herein the term C₁-C₆ alkyl embraces linear or branched radicals having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, n-hexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl and iso-hexyl radicals.

As used herein, the term C₁-C₄ hydroxyalkyl embraces linear or branched alkyl radicals having 1 to 4 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

As used herein, the term C₁₋₂ carboxyalkyl embraces alkyl radicals having 1 or 2 carbon atoms, any one of which may be substituted with one or more carboxy radicals. Examples of such radicals include carboxymethyl and carboxyethyl.

5 As used herein, the term (C₁-C₄)alkylamino embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 4 carbon atoms attached to a divalent -NH- radical. Preferred (C₁-C₄)alkylamino radicals include methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, sec-butylamino and t-butylamino.

10

As used herein, the term di-(C₁-C₂)alkylamino embraces radicals containing a trivalent nitrogen atoms with two linear or branched alkyl radicals of 1 to 2 carbon atoms in each alkyl radical. Preferred di-(C₁-C₂)alkylamino radicals include dimethylamino, diethylamino and methyl(ethyl)amino.

15

As used herein, the term C₁-C₄ alkoxy (or alkyloxy) embraces linear or branched oxy-containing radicals each having alkyl portions of 1 to 4 carbon atoms. Examples of C₁-C₄ alkoxy radicals include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy or t-butoxy.

20

As used herein, the term C₃-C₈ cycloalkyl embraces saturated monocyclic carbocyclic radicals having from 3 to 8 carbon atoms, preferably from 3 to 7 carbon atoms. An optionally substituted C₃-C₈ cycloalkyl radical is typically unsubstituted or substituted by 1, 2 or 3 substituents which may be the same or different. When a C₃-C₈ cycloalkyl radical carries 2 or more substituents, the substituents may be the same or different. Typically the substituents on a C₃-C₈ cycloalkyl group are themselves unsubstituted.

25

Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

30

As used herein, the term C₅-C₈ aryl radical embraces typically a C₅-C₈, preferably C₅-C₆ monocyclic aryl radical such as phenyl. A said optionally substituted C₅-C₈ aryl radical is typically unsubstituted or substituted by 1, 2 or 3 substituents which may be the same or different. When a C₅-C₈ aryl radical carries 2 or more substituents, the substituents may be the same or different. Unless otherwise specified, the substituents on a C₅-C₈ aryl group are typically themselves unsubstituted.

35

As used herein, the term 5- to 14- membered heteroaryl radical embraces typically a 5- to 14- membered ring system, preferably a 5- to 10- membered ring system, more preferably a 5- to 6- membered ring system, comprising at least one heteroaromatic ring and containing at least one heteroatom selected from O, S and N. A 5- to 14- membered heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

A said optionally substituted 5- to 14- membered heteroaryl radical is typically unsubstituted or substituted by 1, 2 or 3 substituents which may be the same or different. When a 5- to 14- membered heteroaryl radical carries 2 or more substituents, the substituents may be the same or different. Unless otherwise specified, the substituents on a 5- to 14- membered heteroaryl radical are typically themselves unsubstituted.

Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, benzofuranyl, oxadiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, benzothiazolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, quinoliziny, cinnolinyl, triazolyl, indoliziny, indoliny, isoindoliny, isoindolyl, imidazolidinyl, pteridinyl, thianthrenyl, pyrazolyl, 2H-pyrazolo[3,4-d]pyrimidinyl, 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d] pyrimidinyl and the various pyrrolopyridyl radicals.

As used herein, the term 4- to 14-membered heterocyclyl radical embraces typically a non-aromatic, saturated or unsaturated C₄-C₁₄ carbocyclic ring system, preferably C₅-C₁₀ carbocyclic ring system, more preferably C₅-C₆ carbocyclic ring system, in which one or more, for example 1, 2, 3 or 4 of the carbon atoms preferably 1 or 2 of the carbon atoms are replaced by a heteroatom selected from N, O and S. A heterocyclyl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. When a 5 to 14-membered heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

A said optionally substituted 4- to 14-membered heterocyclyl radical is typically unsubstituted or substituted by 1, 2 or 3 substituents which may be the same or different. Typically, the substituents on a 4 to 14-membered heterocyclyl radical are themselves unsubstituted.

Examples of 4- to 14-membered heterocyclyl radicals include azetidiny, piperidyl, pyrrolidyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl, imidazolidinyl, imidazolyl, oxiranyl, thiaranyl, aziridinyl, oxetanyl, thiatanyl, azetidiny, 4,5-dihydro-oxazolyl, 2-benzofuran-1(3H)-one, 1,3-dioxol-2-one, tetrahydrofuranyl, 3-aza-tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,4-azathianyl, oxepanyl, thiephanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiezepanyl, 1,4-diazepanyl, tropanyl, (1S,5R)-3-azabicyclo[3.1.0]hexyl, 3,4-dihydro-2H-pyranyl, 5,6-dihydro-2H-pyranyl, 2H-pyranyl, 2,3-hydrobenzofuranyl, 1,2,3,4-tetrahydropyridinyl, 1,2,5,6-tetrahydropyridinyl, isoindolinyl and indolinyl.

Where a 4- to 14-membered heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, some of the atoms, radicals, moieties, chains and cycles present in the general structures of the invention are "optionally substituted". This means that these atoms, radicals, moieties, chains and cycles can be either unsubstituted or substituted in any position by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains and cycles are replaced by chemically acceptable atoms, radicals, moieties, chains and cycles. When two or more substituents are present, each substituent may be the same or different. The substituents are typically themselves unsubstituted.

As used herein, the term halogen atom embraces chlorine, fluorine, bromine and iodine atoms. A halogen atom is typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

Compounds containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, in the form of racemic mixtures and in the form of mixtures enriched in one or more stereoisomer. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers, diastereomers, and stereoisomer-enriched mixtures.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively,

the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or

fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art. Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1 % diethylamine. Concentration of the eluate affords the enriched mixture. Stereoisomer conglomerates may be separated by conventional techniques known to those skilled in the art. See, e.g. "Stereochemistry of Organic Compounds" by Ernest L. Eliel (Wiley, New York, 1994).

As used herein, the term pharmaceutically acceptable salt refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid; and organic acids, for example citric, fumaric, gluconic, glutamic, lactic, maleic, malic, mandelic, mucic, ascorbic, oxalic, pantothenic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic, p-toluenesulphonic acid, xinafoic (1-hydroxy-2-naphthoic acid), napadisilic (1,5-naphthalenedisulfonic acid) and the like. Particularly preferred are salts derived from fumaric, hydrobromic, hydrochloric, acetic, sulfuric, methanesulfonic, xinafoic, and tartaric acids.

Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Particularly preferred are ammonium, calcium, magnesium, potassium and sodium salts.

Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including alkyl amines, arylalkyl amines, heterocyclic amines, cyclic amines, naturally-occurring amines and the like, such as arginine,

betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine
5 resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

Other preferred salts according to the invention are quaternary ammonium compounds wherein an equivalent of an anion (X^-) is associated with the positive charge of the N
10 atom. X^- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and *p*-toluenesulphonate. X^- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate,
15 maleate, oxalate, succinate or trifluoroacetate. More preferably X^- is chloride, bromide, trifluoroacetate or methanesulphonate.

As used herein, an N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

20 The compounds of the invention may exist in both unsolvated and solvated forms. The term solvate is used herein to describe a molecular complex comprising a compound of the invention and an amount of one or more pharmaceutically acceptable solvent molecules. The term hydrate is employed when said solvent is water. Examples of
25 solvate forms include, but are not limited to, compounds of the invention in association with water, acetone, dichloromethane, 2-propanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate.

30 Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a dihydrate. Additionally, it is specifically contemplated that in the present invention less than one solvent molecule may be associated with one
35 molecule of the compounds of the present invention, such as a hemihydrate.

Furthermore, solvates of the present invention are contemplated as solvates of

compounds of the present invention that retain the biological effectiveness of the non-solvate form of the compounds.

The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S . Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, ^3H , and carbon-14, ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

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.

Preferred isotopically-labeled compounds include deuterated derivatives of the compounds of the invention. As used herein, the term deuterated derivative embraces compounds of the invention where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium (D or ^2H) is a stable isotope of hydrogen which is present at a natural abundance of 0.015 molar %.

Hydrogen deuterium exchange (deuterium incorporation) is a chemical reaction in which a covalently bonded hydrogen atom is replaced by a deuterium atom. Said exchange (incorporation) reaction can be total or partial.

Typically, a deuterated derivative of a compound of the invention has an isotopic enrichment factor (ratio between the isotopic abundance and the natural abundance of that isotope, i.e. the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen) for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 3500 (52.5% deuterium incorporation).

In a preferred embodiment, the isotopic enrichment factor is at least 5000 (75% deuterium). In a more preferred embodiment, the isotopic enrichment factor is at least 6333.3 (95% deuterium incorporation). In a most preferred embodiment, the isotopic enrichment factor is at least 6633.3 (99.5% deuterium incorporation). It is understood that the isotopic enrichment factor of each deuterium present at a site designated as a site of deuteration is independent from the other deuteration sites.

The isotopic enrichment factor can be determined using conventional analytical methods known to an ordinary skilled in the art, including mass spectrometry (MS) and nuclear magnetic resonance (NMR).

Prodrugs of the compounds described herein are also within the scope of the invention. Thus certain derivatives of the compounds of the present invention, which derivatives may have little or no pharmacological activity themselves, when administered into or onto the body may be converted into compounds of the present invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

In the case of compounds that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystalline or polymorphic forms, or in an amorphous form, all of which are intended to be within the scope of the present invention.

Typically, R^c is selected from the group consisting of a hydrogen atom, a halogen atom and a methyl group, preferably, a hydrogen atom or a fluorine atom.

- 5 Typically, G_1 is selected from the group consisting of a monocyclic C_{5-8} aryl group, a monocyclic 5- to 8- membered heteroaryl group containing at least one heteroatom selected from O, S and N and a monocyclic 5- to 8- membered heterocyclyl group containing at least one heteroatom selected from O, S and N, wherein the aryl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or two
10 substituents selected from a halogen atom, a hydroxyl group, a C_{1-4} alkyl group and a C_{1-2} hydroxyalkyl group.

- In a preferred embodiment, G_1 is selected from the group consisting of a phenyl group, a pyridyl group and a monocyclic 6- membered heterocyclyl group containing at least
15 one heteroatom selected from O and N, wherein the phenyl, pyridyl and heterocyclyl groups are unsubstituted or substituted by one or two substituents selected from a halogen atom, and a C_{1-2} alkyl group. More preferably, G_1 is selected from the group consisting of a phenyl group, a pyridyl group, a morpholinyl and a piperazinyl group.

- 20 Typically, L_1 is selected from the group consisting of a $-(CH_2)_{(0-1)}-$, $-NR^x-(CH_2)_{(1)}-$ group, wherein R^x is selected from the group consisting of a hydrogen atom and a C_{1-2} alkyl group optionally substituted with $-(CH_2)_{(0-2)}NR'R''$ - group, wherein R' and R'' independently represents a hydrogen atom or a methyl group, preferably, L_1 is selected from the group consisting of direct bond and $-NR^x-(CH_2)_{(1)}-$ group, wherein R^x is
25 selected from the group consisting of a hydrogen atom and a methyl group.

In a still preferred embodiment, L_1 represents a direct bond.

- Typically, L_2 is selected from the group consisting of a $-(CH_2)_p-$, $-(CH_2)_{(0-1)}-C(O)-(CH_2)_{(0-1)}-O-(CH_2)_{(0-1)}-$, and $-NR-$ group, wherein R represents a hydrogen atom or a methyl group, wherein p has a value of 0 or 1, preferably, L_2 is selected from the group consisting of a $-(CH_2)_p-$, $-N(CH_3)-$, $-(CH_2)-C(O)-O-(CH_2)-$, and $-(CH_2)-C(O)-O-$, wherein p has a value of 0 or 1. More preferably, L_2 is selected from the group consisting of
30 $-(CH_2)_p-$, wherein p has a value of 0 or 1

- 35 Typically, R^1 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group, a monocyclic C_{5-8} aryl group, a mono- or bicyclic 5- to 14-

membered heteroaryl group containing at least one heteroatom selected from N and a monocyclic 5- to 8- membered heterocyclyl group containing at least one heteroatom selected from N, wherein the aryl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a
5 halogen atom, a hydroxyl group, a linear or branched C₁₋₅ alkyl group, a linear C₁₋₂ alkoxy group, and $-(O)_{(0-1)}(CH_2)_{(0-3)}-NR'R''$ group, wherein R' and R'' independently represents a hydrogen atom or a methyl group, and q has a value of 0 or 1.

In a preferred embodiment, R¹ is selected from the group consisting of a hydrogen
10 atom, a branched C₃₋₄ alkyl group a monocyclic C₅₋₈ aryl group and a monocyclic 5- to 7- membered heterocyclyl group containing one or two nitrogen atom as heteroatom, wherein the aryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a a linear or branched C₁₋₅ alkyl group, a $-(O)(CH_2)_2-NR'R''$ group and a $-NR'R''$ - group, wherein R' and R''
15 independently represents a hydrogen atom or a methyl group, and q has a value of 0 or 1.

In a still preferred embodiment, R¹ is selected from the group consisting of a hydrogen atom, a phenyl group and a monocyclic 6- to 7- membered heterocyclyl group
20 containing one or two nitrogen atom as heteroatom, wherein the phenyl and heterocyclyl groups are substituted by one substituent selected from the group consisting of a methyl group, $-(O)(CH_2)_2-NR'R''$ group and a $-NR'R''$ - group, wherein both R' and R'' represents a methyl group, and q has a value of 0 or 1.

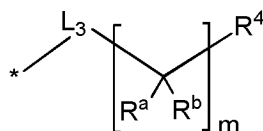
25 Typically, R² is selected from the group consisting of a halogen atom and a C₁₋₂ alkyl group, preferably a fluorine atom and a methyl group, more preferably, a fluorine atom.

Typically, R³ is selected from the group consisting of a hydrogen atom, a C₁₋₂ alkyl group and $-(CH_2)_{(2-4)}NR'R''$ - group, wherein R' and R'' are as defined in claim 1,
30 preferably, R³ is selected from a hydrogen atom and a $-(CH_2)_{(2)}NR'R''$ - group, wherein both R' and R'' represent a methyl group.

Typically, R⁵ is selected from the group consisting of a hydrogen atom and a methyl group, and n has a value of 0 or 1, preferably n has a value of 0.

35 Typically, G₂ is selected from the group consisting of a monocyclic N-containing 6- to 8- membered heteroaryl group and a monocyclic 5- to 8- membered heterocyclyl group

containing at least one heteroatom selected from O, S and N, wherein the heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from a halogen atom, a hydroxyl group, a methyl group and a group of formula (a):



5

wherein

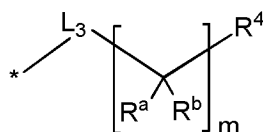
L₃ represents –CO– group, or a –C(O)O– group,

R⁴ is selected from the group consisting of a cyano group, a –CF₃ group, a methyl group,

- 10 R^a and R^b are independently selected from the group consisting of a hydrogen atom, a hydroxyl, a methyl group and,
m has a value of 0 or 1.

In a preferred embodiment, G₂ represents a monocyclic N-containing 6- membered heterocyclyl group which is substituted by a group of formula (a):

15



wherein

L₃ represents –CO– group, both R^a and R^b represent a hydrogen atom, m has a value of 1 and R⁴ represents a ciano group..

20

In a still preferred embodiment, compounds of the present invention having formula (I), wherein:

R^c represents a hydrogen atom or a fluorine atom,

G₁ is selected from the group consisting of a phenyl group, a pyridyl group, a

- 25 morpholinyl group and a piperazinyl group,

L₁ represents a direct bond,

L₂ is selected from the group consisting of a –(CH₂)_p–, wherein p has a value of 0 or 1,

R¹ is selected from the group consisting of a hydrogen atom, a phenyl group and a monocyclic 6- to 7- membered heterocyclyl group containing one or two nitrogen atom

- 30 as heteroatom, wherein the phenyl and heterocyclyl groups are substituted by one substituent selected from the group consisting of a methyl group, –(O)(CH₂)₂–NR'R''

group and a $-NR'R''$ - group, wherein both R' and R'' represents a methyl group, and q has a value of 0 or 1,

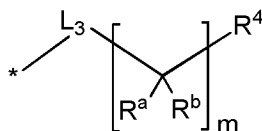
R^2 is a fluorine atom,

R^3 is selected from a hydrogen atom and a $-(CH_2)_{(2)}NR'R''$ - group, wherein both R' and

5 R'' represent a methyl group,

R^5 represents a hydrogen atom and n has a value of 1.

G_2 represents a monocyclic N-containing 6- membered heterocyclyl group which is substituted by a group of formula (a):



10 wherein

L_3 represents $-\text{CO}-$ group,

both R^a and R^b represent a hydrogen atom, m has a value of 1, and

R^4 represents a cyano group.

15 In another embodiment, compounds of the present invention having formula (I) wherein R^c is selected from the group consisting of a hydrogen atom and a fluorine group,

G_1 is selected from the group consisting of a phenyl group, a monocyclic N-containing 6- membered heteroaryl group and a monocyclic 4-8- membered heterocyclyl group

20 containing at least one heteroatom selected from O and N, wherein the aryl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one substituent selected from a fluorine atom, a hydroxyl group, a methyl group, a hydroxymethyl group, a carboxymethyl group, an oxo group, and a hydroxyethyl group,

25 L_1 is selected from the group consisting of a direct bond and $-\text{NH}-$ group,

L_2 is selected from the group consisting of a $-(CH_2)_p-$, $-\text{O}-(CH_2)_{(0-2)}-$, $-\text{C}(\text{O})-\text{O}-(CH_2)-$, $-(CH_2)-\text{C}(\text{O})-\text{O}-(CH_2)-$, $-\text{C}(\text{O})-(CH_2)-\text{O}-(CH_2)-$, $-(CH_2)-\text{C}(\text{O})-\text{O}-$, $-\text{C}(\text{O})-$ and $-\text{N}(\text{CH}_3)-$ group, wherein p has a value of 0 or 1.

30

R^1 is selected from the group consisting of a hydrogen atom, a t-butyl group, a hydroxymethyl group, a phenyl group, a mono- or bicyclic 5- to 9- membered heteroaryl group containing at least one N as heteroatom and a monocyclic 5-7- membered heterocyclyl group containing at least one heteroatom selected from O and N, wherein

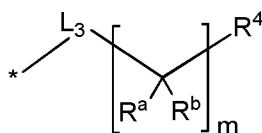
35 the phenyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one

or more substituents selected from the group consisting of a fluoroine atom, a hydroxyl group, a methyl group, a dihydroxypropyl group, a methoxy group, a dimethylamino group, $-(O)-(CH_2)_2-N(CH_3)_2$ group;

5 R^2 is selected from the group consisting of a fluorine atom and a methyl group,

R^3 is selected from the group consisting of a hydrogen atom and a $-(CH_2)_{(2-3)}NR'R''$ -group,

10 G_2 is selected from the group consisting of a pyridyl group substituted with a fluorine atom, and a piperidinyI substituted with a group of formula (a):



wherein

L_3 represents a direct bond, $-CO-$ group, or a $-C(O)O-$ group,

15 R^4 is selected from the group consisting of a phenyl group, hydroxyl group, $-(CH_2)_{(0-1)}-CN$, a $-CF_3$ group, an methyl group, an ethyl group, a methoxy group, a hydroxypropyl group, a hydroxymethyl group optionally substituted with one or two methyl groups,

Both R^a and R^b are a hydrogen atom

20

R^5 is selected from the group consisting of a hydrogen atom and a methyl group,

R' and R'' independently represents a hydrogen atom or a methyl group, or R' and R'' together with the nitrogen atom to which they are attached form a 5 to 6 membered N-containing heterocyclic group optionally containing one or more additional heteroatom selected from N, and O, and optionally substituted with a methyl group or a dimethylamino group,

25

n , m and q independently have a value of 0 or 1.

30

p has a value of 0, 1 or 2.

Particular individual compounds of the invention include:

(R)-benzyl 4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazine-1-carboxylate,

35

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-benzyl 2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetate,

5 (R)-3-(3-((6-(4-(benzyloxy)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(2-(benzyloxy)acetyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

10 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(2-hydroxyacetyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetic acid,

15 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-tert-butyl 2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetate,

20 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

25 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(benzyloxy)piperidin-1-yl)-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

30 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(S)-(1-(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-((1-(5-fluoropyridin-2-yl)ethyl)amino)pyrimidin-4-yl)piperidin-4-yl)methanol,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-hydroxyphenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

35 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methoxybenzyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-hydroxybenzyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(1-(5-fluoropyridin-2-yl)ethyl)-6-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)pyrimidin-4-amine,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(morpholinomethyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

N-(1-benzylpiperidin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-amine,

3-((3R)-3-((6-(4-((1-(2,3-dihydroxypropyl)-1H-benzo[d]imidazol-2-

yl)methyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

N-((1S,2S,4R)-bicyclo[2.2.1]heptan-2-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-4-amine,

4-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octan-1-ol,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(S)-N1-(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)-N1-(1-(5-fluoropyridin-2-yl)ethyl)-N2,N2-dimethylethane-1,2-diamine,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(1,4-diazepan-1-yl)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(6-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-

5 oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methyl-6-(2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

10 (R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(4-(dimethylamino)piperidin-1-yl)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

15 (R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

20 (R)-3-(3-((3-(dimethylamino)propyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-

25 oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)(2-(pyrrolidin-1-yl)ethyl)amino)piperidin-1-yl)-3-

oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(6-(4-(dimethylamino)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-

30 oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(6-(2-(dimethylamino)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-

oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-

35 oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(3-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)(2-(4-methylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)-3-oxopropanenitrile,

2-((3R)-3-([F-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholin-4-yl]pyrimidin-4-yl)amino)piperidin-1-yl)-2-oxoethanol

- 10 or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer or deuterated derivative thereof.

Of outstanding interest are:

(R)-benzyl 2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetate,

(R)-tert-butyl 2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetate

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(1,4-diazepan-1-yl)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(6-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-

oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(6-(2-(dimethylamino)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer or deuterated derivative thereof.

GENERAL SYNTHETIC PROCEDURES

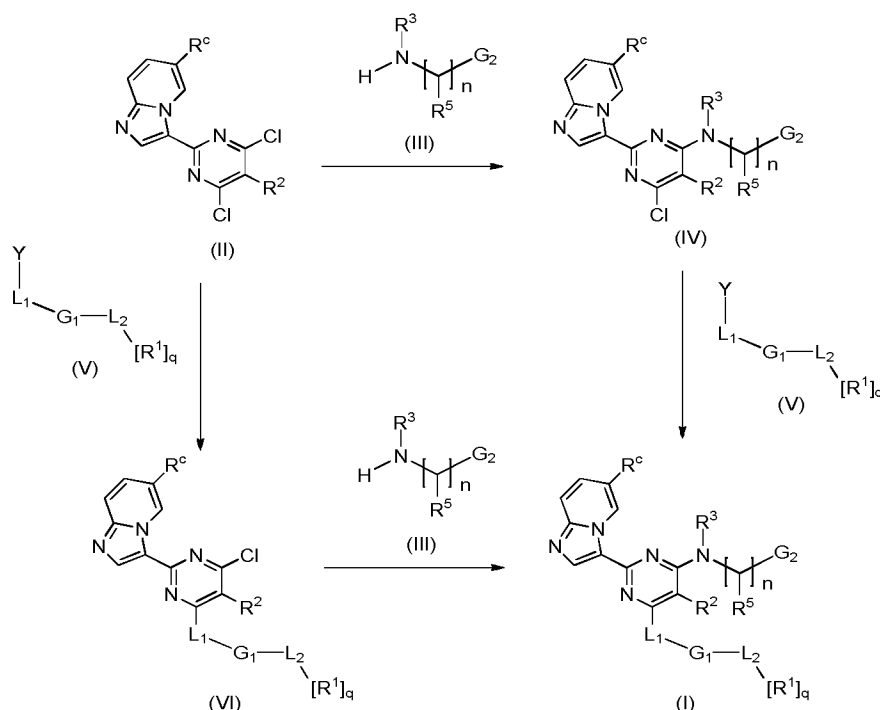
The compounds of the invention can be prepared using the methods and procedures described herein or using similar methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group, as well as suitable conditions for protection and deprotection, are well known in the art. For example, numerous protecting groups, and their introduction and removal

are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

Processes for preparing compounds of the invention are provided as further
5 embodiments of the invention and are illustrated by the procedures below.

According to one embodiment of the present invention, compounds of general formula
(I) may be prepared by the following synthetic route as illustrated in Scheme 1:



Scheme 1

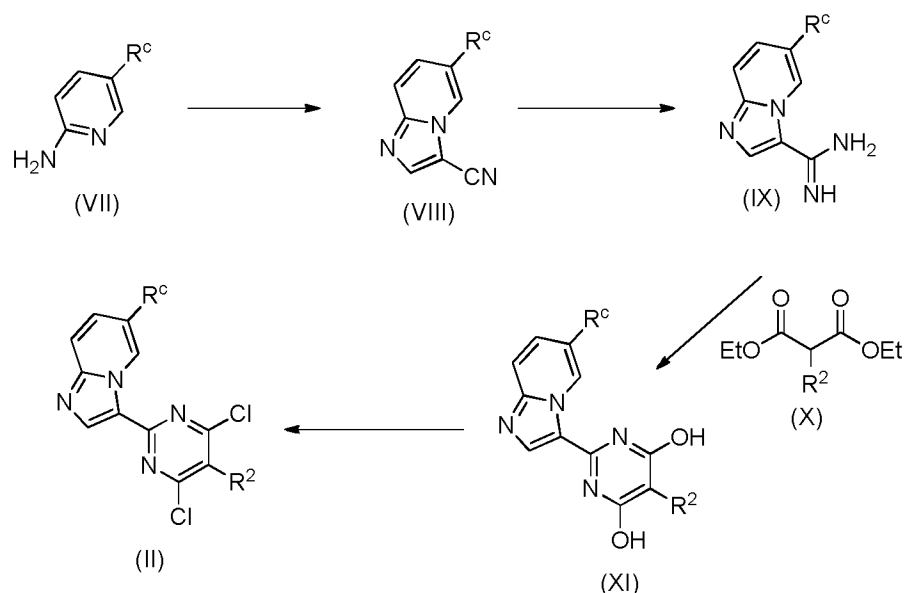
Treatment of dichloropyrimidines of formula (II) with amines of formula (III) in the
15 presence of a base such as triethylamine or sodium hydrogencarbonate in a solvent
such as methanol or ethanol at temperatures ranging from ambient temperature to
reflux gives rise to compounds of formula (IV).

In the particular case where L_1 is a direct bond and G_1 is an aryl or heteroaryl ring,
compounds of formula (I) may be obtained from chloropyrimidines of formula (IV) by
20 reaction with compounds of formula (V), where Y is a boronic acid or a boronate ester,
under Suzuki-Miyaura reaction conditions (Miyaura, N.; Suzuki, A. Chem. Rev. 1995,
95, 2457). Such reactions may be catalysed by a suitable palladium catalyst such as
[1,1'-bis(diphenyl phosphino)ferrocene]dichloropalladium(II) complex with

dichloromethane or tetrakis (triphenylphosphine)palladium(0) in a solvent such as toluene, methanol, 1,4-dioxane or 1,2-dimethoxyethane in the presence of a base such as cesium carbonate or sodium carbonate at temperatures ranging from 80 °C to 110 °C with or without the use of microwave irradiation. Boronic acids or boronates of formula (V) where L_1 is a direct bond, G_1 is an aryl or heteroaryl ring and Y is a boronic acid or boronate ester may be commercially available or may be prepared from the corresponding bromoderivatives of formula (V), where Y is a bromine atom, by treatment with an appropriate boron reagent such as 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane with a palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex, in a solvent such as 1,4-dioxane, in the presence of a base such as potassium acetate at temperatures ranging from 80-120 °C.

In another particular case where L_1 is a direct bond and G_1 is an heterocyclyl group attached to the pyrimidine ring through a nitrogen atom, compounds of formula (I) may be prepared by reaction of chloroderivatives of formula (IV) with heterocyclic amines of formula (V), where Y is an hydrogen atom, in the presence of a base such as sodium hydrogencarbonate or *N*-ethyl-*N*-isopropylpropan-2-amine without the use of a solvent or in a solvent such as *N,N*-dimethylacetamide or 1-methyl-2-pyrrolidine at temperatures ranging from 80-130 °C with or without the use of microvawe irradiation. Alternatively, compounds of formula (I) can be also prepared by reaction of chloropyrimidines of formula (VI) with amines of formula (III) using a suitable catalyst such as tris(dibenzylideneacetone)dipalladium(0), in the presence of a ligand such as 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)-biphenyl, and a base, for example sodium *tert*-butoxide, in a solvent such as toluene at a temperature ranging from 80 °C to reflux. Reaction of dichloropyrimidines of formula (II) with heterocyclic amines of formula (V), where Y is an hydrogen atom, in the presence of a base such as sodium hydrogencarbonate in a solvent such as ethanol at temperatures ranging from 60 °C to reflux provides compounds of formula (VI) where G_1 is an heterocyclyl group attached to the pyrimidine ring through a nitrogen atom.

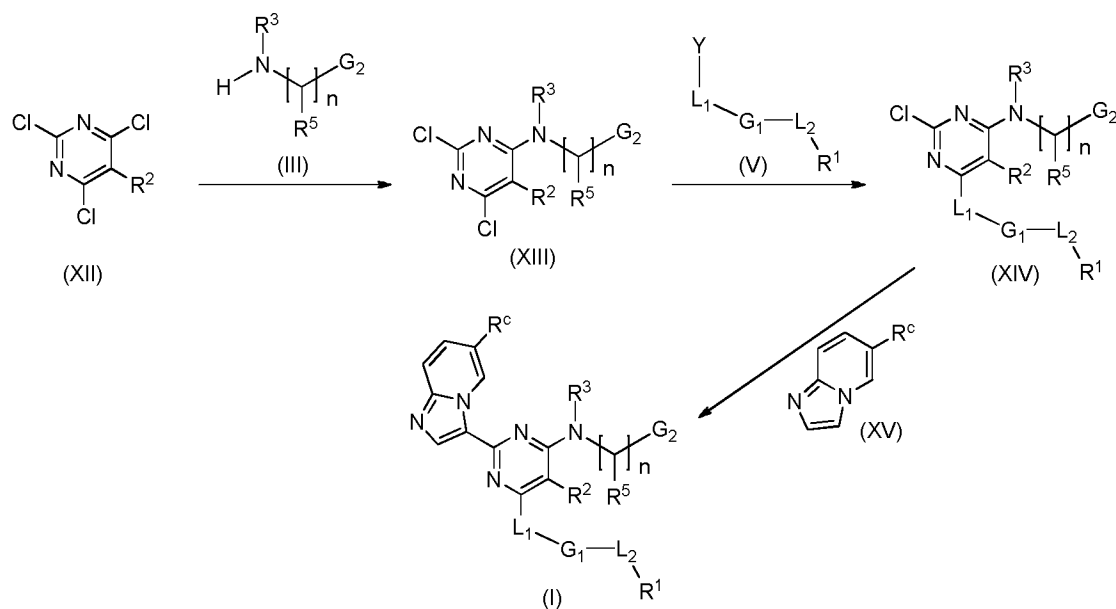
Compounds of formula (II) may be prepared as illustrated in Scheme 2:



Scheme 2

Bicyclic nitriles of formula (VIII) may be prepared by treatment of 2-aminopyridines of formula (VII) with 3-methoxyacrylonitrile in the presence of *N*-bromosuccinimide in a suitable solvent such as a dioxane/water mixture at temperatures ranging from ambient temperature to reflux. Nitriles of formula (VIII) may be converted to the corresponding amidines of formula (IX) by first formation of the corresponding imidate by reaction with alkoxy derivatives such as sodium methoxide or sodium ethoxide in a suitable alcoholic solvent at temperatures ranging from 0 °C to reflux followed by addition of ammonium chloride or ammonium hydroxide. Amidines of formula (IX) may be reacted with malonate esters of formula (X) to give dihydroxypyrimidines of formula (XI). Such reactions may be carried out in the presence of a suitable base such as sodium methoxide in a solvent such as methanol at temperatures ranging from 0 °C to ambient temperature. Dihydroxypyrimidines of formula (XI) may be converted to dichloropyrimidines of formula (II) by treatment with a suitable chlorinating agent, for example phosphorus(V) oxychloride, at temperatures ranging from 25 °C to reflux.

In the particular case where L_1 is a direct bond and G_1 is an aryl or heteroaryl ring, compounds of general formula (I) may also be prepared by an alternative synthetic approach as shown in Scheme 3:



Scheme 3

Treatment of trichloropyrimidines of formula (XII) with amines of formula (III) in the presence of a base such as triethylamine, *N*-ethyl-*N*-isopropylpropan-2-amine or sodium hydrogencarbonate in a solvent such as ethanol at -20 °C gives rise to compounds of formula (XIII). Compounds of formula (XIV) may be obtained from dichloropyrimidines of formula (XIII) by reaction with compounds of formula (V), where Y is a boronic acid or a boronate ester, under Suzuki-Miyaura reaction conditions. Such reactions may be catalysed by a suitable palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) in a solvent such as 1,2-dimethoxyethane in the presence of a base such as sodium carbonate at 80 °C. Reaction of chloropyrimidines of formula (XIV) with imidazopyridines of formula (XV) in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) and a base such as potassium acetate in a solvent such as *N,N*-dimethylacetamide at 150 °C provides compounds of formula (I).

In another particular case, compounds of formula (I), where R³ is an hydrogen atom, may undergo further reaction with a suitable base, such as sodium hydride, in a solvent such as *N,N'*-dimethylformamide, followed by the addition of an alkylating agent, such as (2-chloroethyl)dimethylamine hydrochloride or related haloalkyl derivatives containing one or more tertiary amines at temperatures ranging from ambient temperature to 80 °C, to furnish compounds of formula (I), where R³ is now an alkyl group containing one or more tertiary amine groups.

In yet another particular case, compounds of formula (I), in which the residue at G₁, G₂ or R¹ contains an alcohol, phenol or carboxylic acid moiety functionalized with an appropriate protecting group such as benzyl (Bn) or methoxy (OMe), may be deprotected at the alcohol, phenol or carboxylic acid moiety under standard conditions (5 *Greene's Protective Groups in Organic Synthesis*, ISBN: 0471697540). In the particular case of primary alcohols, the free alcohol may then be oxidized under standard conditions to give the corresponding aldehyde.

In yet another particular case, compounds of formula (I) and compounds of formula (10 (XIV) in which the residue at G₁ contains an aldehyde moiety, may be further reacted with a primary or secondary amine in the presence of a reductive agent, such as sodium triacetoxyborohydride, in a solvent such as dichloromethane at ambient temperature to give compounds of formula (I) and compounds of formula (XIV) in which the residue at G₁ is now a secondary or tertiary amine.

In yet another particular case, compounds of formula (I), in which the residue at G₁, G₂ or R¹ contains an amine moiety functionalized with an appropriate protecting group such as *tert*-butoxycarbonyl (BOC) or benzyloxycarbonyl (CBZ), may be deprotected at the amine moiety under standard conditions (15 *Greene's Protective Groups in Organic Synthesis*, ISBN: 0471697540). The free amine may then be further functionalized under standard conditions to give the corresponding amides, carbamates and *N*-alkylated amines.

Starting compounds are commercially available or may be obtained following the (25 conventional synthetic methods already known in the art.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples (1-51) (including Preparation Examples (Preparations 1-70)) and are given in order to provide a person skilled in the (30 art with a sufficiently clear and complete explanation of the present invention, but should not be considered as limiting of the essential aspects of its subject, as set out in the preceding portions of this description.

PREPARATION 1

(35 **6-Fluoroimidazo[1,2-a]pyridine-3-carboximidamide**
a) 6-Fluoroimidazo[1,2-a]pyridine-3-carbonitrile

1-Bromopyrrolidine-2,5-dione (15.8 g, 89.2 mmol) was added in portions to a solution of (*E*)-3-methoxyacrylonitrile (7.49 mL, 89.2 mmol) in a 3:1 mixture of dioxane/water (600 mL) at 0 °C. The solution was stirred for 30 minutes at 0 °C and then 5-fluoropyridin-2-amine (5.0 g, 44.6 mmol) was added. Temperature was allowed to increase to ambient temperature during 2h and the mixture was stirred for 16h at 60 °C. The organic solvent was removed under reduced pressure and the crude was partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organic phase was separated, dried over sodium sulfate, filtered and the solvent was evaporated to dryness. The crude product was purified by flash chromatography (15 to 50% ethyl acetate in hexanes) to give the title compound as a brown solid (6.7 g, 94%).

LRMS (*m/z*): 162 (*M*+1)⁺

¹H NMR δ (300 MHz, DMSO-*d*₆): 7.71 (ddd, 1H), 7.93 (dd, 1H), 8.49 (s, 1H), 8.98 (bs, 1H).

b) 6-Fluoroimidazo[1,2-*a*]pyridine-3-carboximidamide

Sodium methoxide (0.19 g, 3.4 mmol) was added to a solution of 6-fluoroimidazo[1,2-*a*]pyridine-3-carbonitrile (Preparation 1a, 5.6 g, 34.8 mmol) in methanol (80 mL) and the resulting mixture was stirred at ambient temperature for 17h. Ammonium chloride (2.05 g, 38.3 mmol) was then added and the mixture was heated to reflux for 4h. The solvent was removed under reduced pressure and the resulting solid was washed with ethyl acetate (8x30 mL) and dried to yield the title compound (4.3 g, 58%) as a brown solid that was used in the next synthetic step without further purification.

LRMS (*m/z*): 179 (*M*+1)⁺

¹H NMR δ (300 MHz, DMSO-*d*₆): 7.70 (dd, 1H), 7.89 (dd, 1H), 8.35 (s, 1H), 8.85 (bs, 1H).

PREPARATION 2

3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-*a*]pyridine

a) 5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidine-4,6-diol

6-Fluoroimidazo[1,2-*a*]pyridine-3-carboximidamide (Preparation 1b, 2.0 g, 8.39 mmol,) was added portionwise to a stirred solution of sodium (0.46 g, 20.21 mmol) in methanol (35 mL) at 0 °C. Diethyl 2-fluoromalonate (2.65 mL, 16.8 mmol) was then added and the reaction mixture was stirred from 0 °C to room temperature overnight. The solvent was evaporated to dryness and the resulting crude was dissolved in water (90 mL). After stirring for 30 min, a 2N solution of hydrochloric acid was added until acid pH.

The solid formed was filtered and dried to yield the title compound (0.95 g, 43%) as a brown solid that was used in the next synthetic step without further purification.

LRMS (m/z): 265 (M+1)⁺

¹H NMR δ (300 MHz, DMSO-*d*₆): 7.6 (s, 1H), 7.8 (s, 1H), 8.7 (s, 1H), 10.1 (s, 1H), 12.6 (bs, 1H).

b) 3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridine

A mixture of 5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diol (Preparation 2a, 0.95 g, 3.60 mmol) and phosphorus(V) oxychloride (7.35 mL, 78.7 mmol) was stirred at 110 °C for 24h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was separated, washed with brine, dried over magnesium sulphate and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane/dichloromethane) to yield the title compound (0.71 g, 63%) as a solid.

LRMS (m/z): 302 (M+1)⁺

PREPARATION 3

(*R*)-*Tert*-butyl 3-(6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl) pyrimidin-4-ylamino)piperidine-1-carboxylate

(*R*)-*Tert*-butyl 3-aminopiperidine-1-carboxylate (560 mg, 2.79 mmol) was added to a solution of 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridine (Preparation 2b, 420 mg, 1.39 mmol) and triethylamine (0.55 mL, 4.17 mmol) in ethanol (100 mL) and the resulting mixture was stirred at 80 °C for 48h. After cooling to room temperature, the solvent was evaporated under reduced pressure and water was added. The precipitate formed was filtered and purified by flash chromatography (dichloromethane to dichloromethane/methanol 95:5) to yield the title compound (400 mg, 62%).

LRMS (m/z): 465 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.4 (s, 9H), 1.6 - 2.1 (m, 4H), 3.5 (m, 3H), 3.8 (d, 1H), 4.2 (m, 1H), 5.4 (bs, 1H), 7.3 (m, 1H), 7.7 (dd, 1H), 8.5 (s, 1H), 9.7 (dd, 1H).

PREPARATION 4

(*R*)-Benzyl 4-(6-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazine-1-carboxylate

A mixture of (*R*)-*tert*-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3, 0.62 g, 1.34 mmol) and benzyl piperazine-1-carboxylate (1.29 mL, 6.68 mmol) in 1-methyl-2-pyrrolidone (5 mL) was subjected to microwave irradiation for 2h at 130 °C. After cooling to ambient temperature, the crude was partitioned between water and dichloromethane. The organic layer was separated, washed with brine, dried by Phase Separator and the solvent was evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 9:1) to give the title compound (726 mg, 84%).

LRMS (*m/z*): 650 (*M*+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.65 (s, 9H), 2.85 (t, 4H), 3.38 (t, 6H), 3.64 - 3.75 (m, 6H), 4.19 (m, 1H), 5.18 (s, 2H), 7.17 - 7.34 (m, 3H), 7.35 - 7.41 (m, 4H) 7.64 - 7.69 (dd, 2H).

PREPARATION 5

(*R*)-Benzyl 4-(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)piperazine-1-carboxylate

Trifluoroacetic acid (0.3 mL, 4.02 mmol) was added to a solution of (*R*)-benzyl 4-(6-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)piperazine-1-carboxylate (Preparation 4, 0.27 g, 0.42 mmol) in dichloromethane (5 mL) and the mixture was stirred overnight at room temperature. The mixture was diluted with dichloromethane and washed with water. The organic layer was dried by Phase Separator and the solvent was evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol, 9:1) to give the title compound (171 mg, 75%) as an hygroscopic solid.

LRMS (*m/z*): 550 (*M*+1)⁺

PREPARATION 6

(*R*)-*tert*-Butyl 3-((6-(4-(benzyloxy)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

A mixture of (*R*)-*tert*-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3), 4-(benzyloxy)piperidine, catalytic *N,N*-dimethylpyridin-4-amine and *N*-ethyl-*N*-isopropylpropan-2-amine were reacted according the experimental procedure as described in Preparation 4 heating at 100 °C for 4h. The residue was purified by flash chromatography

(dichloromethane to dichloromethane/methanol 9:1) to give the title compound (75%) as a brown oil.

LRMS (m/z): 621 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.60 (s, 9H), 1.72 - 1.86 (m, 4H), 1.98 - 2.10 (m, 4H), 2.37 (t, 2H), 3.37 - 3.48 (m, 4H), 3.67 - 3.73 (m, 1H), 4.05 - 4.20 (m, 2H), 4.62 (s, 2H), 4.82 - 4.89 (bs, 1H), 7.15 - 7.22 (m, 1H), 7.27 - 7.40 (m, 5H), 7.62 - 7.69 (m, 1H), 8.42 (s, 1H), 9.78 - 9.82 (m, 1H).

PREPARATION 7

10 **(R)-6-(4-(Benzyloxy)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-4-amine**

Obtained as a solid (45%) from (*R*)-*tert*-butyl 3-((6-(4-(benzyloxy)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 6) and trifluoroacetic acid following the experimental
15 procedure as described in Preparation 5.

LRMS (m/z): 521 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.67 - 1.80 (m, 4H), 1.95 - 2.05 (m, 4H), 3.13 - 3.22 (m, 3H), 3.27 - 3.45 (m, 2H), 3.63 - 3.71 (m, 2H), 3.91 - 4.07 (m, 2H), 4.37 - 4.42 (m, 1H), 4.61 (s, 2H), 5.43 (bs, 1H), 7.07 - 7.15 (m, 1H), 7.28 - 7.34 (m, 4H), 7.36 - 7.40 (m, 2H), 7.52 - 7.68 (dd, 1H), 8.27 (s, 1H), 9.50 - 9.54 (dd, 1H).
20

PREPARATION 8

(R)-tert-Butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

25 A mixture of (*R*)-*tert*-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3, 0.10 g, 0.22 mmol) and piperidin-4-yl methanol (0.125 g, 1.09 mmol) was heated in a Kimble vial to 130 °C for 1h. After cooling to ambient temperature, water (10 mL) was added and the solid formed was filtered, washed with water and dried under vacuum to yield the title
30 compound (110 mg, 90%) as a solid.

LRMS (m/z): 544 (M+1)⁺

PREPARATION 9

35 **(R)-(1-(5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)piperidin-4-yl)methanol**

Trifluoroacetic acid (0.16 mL, 2.08 mmol) was added to a solution of (*R*)-*tert*-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(hydroxymethyl)piperidin-1-yl)

pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 8, 0.11 g, 0.2 mmol) in dichloromethane (1 mL) and the mixture was stirred at ambient temperature for 3h. Solvent was evaporated and the resulting crude was partitioned between dichloromethane and a saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate solution, dried over magnesium sulphate and the solvent was evaporated to yield the title compound (74 mg, 80%).

LRMS (m/z): 444 (M+1)+

10 PREPARATION 10

(R)-Tert-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

A mixture of (R)-tert-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3, 0.10 g, 0.22 mmol), azetidin-3-ol hydrochloride (0.125 g, 0.43 mmol) and sodium hydrogencarbonate (0.074 g, 0.88 mmol) was stirred in a Kimble vial to 120 °C for 2h. After cooling to ambient temperature, water (4 mL) was added and the solid formed was filtered, washed with water and dried under vacuum to yield the title compound (87 mg, 78%).

LRMS (m/z): 502 (M+1)+

20

PREPARATION 11

(R)-1-(5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)azetidin-3-ol

Trifluoroacetic acid (0.507 mL, 6.58 mmol) was added to a solution of (R)-tert-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 10, 0.22 g, 0.44 mmol) in dichloromethane (2 mL) and the mixture was stirred at ambient temperature for 8h. Solvent was evaporated and the residue was treated with diethyl ether, filtered and dried *in vacuo* to yield the title compound (0.258 g, 59%) as a trifluoroacetate salt.

30

LRMS (m/z): 402 (M+1)+

PREPARATION 12

3-(4,6-Dichloro-5-methylpyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridine a)2-(6-Fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidine-4,6-diol

35

A mixture of sodium methoxide (prepared from sodium (0.62 g, 27.84 mmol) and methanol (40 mL)), 6-fluoroimidazo[1,2-a]pyridine-3-carboximidamide (Preparation 1b, 2.0 g, 9.32 mmol) and diethyl 2-methylmalonate (3.2 mL, 18.55 mmol) were reacted

according to the experimental procedure as described in Preparation 2a. The solvent was evaporated to dryness, water (70 mL) was added to the residue and the resulting mixture was stirred at ambient temperature for 2h. Dichloromethane was then added and the aqueous layer was separated. 2N Aqueous solution of hydrogen chloride was added to the aqueous layer until the pH was acidic and then the solvent was removed. The residue was treated with diethyl ether and filtered to yield the title compound (0.90 g, 11%) as a solid that was used in the next synthetic step without further purification.

LRMS (m/z): 261 (M+1)⁺

b) 3-(4,6-Dichloro-5-methylpyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridine

A mixture of 2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidine-4,6-diol (Preparation 12a, 0.90 g, 3.46 mmol) and phosphorous(V) oxychloride (5 mL) were reacted according to the experimental procedure as described in Preparation 2b. The reaction mixture was evaporated to dryness with an ice trap and the residue was partitioned between water and dichloromethane. The organic layer was separated by Phase Separator and the solvent was evaporated to dryness to give the title compound (155 mg, 13%) as a brown oil.

LRMS (m/z): 297/299 (M+1)⁺

PREPARATION 13

(R)-tert-Butyl 3-((6-chloro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate

Obtained as a dark yellow solid (99%) from 3-(4,6-dichloro-5-methylpyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridine (Preparation 12b) and (R)-tert-butyl 3-aminopiperidine-1-carboxylate following the experimental procedure as described in Preparation 3 followed by purification of the crude product by flash chromatography (dichloromethane/methanol 9:1).

LRMS (m/z): 461 (M+1)⁺

¹H NMR δ (400 MHz, CDCl₃): 1.24 - 1.76 (m, 4H), 2.15 (s, 3H), 3.25 - 3.77 (m, 4H), 4.25 (bs, 1H), 7.21 - 7.27 (m, 1H), 7.68 (dd, 1H), 8.54 (s, 1H), 9.84 (dd, 1H).

PREPARATION 14

(R)-tert-Butyl 3-((6-(4-(benzyloxy)piperidin-1-yl)-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate

A mixture of (R)-tert-butyl 3-((6-chloro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 13, 0.25 g, 0.54

mmol), 4-(benzyloxy)piperidine (0.618 g, 3.23 mmol), catalytic *N,N*-dimethylpyridin-4-amine (5 mg), *N*-ethyl-*N*-isopropyl propano-2-amine (0.142 mL, 0.82 mmol) and 1-methyl-2-pyrrolidone (4 mL) was subjected to microwave irradiation for 4h at 130 °C. After cooling to ambiente temperature, the crude was partitioned between water and dichloromethane. The organic layer was separated, washed with brine, dried by Phase Separator and the solvent evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 9:1) to give the title compound (158 mg, 43%).

LRMS (m/z): 616 (M+1)⁺

PREPARATION 15

(*R*)-6-(4-(Benzyloxy)piperidin-1-yl)-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methyl-*N*-(piperidin-3-yl)pyrimidin-4-amine

Obtained as a solid (90%) from (*R*)-*tert*-butyl 3-((6-(4-(benzyloxy)piperidin-1-yl)-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 14) and trifluoroacetic acid following the experimental procedure described in Preparation 9.

LRMS (m/z): 516 (M+1)⁺

PREPARATION 16

(*S*)-6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-*N*-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidin-4-amine

A mixture of 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-*a*]pyridine (Preparation 2b, 0.50 g, 1.66 mmol), (*S*)-1-(5-fluoropyridin-2-yl)ethanamine hydrochloride (0.39 g, 2.78 mmol) and sodium hydrogencarbonate (0.60 g, 7.14 mmol) in ethanol (10 mL) was heated to 85 °C overnight. After cooling to ambient temperature, water was added and the brown solid formed was filtered, washed with water and dried under vacuum to yield the title compound (0.61 g, 87%).

LRMS (m/z): 405 (M+1)⁺

PREPARATION 17

(*R*)-*tert*-Butyl 3-((6-(4-(benzyloxy)phenyl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

A Schlenk tube was charged with (*R*)-*tert*-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3, 0.18 g, 0.38 mmol), (4-(benzyloxy)phenyl)boronic acid (0.09 g, 0.38 mmol), sodium carbonate (0.08 g, 0.75 mmol), toluene (5 mL) and methanol (1.5 mL).

The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated at 90 °C for 72h. After cooling at ambient temperature, the mixture was diluted with ethyl acetate, washed with 4% aqueous solution of sodium hydrogencarbonate and brine, separated by Phase Separator and the solvent evaporated to dryness. The residue was purified by flash chromatography to give the title compound (212 mg, 81%).

LRMS (m/z): 613 (M+1)⁺

PREPARATION 18

(R)-6-(4-(Benzyloxy)phenyl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-4-amine

Obtained (38%) from (*R*)-*tert*-butyl 3-((6-(4-(benzyloxy)phenyl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 17) and trifluoroacetic acid following the experimental procedure as described in Preparation 9 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol/ ammonia 90:10:1).

LRMS (m/z): 513 (M+1)⁺

PREPARATION 19

(R)-3-(3-((6-(4-(Benzyloxy)phenyl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

Triethylamine (0.065 mL, 0.47 mmol) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile (prepared as described in BE875054(A1)), 0.032 g, 0.18 mmol) were added to a solution of (*R*)-6-(4-(benzyloxy)phenyl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-*N*-(piperidin-3-yl) pyrimidin-4-amine (Preparation 18, 0.06 g, 0.12 mmol) in dichloromethane (3 mL) and the resulting mixture was stirred at ambient temperature for 30 min. Additional dichloromethane was added and the mixture was washed with water and brine. The organic layer was separated by Phase separator and the solvent was evaporated to dryness to yield the title compound (66 mg, 97%).

LRMS (m/z): 580 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.73 - 2.05 (m, 4H), 3.33 - 3.60 (m, 6H), 4.25 - 4.36 (m, 1H), 5.18 (s, 2H), 7.12 - 7.18 (m, 2H), 7.23 - 7.30 (m, 2H), 7.35 - 7.50 (m, 4H), 7.66 - 7.75 (m, 1H), 8.05 - 8.12 (d, 2H), 8.45 - 8.60 (d, 1H), 9.91 - 9.99 (m, 1H).

PREPARATION 20**(*R*)-*tert*-Butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(4-methoxybenzyl) piperazin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate**

A mixture of (*R*)-*tert*-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3, 0.25 g, 0.54 mmol), 1-(4-methoxybenzyl) piperazine (0.133 g, 0.64 mmol) and sodium hydrogencarbonate (0.135 g, 1.61 mmol) in *N,N*-dimethylacetamide (1 mL) was heated at 130 °C overnight. After cooling to ambient temperature, water was added and the precipitate formed was filtered and dried to give the title compound (0.34 g, 99%) as a yellow solid.

LRMS (*m/z*): 636 (*M*+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.71 (s, 9H), 2.05 - 2.16 (m, 4H), 2.55 - 2.60 (m, 4H), 3.42 - 3.47 (m, 4H), 3.52 (s, 2H), 3.72 - 3.77 (t, 4H), 3.82 (s, 3H), 4.18 (bs, 1H), 6.87 (s, 1H), 6.90 (s, 1H), 7.18 - 7.25 (m, 1H), 7.28 (s, 2H), 7.65 (dd, 1H), 8.38 (s, 1H), 9.74 - 9.77 (m, 1H).

PREPARATION 21**(*R*)-5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(4-methoxybenzyl) piperazin-1-yl)-*N*-(piperidin-3-yl)pyrimidin-4-amine**

Obtained as a yellow foam (92%) from (*R*)-*tert*-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(4-methoxybenzyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 20) and trifluoroacetic acid following the experimental procedure as described in Preparation 9.

LRMS (*m/z*): 535 (*M*+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.75 - 1.87 (m, 4H), 2.57 (t, 4H), 2.77 - 3.00 (m, 4H), 3.51 (s, 2H), 3.70 - 3.75 (m, 4H), 3.82 (s, 3H), 6.87 (s, 1H), 6.89 (s, 1H), 7.15 - 7.20 (m, 1H), 7.28 (s, 2H), 7.63 (dd, 1H), 8.38 (s, 1H), 9.74 - 9.77 (m, 1H).

PREPARATION 22**(*R*)-4-((4-(5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)piperazin-1-yl)methyl)phenol**

1M Solution of boron tribromide in dichloromethane (0.56 mL, 0.56 mmol) was added dropwise to a solution of (*R*)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(4-methoxybenzyl) piperazin-1-yl)-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 21, 0.08 g, 0.14 mmol) in dichloromethane (2 mL) at 0 °C and the resulting mixture was stirred at room temperature for 3h. Methanol was added dropwise and the reaction mixture was stirred at ambient temperature for 1h. Solvents were evaporated to

dryness to yield the crude product (114 mg) that was used in the next synthetic step without further purification.

LRMS (m/z): 521 (M+1)⁺

5 PREPARATION 23

(R)-3-(3-((6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

a) (R)-6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-4-amine

- 10 Obtained as a yellow solid (82%) from (*R*)-*tert*-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3) and trifluoro acetic acid following the experimental procedure as described in Preparation 9.

LRMS (m/z): 365 (M+1)⁺

- 15 ¹H NMR δ (300 MHz, CDCl₃): 1.67 - 1.78 (m, 4H), 2.82 - 2.92 (m, 3H), 3.20 (dd, 1H), 4.30 (bs, 1H), 5.84 (bs, 1H), 7.22 - 7.29 (m, 1H), 7.69 (dd, 1H), 8.49 (s, 1H), 9.77 (dd, 1H).

b) (R)-3-(3-((6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

- 20 Obtained as a yellow solid (96%) from 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropane nitrile (prepared as described in BE875054(A1)), ((*R*)-6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a] pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-4-amine (Preparation 23a) and triethylamine following the experimental procedure as described in Preparation 19.

- 25 LRMS (m/z): 432 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.75 - 2.00 (m, 4H), 2.17 - 2.26 (m, 2H), 3.26 - 3.35 (m, 2H), 3.41 - 3.51 (m, 2H), 3.55 - 3.65 (m, 2H), 7.21 - 7.35 (m, 1H), 7.66 - 7.76 (m, 1H), 8.43 - 8.57 (m, 1H), 9.70 - 9.77 (m, 1H).

30 PREPARATION 24

1-[(1-Methyl-1*H*-imidazol-2-yl)methyl]piperazine

a) *tert*-Butyl 4-[(1-methyl-1*H*-imidazol-2-yl)methyl]piperazine-1-carboxylate

- A mixture of *tert*-butyl 1-piperazinecarboxylate (0.5 g, 2.68 mmol), 2-(chloromethyl)-1-methyl-1*H*-imidazole hydrochloride (0.45 g, 2.68 mmol), triethylamine (0.79 mL, 5.67 mmol) and acetonitrile (20 mL) was stirred for 24h at 65 °C. The solvent was
35 evaporated and the crude was partitioned between ethyl acetate and water. The

organic phase was separated, washed with water, dried over magnesium sulphate and the solvent was evaporated to give the title compound (0.59 g, 74%).

LRMS (m/z): 281 (M+1)⁺

5 **b) 1-[(1-Methyl-1*H*-imidazol-2-yl)methyl]piperazine**

A mixture of *tert*-butyl 4-[(1-methyl-1*H*-imidazol-2-yl)methyl]piperazine-1-carboxylate (Preparation 24a, 0.59 g, 2.10 mmol) and 1.25 M hydrogen chloride solution in ethanol (30 mL) was stirred at ambient temperature for 8h. The solvent was evaporated and the residue was treated with diethyl ether, filtered, washed with acetonitrile and dried to
10 yield the hydrochloride salt of the title compound (0.46 g, 67%) as a white solid.

LRMS (m/z): 181 (M+1)⁺

PREPARATION 25

***N*-(1-Benzylpiperidin-4-yl)-6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-amine**

15 Obtained (94%) from 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-*a*]pyridine (Preparation 2b) and 1-benzylpiperidin-4-amine following the experimental procedure as described in Preparation 3.

LRMS (m/z): 455 (M+1)⁺

PREPARATION 26

1-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-2-(piperazin-1-ylmethyl)-1*H*-benzo[d]imidazole

a) Ethyl 4-((1*H*-benzo[d]imidazol-2-yl)methyl)piperazine-1-carboxylate

25 A solution of 2-(chloromethyl)-1*H*-benzo[d]imidazole (10 g, 60 mmol) in a 4:1 mixture of ethanol/*N,N'*-dimethylformamide (125 mL) was added dropwise to a solution of ethyl piperazine-1-carboxylate (22 mL, 150 mmol) in ethanol (70 mL) at 60 °C and the resulting mixture was stirred at the same temperature for 2h. Solvents were evaporated and brine (50 mL) and 4N aqueous solution of sodium hydroxide (40 mL) were added
30 to the residue. The aqueous solution was washed with chloroform (x3) and the combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent evaporated to dryness. The residue was treated with diethyl ether and filtered to yield the title compound (9.35 g, 54%) as a white solid.

35 **b) Ethyl 4-((1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)methyl) piperazine-1-carboxylate**

Sodium hydride (60% dispersion in mineral oil, 0.9 g, 23 mmol) was added to a suspension of ethyl 4-((1*H*-benzo[d]imidazol-2-yl)methyl)piperazine-1-carboxylate (Preparation 26a, 5.0 g, 17 mmol) in *N,N'*-dimethylformamide (35 mL) and the resulting mixture was stirred at ambient temperature for 30 min. 4-(Chloromethyl)-2,2-dimethyl-1,3-dioxolane (3.7 g, 24 mmol) was then added portionwise and the reaction mixture was stirred at 80 °C overnight before being poured onto ice. Ethyl acetate was added and the organic layer was separated, dried over magnesium sulphate and the solvent was evaporated to dryness. The residue was purified by flash chromatography (dichloromethane/methanol 50:1) to yield the title compound (3.53 g, 51%) as a yellow oil.

c) 1-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-2-(piperazin-1-ylmethyl)-1*H*-benzo[d]imidazole

Potassium hydroxide (0.49 g, 7.5 mmol) was added to a suspension of ethyl 4-((1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)methyl)piperazine-1-carboxylate (Preparation 26b, 0.3 g, 0.7 mmol) in propan-2-ol (6 mL) and the resulting mixture was heated to reflux for 30 min. Solvent was evaporated and a mixture of water and ice was added to the residue. Dichloromethane was then added and the organic layer was separated, washed with water and brine and dried over magnesium sulfate. The solvent was evaporated to dryness to yield the title compound (0.07 g, 28%) as a yellow oil.

PREPARATION 27

3-((*R*)-3-((6-(4-((1-(((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)methyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile and 3-((*R*)-3-((6-(4-((1-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)methyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

A mixture of (*R*)-3-(3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl) amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 23, 0.133 g, 0.31 mmol), racemic 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-(piperazin-1-ylmethyl)-1*H*-benzo[d]imidazole (Preparation 26c, 0.125 g, 0.38 mmol) and sodium hydrogencarbonate (0.08 g, 0.93 mmol) in *N,N*-dimethylacetamide (3 mL) was heated to 90 °C for 16h. After cooling to ambient temperature, water was added and the precipitate formed was filtered, washed with water and dried under vacuum. The solid was purified by flash

chromatography (dichloromethane to dichloromethane/methanol 93:7) to yield the title compound (20 mg, 9%) as a mixture of diastereoisomers.

LRMS (m/z): 727 (M+2)⁺

5 PREPARATION 28

3-(4-Chloro-5-fluoro-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-2-yl)-6-fluoro imidazo[1,2-a]pyridine

A mixture of 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-a]pyridine, (Preparation 2b, 0.309 g, 1.03 mmol), 4-(pyrrolidin-1-ylmethyl)piperidine dihydrochloride (0.289 g, 1.20 mmol) and triethylamine (0.555 mL, 3.99 mmol) in methanol (1.5 mL) was heated to 70 °C for 5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and saturated aqueous solution of sodium hydrogencarbonate. The organic phase was separated, dried over magnesium sulfate and the solvent was evaporated under vacuum to yield the title compound (79%).

LRMS (m/z): 433 (M+1)⁺

PREPARATION 29

20 **(R)-Tert-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholino pyrimidin-4-yl)amino)piperidine-1-carboxylate**

A solution of (R)-tert-butyl 3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 3, 0.30 g, 0.65 mmol) in morpholine (0.28 mL, 3.21 mmol) was stirred at 100 °C for 3h. Excess of morpholine was evaporated under reduced pressure and water was added to the residue. The solid formed was filtered, washed with water and dried under vacuum to yield the title compound (257 mg, 75%).

LRMS (m/z): 516 (M+1)⁺

PREPARATION 30

30 **(R)-tert-Butyl 3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidine-1-carboxylate**

Sodium hydride (60% dispersion in mineral oil, 0.035 g, 0.88 mmol) was added portionwise to a suspension of (R)-tert-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholino pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 29, 0.15 g, 0.29 mmol) and (2-chloroethyl)dimethylamine hydrochloride (0.051 g, 0.35 mmol) in N,N'-dimethylformamide (1 mL) and the resulting mixture was stirred overnight at room temperature. Additional 2-chloroethyl)dimethylamine hydrochloride

(0.051 g, 0.35 mmol) and sodium hydride (0.011 g, 0.29 mmol) were added and the mixture was stirred for further 24 h at room temperature. A third addition of 2-chloroethyl)dimethylamine hydrochloride (0.023 g, 0.17 mmol) and sodium hydride (0.011 g, 0.29 mmol) was made and the reaction mixture was stirred for additional 24h
5 at room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic phase was separated, washed with water, dried over magnesium sulfate and the solvent was evaporated to dryness to yield the title compound as a brown gum (0.15 g, 74%).

LRMS (m/z): 587 (M+1)+

10 PREPARATION 31

(R)-N1-(5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)-N2,N2-dimethyl-N1-(piperidin-3-yl)ethane-1,2-diamine

4M Solution of hydrogen chloride in dioxane (2 mL) was added to a solution of (*R*)-*tert*-butyl
15 3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 30, 0.15 g, 0.25 mmol) in methanol (4 mL) and the resulting mixture was stirred at ambient temperature for 4h. The solvents were evaporated and the residue was treated with diethyl ether and filtered to yield the hydrochloride salt of the title compound (146 mg, 81%) as a
20 solid.

LRMS (m/z): 487 (M+1)+

PREPARATION 32

(S)-5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(1-(5-fluoropyridin-2-yl)ethyl)-6-morpholinopyrimidin-4-amine

Obtained as a solid (80%) from (*S*)-6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-*N*-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidin-4-amine (Preparation 16) and morpholine following the experimental procedure as described in Preparation 29 heating at 130 °C for 1h.

30 LRMS (m/z): 456 (M+1)+

PREPARATION 33

(2-(4-Methyl-1,4-diazepan-1-yl)pyridin-4-yl)boronic acid a) 1-(4-Bromopyridin-2-yl)-4-methyl-1,4-diazepane

35 A mixture of 4-bromo-2-fluoropyridine (4.25 g, 24.15 mmol), 1-methyl-1,4-diazepane (3.6 mL, 29 mmol) and potassium carbonate (10.0 g, 72.3 mmol) in dimethylsulfoxide (30 mL) was heated at 100 °C overnight. After cooling to ambient temperature the

reaction mixture was poured into water and extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was concentrated to dryness to yield the title compound (6.1 g, 89%).

LRMS (m/z): 270, 272 (M, M+2)⁺

5 ¹H-NMR $\square$ (300 MHz, CDCl₃): 1.92 - 2.09 (m, 2H), 2.38 (s, 3H), 2.50 - 2.62 (m, 2H), 2.63 - 2.73 (m, 2H), 3.60 (t, 2H), 3.77 - 3.85 (m, 2H), 6.64 (d, 1H), 6.66 - 6.70 (m, 1H), 7.95 (d, 1H).

b) (2-(4-Methyl-1,4-diazepan-1-yl)pyridin-4-yl)boronic acid

10 A Schlenk tube was charged with 1-(4-bromopyridin-2-yl)-4-methyl-1,4-diazepane (Preparation 33a, 0.67 g, 2.48 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (0.76 g, 2.98 mmol), potassium acetate (0.73 g, 7.44 mmol) and 1,4-dioxane (8 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then [1,1'-bis (diphenylphosphino)ferrocene]palladium(II)
15 dichloride (0.10 g, 0.12 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated at 80 °C for 4h. The mixture was cooled, filtered through diatomaceous earth (Celite[®]) and the solvent was concentrated to dryness. The residue was treated with petroleum ether, filtered and the solvent was evaporated to dryness to yield the title
20 compound (0.5 g, 86%) as a yellow oil.

LRMS (m/z): 236 (M+1)⁺

PREPARATION 34

(2-(4-(Dimethylamino)piperidin-1-yl)pyridin-4-yl)boronic acid

25 **a) 1-(4-Bromopyridin-2-yl)-N,N-dimethylpiperidin-4-amine**

Obtained as a yellow solid (90%) from 4-bromo-2-fluoropyridine and N,N-dimethylpiperidin-4-amine following the experimental procedure as described in Preparation 33a.

LRMS (m/z): 284, 286 (M, M+2)⁺

30

b) (2-(4-(Dimethylamino)piperidin-1-yl)pyridin-4-yl)boronic acid

Obtained as an orange oil (100%) from 1-(4-bromopyridin-2-yl)-N,N-dimethylpiperidin-4-amine (Preparation 34a) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane following the experimental procedure as described in Preparation 33b.

35

LRMS (m/z): 250 (M+1)⁺

PREPARATION 35***N,N*-Dimethyl-2-(4-(piperazin-1-ylmethyl)phenoxy)ethanamine****a) 4-[2-(Dimethylamino)ethoxy]benzaldehyde**

A mixture of 4-hydroxybenzaldehyde (6.0 g, 49.1 mmol), 2-chloro-*N,N*-dimethylethanamine hydrochloride (10.61 g, 73.70 mmol) and potassium carbonate (20.37 g, 147.4 mmol) in *N,N*-dimethylformamide (60 mL) was stirred overnight at 90 °C. The solvent was evaporated and the residue partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over sodium sulphate and the solvent evaporated to yield the title compound (7.25 g, 72%) as a brown oil.

LRMS (m/z): 194 (M+1)⁺

b) *N,N*-Dimethyl-2-(4-(piperazin-1-ylmethyl)phenoxy)ethanamine

A mixture of 4-[2-(dimethylamino)ethoxy]benzaldehyde (Preparation 35a, 7.25 g, 37.5 mmol), *tert*-butyl piperazine-1-carboxylate (6.98 g, 37.5 mmol) and sodium triacetoxyborohydride (9.54 g, 45.0 mmol) in dichloromethane (30 mL) was stirred at room temperature for 48h. The reaction mixture was washed with 2N aqueous solution of sodium hydroxide and with 0.1N aqueous solution of hydrogen chloride. The solvent was evaporated, 4.0 M solution of hydrogen chloride in 1,4-dioxane (94 mL) was added to the crude and the resulting mixture was stirred at ambient temperature for 1h. The solvent was evaporated and the residue was co-evaporated with 1,4-dioxane and toluene to dryness to yield the title compound (11.05 g, 71%) as an hydrochloride salt.

LRMS (m/z): 264 (M+1)⁺

¹H-NMR δ (300 MHz, CD₃OD): 3.0 (s, 6H), 3.6 (s, 10H), 4.3 - 4.5 (m, 4H), 7.2 (d, 2H), 7.6 (d, 2H).

PREPARATION 36**{2-[4-(*tert*-Butoxycarbonyl)-1,4-diazepan-1-yl]pyridin-4-yl}boronic acid****a) *tert*-Butyl 4-(4-bromopyridin-2-yl)-1,4-diazepane-1-carboxylate**

Obtained as a white solid (69%) from 4-bromo-2-fluoropyridine and *tert*-butyl 1,4-diazepane-1-carboxylate following the experimental procedure as described in Preparation 33a.

LRMS (m/z): 356, 358 (M, M+2)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.44 (s, 9H), 1.96 (m, 2H), 3.31 (m, 2H), 3.60 (m, 4H), 3.76 (m, 2H), 6.68 (s, 2H), 7.95 (s, 1H).

b) {2-[4-(*tert*-Butoxycarbonyl)-1,4-diazepan-1-yl]pyridin-4-yl}boronic acid

Obtained as a brown oil (100%) from *tert*-butyl 4-(4-bromopyridin-2-yl)-1,4-diazepane-1-carboxylate (Preparation 36a) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane following the experimental procedure as described in Preparation 33b.

LRMS (m/z): 322 (M+1)⁺

5

PREPARATION 37

***Tert*-butyl 4-{4-[6-{[(3*R*)-1-(cyanoacetyl)piperidin-3-yl]amino}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]pyridin-2-yl}-1,4-diazepane-1-carboxylate**

- 10 A Schlenk tube was charged with 3-((3*R*)-3-{[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile (Preparation 23b, 0.15 g, 0.35 mmol), {2-[4-(*tert*-butoxycarbonyl)-1,4-diazepan-1-yl]pyridin-4-yl}boronic acid (Preparation 36b, 0.163 g, 0.51 mmol), 2M aqueous cesium carbonate solution (0.52 mL, 1.04 mmol) and 1,4-dioxane (3 mL). The Schlenk tube was subjected to
- 15 three cycles of evacuation-backfilling with argon and then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.017 g, 0.02 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred overnight at 90 °C. The solvent was removed and the residue was purified by reverse phase
- 20 chromatography (water to methanol) to yield the title compound (53 mg, 23%) as a solid.

LRMS (m/z): 674 (M+1)⁺

- ¹H-NMR δ (300 MHz, CDCl₃): 1.38 (s, 9 H), 1.55 - 1.69 (m, 4H), 1.79 - 2.13 (m, 4H), 2.18 - 2.32 (m, 1H), 3.23 - 3.36 (m, 2H), 3.42 - 3.54 (m, 2H), 3.54 - 3.66
- 25 (m, 3H), 3.69 - 3.80 (m, 2H), 3.85 - 3.98 (m, 2H), 4.23 - 4.47 (m, 1H), 5.29 - 5.35 (m, 1H), 7.10 - 7.39 (m, 3H), 7.63 - 7.83 (m, 1H), 8.32 (t, 1H), 8.52 (d, 1H), 9.83 - 10.02 (m, 1H).

PREPARATION 38

- 30 **[6-(4-Methyl-1,4-diazepan-1-yl)pyridin-3-yl]boronic acid**
a) 1-(5-Bromopyridin-2-yl)-4-methyl-1,4-diazepane

Obtained as an oil (90%) from 5-bromo-2-fluoropyridine and 1-methyl-1,4-diazepane following the experimental procedure as described in Preparation 33a.

LRMS (m/z): 270, 272 (M, M+2)⁺

35

b) [6-(4-Methyl-1,4-diazepan-1-yl)pyridin-3-yl]boronic acid

Obtained as a brown oil (93%) from 1-(5-bromopyridin-2-yl)-4-methyl-1,4-diazepane (Preparation 38a) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane following the experimental procedure as described in Preparation 33b.

LRMS (m/z): 236 (M+1)⁺

5

PREPARATION 39

(*R*)-*Tert*-butyl 3-((2-chloro-5-fluoro-6-(4-(hydroxymethyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

10 **a) (*R*)-*Tert*-butyl 3-((2,6-dichloro-5-fluoropyrimidin-4-yl)amino)piperidine-1-carboxylate**

A solution of 2,4,6-trichloro-5-fluoropyrimidine (0.5 g, 2.48 mmol) in ethanol (10 mL) was added dropwise to a cooled (-20 °C) solution of (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate (0.55 g, 2.73 mmol) in ethanol (10 mL) and the resulting mixture was stirred at -20 °C for 1h. The solvent was evaporated and the crude was partitioned
15 between water and chloroform. The organic layer was separated, dried over magnesium sulphate and the solvent was evaporated to dryness. The residue was purified by flash chromatography (hexanes to ethyl acetate) to give the title compound (785 mg, 86%) as a colourless oil.

LRMS (m/z): 365/367 (M+1)⁺

20

b) (*R*)-*Tert*-butyl 3-((2-chloro-5-fluoro-6-(4-(hydroxymethyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

Obtained as an oil (26%) from (*R*)-*tert*-butyl 3-((2,6-dichloro-5-fluoropyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 39a) and (4-(hydroxymethyl)phenyl)
25 boronic acid in 1,2-dimethoxyethane following the experimental procedure as described in Preparation 17 followed by purification of the crude product by flash chromatography (hexanes/ethyl acetate).

LRMS (m/z): 437/439 (M+1)⁺

30 PREPARATION 40

(*R*)-*Tert*-butyl 3-((2-chloro-5-fluoro-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

a) (*R*)-*Tert*-butyl 3-((2-chloro-5-fluoro-6-(4-formylphenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate

35 Manganese (IV) oxide (1.04 g, 11.97 mmol) was slowly added to a solution of (*R*)-*tert*-butyl 3-((2-chloro-5-fluoro-6-(4-(hydroxymethyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 39b, 0.52 g, 1.20 mmol) in chloroform (6 mL) and the

mixture was stirred at 45 °C for 2h. The solid was filtered and the solvent was concentrated to dryness. The residue was purified by flash chromatography (hexanes/ethyl acetate) to give the title compound (336 mg, 61%) as a solid.

LRMS (m/z): 435/437 (M+1)⁺.

5

b) (R)-tert-Butyl 3-((2-chloro-5-fluoro-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl) pyrimidin-4-yl)amino)piperidine-1-carboxylate

Sodium triacetoxyborohydride (0.26 g, 1.24 mmol) and 1-methyl-1,4-diazepane (0.13 mL, 1.08 mmol) were added to a solution of (R)-tert-butyl 3-((2-chloro-5-fluoro-6-(4-formylphenyl) pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 40a, 0.34 g, 0.77 mmol) in dichloromethane (14 mL) and the mixture was stirred at room temperature for 2h. The crude was washed with water and the organic layer was dried over magnesium sulphate and filtered. The solvent was evaporated to dryness to give the title compound (292 mg, 70%) as a solid.

15 LRMS (m/z): 534/536 (M+1)⁺

PREPARATION 41

(R)-5-Fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl) phenyl)-N-(piperidin-3-yl)pyrimidin-4-amine

20 **a) (R)-tert-Butyl 3-((5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate**

A Schlenk tube was charged with (R)-tert-butyl 3-((2-chloro-5-fluoro-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 40b, 0.09 g, 0.17 mmol), imidazo[1,2-a]pyridine (0.04 g, 0.34 mmol), 25 potassium acetate (25 mg, 0.25 mmol) and N,N-dimethylacetamide (2 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then tetrakis(triphenylphosphine)palladium(0) (0.02 g, 0.02 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred at 150 °C for 90 min. The suspension was filtered over 30 diatomaceous earth (Celite[®]) and the solid was washed with ethyl acetate. The organic phases were combined, washed with water and brine, dried over magnesium sulfate, filtered and the solvent was evaporated to dryness. The residue was purified by reverse phase chromatography to give the title compound (12 mg, 11%).

LRMS (m/z): 616 (M+2)⁺

35

b) (R)-5-Fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl) phenyl)-N-(piperidin-3-yl)pyrimidin-4-amine

Obtained as hydrochloride salt (99%) from (*R*)-*tert*-butyl 3-((5-fluoro-2-(imidazo[1,2-*a*]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 41a) following the experimental procedure as described in Preparation 31.

5 LRMS (m/z): 516 (M+2)⁺

PREPARATION 42

3-((3*R*)-3-([5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-formylphenyl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

10 **a) 3-((3*R*)-3-([5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(hydroxymethyl)phenyl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile**

A Schlenk tube was charged with 3-((3*R*)-3-([6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 23b, 0.3 g, 0.69 mmol), 4-(hydroxymethyl)phenylboronic acid (0.158 g, 1.04 mmol), 2.0 M aqueous sodium carbonate solution (0.38 mL, 0.76 mmol) and 1,2-dimethoxyethane (5 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then tetrakis (triphenylphosphine)palladium(0) (80 mg, 0.07 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated at 80 °C overnight. The solvent was removed and the residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 95:5) to yield the title compound (0.14 g, 40%) as a solid.

LRMS (m/z): 504 (M+1)⁺.

b) 3-((3*R*)-3-([5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-

25 **formylphenyl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a yellow oil (53%) from 3-((3*R*)-3-([5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(hydroxymethyl)phenyl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 42a) following the experimental procedure described in Preparation 40a followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol 95:5).

LRMS (m/z): 502 (M+1)⁺

PREPARATION 43

3-((3*R*)-3-([6-Chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

35 **a) 6-Chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methyl-*N*-[(3*R*)-piperidin-3-yl]pyrimidin-4-amine**

Obtained as hydrochloride salt (100%) from *tert*-butyl (3*R*)-3-[[6-chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino]piperidine-1-carboxylate (Preparation 13) following the experimental procedure as described in Preparation 31.

LRMS (*m/z*): 361 (*M*+1)⁺

5

b) 3-((3*R*)-3-[[6-Chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile

Obtained as a white solid (92%) from 6-chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methyl-*N*-[(3*R*)-piperidin-3-yl]pyrimidin-4-amine hydrochloride salt (Preparation 43a) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile in *N,N'*-dimethylformamide following the experimental procedure as described in Preparation 19.

10

LRMS (*m/z*): 428 (*M*+1)⁺

PREPARATION 44

15 **Imidazo[1,2-*a*]pyridine-3-carboximidamide**

A solution of sodium methoxide (prepared from sodium (0.13 g, 5.65 mmol) and methanol (10 mL)) was added dropwise to a suspension of imidazo[1,2-*a*]pyridine-3-carbonitrile (4.0 g, 27.94 mmol) in methanol (15 mL) and the resulting mixture was stirred at ambient temperature overnight. Ammonium chloride (1.64 g, 30.7 mmol) was then added and the mixture was heated at 90 °C for 4h. The solvent was removed under reduced pressure and the resulting solid was treated with diethyl ether, filtered and purified by flash chromatography (dichloromethane/ ethanol) to give the title compound (4.47 g, 99%) as a white solid.

20

LRMS (*m/z*): 161 (*M*+1)⁺

25

¹H NMR δ (300 MHz, DMSO-*d*₆): 7.21 (t, 1H), 7.56 (t, 1H), 7.79 (d, 1H), 8.26 (s, 1H), 8.67 (d, 1H).

PREPARATION 45

3-(4,6-Dichloro-5-methylpyrimidin-2-yl)imidazo[1,2-*a*]pyridine

30 **a) 2-(Imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidine-4,6-diol**

Obtained as a white solid (72%) from imidazo[1,2-*a*]pyridine-3-carboximidamide (Preparation 44) and diethyl 2-methylmalonate following the experimental procedure as described in Preparation 2a.

LRMS (*m/z*): 243 (*M*+1)⁺

35

¹H NMR δ (300 MHz, DMSO-*d*₆): 1.84 (s, 3H), 7.37 - 7.45 (m, 2H), 7.78 (t, 1H), 7.92 (d, 1H), 8.77 (s, 1H), 10.19 (d, 1H).

b) 3-(4,6-Dichloro-5-methylpyrimidin-2-yl)imidazo[1,2-a]pyridine

Obtained as a white solid (72%) from 2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidine-4,6-diol (Preparation 45a) following the experimental procedure as described in Preparation 2b.

5 LRMS (m/z): 279/281 (M+1)⁺

PREPARATION 46**(R)-tert-Butyl 3-((6-chloro-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate**

10 Obtained as an oil (67%) from 3-(4,6-dichloro-5-methylpyrimidin-2-yl)imidazo[1,2-a]pyridine (Preparation 45b) and (R)-tert-butyl 3-aminopiperidine-1-carboxylate following the experimental procedure as described in Preparation 3.

LRMS (m/z): 443/445 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.25 - 1.47 (m, 13H), 2.17 (s, 3H), 3.52 - 3.75 (m, 4H), 4.23 - 4.35 (m, 1H), 6.98 (td, 1H), 7.28 - 7.35 (m, 1H), 7.68 - 7.73 (m, 1H), 8.52 (s, 1H), 9.81 (d, 1H).

PREPARATION 47**(R)-6-Chloro-2-(imidazo[1,2-a]pyridin-3-yl)-5-methyl-N-(piperidin-3-yl)pyrimidin-4-amine**

20 Obtained as an hydrochloride salt (92%) from (R)-tert-butyl 3-((6-chloro-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 46) following the experimental procedure as described in Preparation 31.

LRMS (m/z): 344/346 (M+1)⁺

PREPARATION 48**(R)-3-(3-((6-Chloro-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile**

30 Obtained as a white solid (36%) from 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile and (R)-6-chloro-2-(imidazo[1,2-a]pyridin-3-yl)-5-methyl-N-(piperidin-3-yl)pyrimidin-4-amine (Preparation 47) following the experimental procedure as described in Preparation 19.

LRMS (m/z): 410/412 (M+1)⁺

¹H NMR δ (300 MHz, DMSO-*d*₆): 1.60 - 1.82 (m, 4H), 2.15 (s, 3H), 2.40 - 2.61 (m, 2H), 2.94 - 3.09 (m, 2H), 3.61 - 3.77 (m, 2H), 4.20 - 4.25 (m, 1H), 4.68 (d, 1H), 6.94 - 7.02 (m, 1H), 7.16 (t, 1H), 7.43 (t, 1H), 7.69 - 7.78 (m, 1H), 8.46 (d, 1H), 9.63 - 9.71 (m, 1H).

PREPARATION 49**3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)imidazo[1,2-a]pyridine****a) 5-Fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diol**

- 5 Obtained as a brown solid (88%) from imidazo[1,2-a]pyridine-3-carboximidamide (Preparation 44) and diethyl 2-fluoromalonate following the experimental procedure as described in Preparation 2a.

LRMS (m/z): 247 (M+1)+

10 **b) 3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)imidazo[1,2-a]pyridine**

Obtained as a yellow solid (44%) from 5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidine-4,6-diol (Preparation 49a) following the experimental procedure as described in Preparation 2b.

LRMS (m/z): 284 (M+1)+

15

PREPARATION 50**(R)-Tert-butyl 3-((6-chloro-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate**

- Obtained as a beige solid (90%) from (R)-tert-butyl 3-aminopiperidine-1-carboxylate and 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)imidazo[1,2-a]pyridine (Preparation 49b) following the experimental procedure as described in Preparation 3.

LRMS (m/z): 447 (M+1)+

PREPARATION 51

- 25 **(R)-tert-Butyl 3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate**

- Obtained as a beige solid (73%) from (R)-tert-butyl 3-((6-chloro-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 50) and N,N'-dimethyl-2-(4-(piperazin-1-ylmethyl)phenoxy)ethanamine (Preparation 35b) in N,N'-dimethylacetamide following the experimental procedure as described in Preparation 16.

LRMS (m/z): 674 (M+1)+

PREPARATION 52

- 35 **(R)-6-(4-(4-(2-(Dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-4-amine**

4M Solution of hydrogen chloride in 1,4-dioxane (3 mL, 12 mmol) was added to a solution of (*R*)-*tert*-butyl 3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 51, 0.4 g, 0.59 mmol) in methanol (3 mL) and the resulting mixture was stirred at ambient temperature for 4h. The solvents were evaporated, the residue was dissolved in water and solid potassium carbonate was added until the pH was basic. Dichloromethane was then added and the organic layer was separated, dried over magnesium sulphate and the solvent evaporated to dryness to yield the title compound (0.37 g, 98%) as a brown solid.

LRMS (*m/z*): 574 (*M*+2)+

PREPARATION 53

1-(2-Chloroethyl)-*N,N*-dimethylpiperidin-4-amine

a) 2-[4-(Dimethylamino)piperidin-1-yl]ethanol hydrobromide

2-Bromoethanol (0.61 mL, 8.6 mmol) was added to a suspension of *N,N*-dimethylpiperidin-4-amine (0.55 g, 4.3 mmol) and potassium carbonate (1.8 g, 13 mmol) in acetonitrile (20 mL) and the reaction mixture was stirred overnight at 82 °C. The solvent was evaporated and the crude was used for the next reaction without any further purification.

LRMS (*m/z*): 173 (*M*+1)+

b) 1-(2-Chloroethyl)-*N,N*-dimethylpiperidin-4-amine

Thionyl chloride (3.0 mL, 41.3 mmol) was added to a solution of 2-[4-(dimethylamino)piperidin-1-yl]ethanol hydrobromide (Preparation 53a, 0.74 g, 4.3 mmol) in 1,2-dichloroethane (20 mL) and the resulting mixture was stirred at 80 °C for 4h. The solvent was evaporated and the residue was triturated with diethyl ether, filtered and dried *in vacuo* to yield the title compound (0.996 g, 88%) as a hydrochloride salt.

LRMS (*m/z*): 191 (*M*+1)+

PREPARATION 54

N-{2-[4-(Dimethylamino)piperidin-1-yl]ethyl}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-yl-*N*-[(3*R*)-piperidin-3-yl]pyrimidin-4-amine

a) *Tert*-butyl (3*R*)-3-{[2-[4-(dimethylamino)piperidin-1-yl]ethyl][5-fluoro-2-(6-fluoroimidazo [1,2-*a*]pyridin-3-yl)-6-morpholin-4-ylpyrimidin-4-yl]amino}-piperidine-1-carboxylate

Obtained as a solid (37%) from (*R*)-*tert*-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 29) and 1-(2-chloroethyl)-*N,N*-dimethylpiperidin-4-amine hydrochloride (Preparation 53b) following the experimental procedure as described in Preparation 30 heating at 55 °C followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane /methanol/ammonia 40:4:0.2).

LRMS (*m/z*): 671 (*M*+1)⁺

b) *N*-{2-[4-(Dimethylamino)piperidin-1-yl]ethyl}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-yl-*N*-[(3*R*)-piperidin-3-yl]pyrimidin-4-amine

Obtained as a hydrochloride salt (100%) from *tert*-butyl (3*R*)-3-{{2-[4-(dimethylamino)piperidin-1-yl]ethyl}[5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-ylpyrimidin-4-yl]amino}piperidine-1-carboxylate (Preparation 54a) following the experimental procedure as described in Preparation 31.

LRMS (*m/z*): 571 (*M*+1)⁺

PREPARATION 55

(*R*)-*Tert*-butyl 3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate

a) 2-(4-((4-(6-Chloro-2-(imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl)piperazin-1-yl) methyl)phenoxy)-*N,N*-dimethylethanamine

Obtained as a brown foam (59%) from 3-(4,6-dichloro-5-methylpyrimidin-2-yl)imidazo[1,2-*a*]pyridine (Preparation 45b) and *N,N*-dimethyl-2-(4-(piperazin-1-yl)methyl)phenoxy)ethanamine (Preparation 35b) following the experimental procedure as described in Preparation 16.

LRMS (*m/z*): 507 (*M*+1)⁺

b) (*R*)-*Tert*-butyl 3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate

A Schlenk tube was charged with 2-(4-((4-(6-chloro-2-(imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl)piperazin-1-yl)methyl)phenoxy)-*N,N*-dimethylethanamine (Preparation 55a, 0.36 g, 0.72 mmol), (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate (0.29 g, 1.45 mmol), sodium *tert*-butoxide (0.14 g, 1.50 mmol), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)-biphenyl (0.09 g, 0.22 mmol) and toluene (15 mL). The Schlenk tube was subjected to three cycles of evacuation-

backfilling with argon and then tris(dibenzylideneacetone)dipalladium(0) (66 mg, 0.07 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred at 90 °C for 2h. The solvent was removed under reduced pressure and the residue was partitioned between water and dichloromethane. The organic layer was separated, washed with water and brine, dried with a Phase Separator and the solvent was evaporated to dryness. The residue was purified by flash chromatography (gradient from hexanes to ethyl acetate to methanol) to give the title compound (175 mg, 36%).

LRMS (m/z): 671 (M+2)⁺

PREPARATION 56

(R)-6-(4-(4-(2-(Dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methyl-N-(piperidin-3-yl)pyrimidin-4-amine

Obtained as a yellow solid (79%) from of (R)-*tert*-butyl 3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidine-1-carboxylate (Preparation 55b) following the experimental procedure as described in Preparation 52.

LRMS (m/z): 571 (M+2)⁺

PREPARATION 57

***Tert*-butyl (3R)-3-{[2-(dimethylamino)ethyl]amino}piperidine-1-carboxylate**

37% Aqueous hydrogen chloride solution (0.5 mL, 16.3 mmol) was added to (2,2-dimethoxy ethyl)dimethylamine (0.25 g, 1.90 mmol) in a sealed tube and the mixture was stirred at 100 °C for 1h. The solution was cooled to 0 °C and 6N aqueous sodium hydroxide solution was added until a basic pH was reached. A solution of *tert*-butyl (3R)-3-aminopiperidine-1-carboxylate (0.19 g, 0.95 mmol) in 1,2-dichloroethane (10 mL) was added and the reaction mixture was stirred at ambient temperature for 15 min. Sodium triacetoxyborohydride (0.6 g, 2.85 mmol) was then added and the reaction mixture was stirred at ambient temperature for 2h. The solvents were evaporated and the crude residue was purified by cationic exchange chromatography. The desired product was eluted with 2N ammonia in methanol solution and the solvent was evaporated under reduced pressure. Purification of the crude residue by reverse phase chromatography (gradient from water with 0.1% formic acid to methanol) gave the title compound (0.257 g, 25 %).

LRMS (m/z): 272 (M+1)⁺

PREPARATION 58

***N*-[6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]-*N*',*N*'-dimethyl-*N*-[(3*R*)-piperidin-3-yl]ethane-1,2-diamine**

a) *tert*-Butyl (3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl] [2-(dimethylamino)ethyl]amino}piperidine-1-carboxylate

Obtained (47%) from 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-6-fluoroimidazo[1,2-*a*]pyridine (Preparation 2b) and *tert*-butyl (3*R*)-3-[[2-(dimethylamino)ethyl] amino}piperidine-1-carboxylate (Preparation 57) following the experimental procedure as described in Preparation 3 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/ methanol/ammonia 40:4:2).

LRMS (m/z): 537 (M+1)⁺

b) *N*-[6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]-*N*',*N*'-dimethyl-*N*-[(3*R*)-piperidin-3-yl]ethane-1,2-diamine

Obtained as an hydrochloride salt (98%) from *tert*-butyl (3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl][2-(dimethylamino)ethyl]amino}-piperidine-1-carboxylate (Preparation 58a) following the experimental procedure described in Preparation 31.

LRMS (m/z): 436 (M+1)⁺

PREPARATION 59

3-((3*R*)-3-[[6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl] [2-(dimethylamino)ethyl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (81%) from *N*-[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]-*N*',*N*'-dimethyl-*N*-[(3*R*)-piperidin-3-yl]ethane-1,2-diamine (Preparation 58b) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Preparation 19.

LRMS (m/z): 504 (M+1)⁺

PREPARATION 60

***tert*-Butyl (3*R*)-3-[[3-(dimethylamino)propyl]{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino}piperidine-1-carboxylate**

a) *Tert*-butyl (3*R*)-3-((5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl)amino}piperidine-1-carboxylate

Obtained as a solid (66%) from *tert*-butyl (3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidine-1-carboxylate

(Preparation 3) and 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine following the experimental procedure as described in Preparation 37 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol/ammonia 40:8:1).

5 LRMS (m/z): 605 (M+1)⁺

b) *Tert*-butyl (3*R*)-3-([3-(dimethylamino)propyl]{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidine-1-carboxylate

10 Obtained as a solid (58%) from *tert*-butyl (3*R*)-3-({5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidine-1-carboxylate (Preparation 60a) and 3-chloro-*N,N*-dimethylpropan-1-amine hydrochloride following the experimental procedure described in Preparation 30.

LRMS (m/z): 690 (M+1)⁺

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PREPARATION 61

***N*-{5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}-*N',N'*-dimethyl-*N*-[(3*R*)-piperidin-3-yl]propane-1,3-diamine**

Obtained as an hydrochloride salt (100%) from *tert*-butyl (3*R*)-3-([3-(dimethylamino)propyl]{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl} amino)piperidine-1-carboxylate (Preparation 60b) following the experimental procedure as described in Preparation 31.

LRMS (m/z): 590 (M+1)⁺.

25 PREPARATION 62

***Tert*-butyl (3*R*)-3-([2-(dimethylamino)ethyl]{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidine-1-carboxylate**

Obtained as a solid (93%) from *tert*-butyl (3*R*)-3-({5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidine-1-carboxylate (Preparation 60a) and 2-chloro-*N,N*-dimethylethanamine hydrochloride following the experimental procedure described in Preparation 30.

LRMS (m/z): 676 (M+1)⁺

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PREPARATION 63

***N*-{5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}-*N,N'*-dimethyl-*N*-[(3*R*)-piperidin-3-yl]ethane-1,2-diamine**

Obtained as an hydrochloride salt (80%) from *tert*-butyl (3*R*)-3-([2-(dimethylamino)ethyl]{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)

- 5 phenyl]pyrimidin-4-yl} amino)piperidine-1-carboxylate (Preparation 62) following the experimental procedure as described in Preparation 31.

LRMS (m/z): 576 (M+1)⁺.

PREPARATION 64

- 10 ***Tert*-butyl (3*R*)-3-[{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}(2-pyrrolidin-1-ylethyl)amino]piperidine-1-carboxylate**

Obtained as a solid (34%) from *tert*-butyl (3*R*)-3-({5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidine-1-

- 15 carboxylate (Preparation 60a) and 1-(2-chloroethyl)pyrrolidine hydrochloride following the experimental procedure as described in Preparation 30 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane /metanol 9:1).

LRMS (m/z): 702 (M+1)⁺

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PREPARATION 65

5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]-*N*-[(3*R*)-piperidin-3-yl]-*N*-(2-pyrrolidin-1-ylethyl)pyrimidin-4-amine

Obtained as an hydrochloride salt (96%) from *tert*-butyl (3*R*)-3-[{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}(2-pyrrolidin-1-ylethyl)amino]piperidine-1-carboxylate (Preparation 64) following the experimental procedure as described in Preparation 31.

- 25 LRMS (m/z): 602 (M+1)⁺

- 30 PREPARATION 66

**[2-(Dimethylamino)pyridin-4-yl]boronic acid
a) 4-Bromo-*N,N*-dimethylpyridin-2-amine**

A mixture of 4-bromo-2-fluoropyridine (0.8 g, 4.55 mmol) and 2M solution of dimethylamine in tetrahydrofuran (9 mL, 18 mmol) was placed in a microwave vessel and was subjected to microwave irradiation for 2h at 100 °C. The solvent was evaporated and the crude was partitioned between ethyl acetate and water. The organic phase was separated, washed with water, dried over magnesium sulfate and

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the solvent was evaporated under reduced pressure. Purification of the residue by flash chromatography (hexane to ethyl acetate) gave the title compound (0.29 g, 32%) as a solid.

LRMS (m/z): 201-203 (M+1)⁺

b) [2-(Dimethylamino)pyridin-4-yl]boronic acid

Obtained (100%) from 4-bromo-*N,N*-dimethylpyridin-2-amine (Preparation 66a) following the experimental procedure as described in Preparation 33b.

LRMS (m/z): 167 (M+1)⁺

PREPARATION 67

1-Methyl-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine

a) 1-(3-Bromophenyl)-4-methylpiperazine

A Schlenk tube was charged with 1-bromo-3-iodobenzene (0.70 mL, 5.49 mmol), 1-methyl piperazine (0.61 mL, 5.50 mmol), sodium *tert*-butoxide (1.48 g, 15.40 mmol) and toluene (8 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then tris(dibenzylideneacetone)dipalladium(0) (0.20 g, 0.22 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (0.27 g, 0.43 mmol) were added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated overnight at 100 °C. The suspension was cooled, filtered through diatomaceous earth (Celite®) and the solvent was concentrated to dryness. Purification of the residue by flash chromatography (hexane/ethyl acetate) gave the title compound (0.48 g, 29%).

LRMS (m/z): 255-257 (M+1)⁺

b) 1-Methyl-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine

Obtained (89%) from 1-(3-bromophenyl)-4-methylpiperazine (Preparation 67a) following the experimental procedure as described in Preparation 33b.

LRMS (m/z): 303 (M+1)⁺

PREPARATION 68

***Tert*-butyl (3*R*)-3-({5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}[2-(4-methylpiperazin-1-yl)ethyl]amino} piperidine-1-carboxylate**

Obtained as a solid (39%) from *tert*-butyl (3*R*)-3-({5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidine-1-carboxylate (Preparation 60a) and 1-(2-chloroethyl)-4-methylpiperazine dihydrochloride

following the experimental procedure as described in Preparation 30 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol 90:10 then dichloromethane/ methanol/ammonia 40:8:1).

LRMS (m/z): 731 (M+1)⁺

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PREPARATION 69

(R)-5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(2-(4-methylpiperazin-1-yl)ethyl)-6-(4-(4-methylpiperazin-1-yl)phenyl)-N-(piperidin-3-yl)pyrimidin-4-amine

Obtained as an hydrochloride salt (93%) from *tert*-butyl (3*R*)-3-{{5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}[2-(4-methylpiperazin-1-yl)ethyl] amino}piperidine-1-carboxylate (Preparation 68) following the experimental procedure described in Preparation 31.

LRMS (m/z): 631 (M+1)⁺.

15 PREPARATION 70

2-((3*R*)-3-{{6-Chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl}amino} piperidin-1-yl)-2-oxoethanol

Triethylamine (0.32 mL, 0.85 mmol) was added to a solution of (*R*)-3-(3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 23a, 0.28 g, 0.65 mmol) in *N,N'*-dimethylformamide (1.5 mL) and the reaction mixture was stirred at room temperature for 30 minutes. A mixture of 2-hydroxyacetic acid (0.060 g, 0.79 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (0.32 g, 0.85 mmol) in *N,N'*-dimethylformamide (1.5 mL) was stirred at room temperature for 30 minutes and poured into the first solution. The resulting mixture was stirred at room temperature for 4h. Water was added and the resulting precipitate was filtered, washed with water and dried to yield the title compound (0.27 g, 100%) as a white solid.

LRMS (m/z): 423 (M+1)⁺.

30 **EXAMPLES**

EXAMPLE 1

Benzyl 4-[6-(((3*R*)-1-(cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl]piperazine-1-carboxylate

35 3-[(2,5-Dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile (prepared as described in BE875054(A1), 0.18 g, 1.03 mmol) was added to a solution of (*R*)-benzyl 4-(5-fluoro-2-(6-fluoroimidazo[1,2-a] pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)piperazine-1-

carboxylate (Preparation 5, 0.38 g, 0.69 mmol) and triethylamine (0.35 mL, 2.51 mmol) in dichloromethane (20 mL) and the resulting mixture was stirred for 2h at ambient temperature. The solvent was evaporated and the residue was purified by flash chromatography (dichloromethane to dichloromethane/ methanol 95:5) to give the title compound (333 mg, 79%) as a yellow solid.

LRMS (m/z): 617 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.75 - 1.87 (m, 4H), 3.63 - 3.77 (m, 14H), 4.22 (bs, 1H), 4.75 - 4.85 (m, 1H), 5.30 (s, 2H), 7.17- 7.25 (m, 2H), 7.33 - 7.40 (m, 4H), 7.62 - 7.77 (m, 1H), 8.42 (s, 1H), 9.62 - 9.72 (m, 1H).

EXAMPLE 2

3-((3*R*)-3-[[5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-ylpyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile

A solution of benzyl 4-[6-[[[(3*R*)-1-(cyanoacetyl)piperidin-3-yl]amino]-5-fluoro-2-(6-fluoroimidazo [1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]piperazine-1-carboxylate (Example 1, 0.15 g, 0.24 mmol) in ethanol (4 mL) and tetrahydrofuran (2 mL) was hydrogenated by H-Cube hydrogenator (ambient pressure, 40 °C and 0.5 mL/min) using a Pd/C 10% cartridge. The solvent was evaporated and the residue was dried to give the title compound (118 mg, 99%) as a yellow solid.

LRMS (m/z): 483 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.73 - 1.87 (m, 4H), 2.06 - 2.20 (m, 4H), 3.00 - 3.08 (m, 4H), 3.70 - 3.81 (m, 10H), 4.20 (bs, 1H), 4.93 - 5.00 (m, 1H), 7.20 - 7.30 (m, 1H), 7.62 - 7.73 (m, 1H), 8.37 (d, 1H), 9.68 - 9.75 (m, 1H).

EXAMPLE 3

Benzyl {4-[6-[[[(3*R*)-1-(cyanoacetyl)piperidin-3-yl]amino]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*] pyridin-3-yl)pyrimidin-4-yl]piperazin-1-yl}acetate

A mixture of 3-((3*R*)-3-[[5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-ylpyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile (Example 2, 0.15 g, 0.31 mmol), benzyl 2-bromoacetate (0.05 mL, 0.34 mmol) and triethylamine (0.08 mL, 0.61 mmol) in tetrahydrofuran (2 mL) was stirred overnight at ambient temperature. The solvent was evaporated and the crude was partitioned between water and dichloromethane. The organic layer was separated, washed with brine, dried by Phase Separator and evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 95:5) to give the title compound (152 mg, 74%).

LRMS (m/z): 629 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.70 - 1.85 (m, 4H), 2.70 - 2.78 (m, 4H), 3.30 - 3.55 (m, 4H), 3.75 - 3.85 (m, 6H), 4.20 (bs, 1H), 4.70 - 4.82 (m, 1H), 5.19 (s, 2H), 7.15 - 7.25 (m, 1H), 7.33 - 7.40 (m, 5H), 7.62 - 7.75 (m, 1H), 8.38 (d, 1H), 9.65 - 9.73 (m, 1H).

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EXAMPLE 4

3-((3*R*)-3-([6-[4-(Benzyloxy)piperidin-1-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

Obtained as a yellow solid (86%) from 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile and (*R*)-6-(4-(benzyloxy)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 7) following the experimental procedure as described in Example 1 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol 95:5).

LRMS (m/z): 587 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.73 - 1.87 (m, 4H), 2.01 - 2.09 (m, 4H), 3.38 - 3.60 (m, 4H), 3.68 - 3.79 (m, 4H), 4.05 - 4.15 (m, 2H), 4.17 - 4.23 (m, 1H), 4.62 (s, 2H), 4.68 - 4.80 (m, 1H), 7.15 - 7.25 (m, 1H), 7.27 - 7.35 (m, 2H), 7.36 - 7.40 (m, 4H), 7.62 - 7.73 (m, 1H), 8.35 - 8.43 (d, 1H), 9.71 - 9.76 (m, 1H).

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EXAMPLE 5

3-((3*R*)-3-([6-{4-[(Benzyloxy)acetyl]piperazin-1-yl}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

A mixture of 3-((3*R*)-3-([5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-yl]pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Example 2, 0.20 g, 0.42 mmol), 2-(benzyloxy) acetic acid (0.14 mL, 1.09 mmol), *N,N*-dimethylpyridin-4-amine (0.12 g, 0.98 mmol) and 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1,1,3,3-tetramethyl isouronium tetrafluoroborate (0.32 g, 1.00 mmol) in dichloromethane (12 mL) was stirred at ambient temperature for 48h. The reaction mixture was washed with a saturated aqueous solution of sodium carbonate, dried by Phase Separator and the solvent evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 95:5) to give the title compound (140 mg, 31%) as a colourless oil.

LRMS (m/z): 629 (M+1)⁺.

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EXAMPLE 6

3-((3*R*)-3-[[5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-glycoloylpiperazin-1-yl)pyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (36%) from 3-((3*R*)-3-[[5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-ylpyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile (Example 2),
2-hydroxy acetic acid, *N*-ethyl-*N*-isopropylpropan-2-amine and 2-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate in *N,N*-dimethylformamide following the experimental procedure as described in Example 5 followed by purification of the crude product by flash chromatography.

LRMS (*m/z*): 540 (*M*+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.75 - 2.00 (m, 4H), 3.35 - 3.51 (m, 4H), 3.52 - 3.72 (m, 4H), 3.73 - 3.90 (m, 4H), 4.17 - 4.30 (m, 4H), 4.82 - 4.93 (m, 1H), 7.17 - 7.30 (m, 1H), 7.62 - 7.73 (m, 1H), 8.34 - 8.45 (d, 1H), 9.60 - 9.70 (m, 1H).

EXAMPLE 7**{4-[6-[[3-((3*R*)-1-(Cyanoacetyl)piperidin-3-yl]amino)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]piperazin-1-yl}acetic acid**

Lithium hydroxide monohydrate (0.01 g, 0.24 mmol) was added to a mixture of benzyl {4-[6-[[3-((3*R*)-1-(cyanoacetyl)piperidin-3-yl]amino)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]piperazin-1-yl}acetate (Example 3, 0.14 g, 0.22 mmol), tetrahydrofuran (4 mL) and water (4 mL) and the reaction mixture was stirred overnight at ambient temperature. The organic solvent was evaporated, additional water was added and the aqueous solution was acidified with 1N solution of hydrochloric acid. Dichloromethane was added, the organic layer was separated, dried by Phase Separator and the solvent was evaporated to dryness. The residue was purified by reverse phase chromatography to give the title compound (65 mg, 53%) as a white solid.

LRMS (*m/z*): 540 (*M*+1)⁺

¹H NMR δ (300 MHz, DMSO-*d*₆): 1.76 - 1.86 (m, 4H), 2.05 - 2.20 (m, 4H), 2.75 (s, 2H), 3.80 - 4.25 (m, 10H), 7.09 - 7.20 (m, 1H), 7.49 - 7.58 (m, 1H), 7.77 - 7.86 (m, 1H), 8.42 - 8.48 (m, 1H), 9.70 - 9.83 (m, 1H).

EXAMPLE 8**3-((3*R*)-3-[[5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a solid (8%) from 3-((3*R*)-3-[[6-[4-(benzyloxy)piperidin-1-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile (Example 4) following the experimental procedure as described in Example 2 (under

the following conditions: 50 bar, 50 °C and 1.0 mL/min) followed by reverse phase chromatography.

LRMS (m/z): 497 (M+1)⁺.

¹H NMR δ (300 MHz, CDCl₃): 1.50 - 1.78 (m, 4H), 1.80 - 2.01 (m, 4H), 2.95 - 3.40 (m, 4H), 3.70 - 3.95 (m, 3H), 4.00 - 4.25 (m, 4H), 4.70 - 4.80 (m, 1H), 7.31 - 7.48 (m, 1H), 7.58 - 7.73 (m, 1H), 8.30 - 8.41 (m, 1H), 9.78 - 10.00 (m, 1H).

EXAMPLE 9

***Tert*-butyl {4-[6-[(*(3R)*-1-(cyanoacetyl)piperidin-3-yl]amino}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]piperazin-1-yl}acetate**

Obtained as a solid (37%) from 3-((*(3R)*-3-[[5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-ylpyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile (Example 2) and *tert*-butyl 2-bromoacetate following the experimental procedure as described in Example 3 followed by purification of the crude product by flash chromatography.

LRMS (m/z): 596 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.75 - 1.80 (m, 13H), 2.76 (s, 2H), 3.50 - 3.80 (m, 14H), 4.13 - 4.27 (m, 1H), 4.70 - 4.82 (m, 1H), 7.18 - 7.28 (m, 1H), 7.63 - 7.73 (m, 1H), 8.33 - 8.44 (d, 1H), 9.67 - 9.75 (m, 1H).

EXAMPLE 10

3-[(*(3R)*-3-[(5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(hydroxymethyl)piperidin-1-yl]pyrimidin-4-yl]amino)piperidin-1-yl]-3-oxopropanenitrile

Obtained as a solid (64%) from (*(R)*)-(1-(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)piperidin-4-yl)methanol (Preparation 9) and 3-[(2,5-dioxo pyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Example 1 followed by purification of the crude product by flash chromatography.

LRMS (m/z): 511 (M+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.24 - 1.55 (m, 3H), 1.67 - 2.05 (m, 5H), 2.06 - 2.27 (m, 1H), 2.94 - 3.16 (m, 2H), 3.17 - 3.31 (dd, 1H), 3.31 - 3.40 (m, 1H), 3.40 - 3.44 (s, 1H), 3.50 - 3.61 (m, 3H), 3.61 - 3.83 (m, 2H), 4.12 - 4.28 (m, 4H), 4.32 - 4.57 (m, 2H), 4.66 - 4.82 (m, 1H), 7.14 - 7.25 (m, 1H), 7.59 - 7.74 (m, 1H), 8.32 - 8.38 (s, 1H), 8.40 - 8.45 (s, 1H), 9.70 - 9.80 (m, 1H).

EXAMPLE 11

3-((3*R*)-3-[(5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-{4-[(1-methyl-1*H*-imidazol-2-yl)methyl]piperazin-1-yl}pyrimidin-4-yl)amino]piperidin-1-yl)-3-oxopropanenitrile

A mixture of 3-((3*R*)-3-[(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-yl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Example 2, 0.08 g, 0.17 mmol), 2-(chloromethyl)-1-methyl-1*H*-imidazole (0.07 g, 0.42 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.30 mL, 1.72 mmol) in dichloromethane (6 mL) was stirred at ambient temperature for 3h. Additional *N*-ethyl-*N*-isopropylpropan-2-amine (0.30 mL, 1.72 mmol) and 2-(chloromethyl)-1-methyl-1*H*-imidazole (0.07 g, 0.42 mmol) were added and the mixture was stirred overnight. The crude was partitioned between water and dichloromethane. The organic layer was separated, washed with water and 4% aqueous solution of sodium hydrogencarbonate, dried by Phase Separator and the solvent was evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 9:1) to give the title compound (43 mg, 45%).

LRMS (*m/z*): 576 (*M*+1)⁺.

¹H NMR δ (300 MHz, CDCl₃): 1.73 - 1.87 (m, 4H), 2.57 - 2.65 (m, 4H), 3.66 - 3.77 (m, 13H), 4.20 (bs, 1H), 4.70 - 4.80 (m, 1H), 6.89 (d, 1H), 6.96 (d, 1H), 7.16 - 7.24 (m, 1H), 7.61 - 7.72 (m, 1H), 8.34 - 8.42 (d, 1H), 9.66 - 9.73 (m, 1H).

EXAMPLE 12

3-((3*R*)-3-[(5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

Obtained as a brown solid (54%) from (*R*)-1-(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)azetidin-3-ol (Preparation 11) and 3-[(2,5-dioxopyrrolidin-1-yl) oxy]-3-oxopropanenitrile in *N,N'*-dimethylformamide following the experimental procedure as described in Example 1.

LRMS (*m/z*): 469 (*M*+1)⁺.

¹H-NMR δ (300 MHz, DMSO-*d*₆): 1.20 - 1.37 (m, 1H), 1.38 - 1.69 (m, 2H), 1.72 - 1.85 (m, 1H), 1.94 - 2.10 (m, 1H), 2.53 - 2.80 (dt, 1H), 2.94 - 3.10 (m, 1H), 3.56 - 3.77 (dd, 1H), 3.79 - 4.03 (m, 2H), 4.03 - 4.24 (m, 1H), 4.33 - 4.46 (dd, 1H), 4.56 - 4.70 (m, 1H), 5.73 - 5.82 (dd, 1H), 6.96 - 7.09 (m, 1H), 7.45 - 7.57 (m, 1H), 7.74 - 7.85 (m, 1H), 8.35 - 8.46 (d, 1H), 9.75 - 9.88 (m, 1H).

EXAMPLE 13

3-((3*R*)-3-([6-[4-(Benzyloxy)piperidin-1-yl]-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methyl pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

Obtained as a red solid (66%) from (*R*)-6-(4-(benzyloxy)piperidin-1-yl)-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methyl-*N*-(piperidin-3-yl)pyrimidin-4-amine

- 5 (Preparation 15) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Example 1.

LRMS (*m/z*): 583 (*M*+1)⁺.

¹H NMR δ (300 MHz, CDCl₃): 1.60 - 1.90 (m, 4H), 2.00 - 2.15 (m, 4H), 2.17 (s, 3H), 3.05 - 3.18 (m, 2H), 3.53 - 3.73 (m, 8H), 4.25 - 4.37 (m, 2H), 4.63 (s, 2H),
10 7.15 - 7.24 (m, 1H), 7.30 - 7.40 (m, 5H), 7.60 - 7.72 (m, 1H), 8.40 - 8.50 (d, 1H), 9.90 - 9.95 (m, 1H).

EXAMPLE 14**3-[(3*R*)-3-({5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(2-hydroxyethyl) piperazin-1-yl]pyrimidin-4-yl]amino)piperidin-1-yl]-3-oxopropanenitrile**

Obtained as a solid (28%) from 3-((3*R*)-3-([5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-piperazin-1-ylpyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Example 2) and 2-bromo ethanol in dichloromethane following the experimental procedure described in Example 3.

20 LRMS (*m/z*): 526 (*M*+1)⁺

EXAMPLE 15**[1-(5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[(1*S*)-1-(5-fluoropyridin-2-yl) ethyl]amino)pyrimidin-4-yl)piperidin-4-yl]methanol**

- 25 A mixture of (*S*)-6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-*N*-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidin-4-amine (Preparation 16, 0.075 g, 0.19 mmol), and piperidin-4-ylmethanol (0.107 g, 0.93 mmol) was heated at 130 °C for 1h. Water was added and the suspension was stirred to obtain a solid. The solid was filtered, washed with water and dried under vacuum to yield the title compound (80 mg, 86%) as a solid.

30 LRMS (*m/z*): 484 (*M*+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.28 - 1.47 (m, 2H), 1.75 - 1.94 (m, 3H), 2.93 - 3.10 (t, 2H), 3.52 - 3.61 (d, 2H), 4.41 - 4.54 (d, 2H), 5.30 - 5.43 (q, 1H), 5.66 - 5.75 (m, 1H), 7.12 - 7.23 (m, 1H), 7.32 - 7.44 (m, 2H), 7.58 - 7.68 (dd, 1H), 8.31 - 8.39 (s, 1H), 8.42 - 8.50 (d, 1H), 9.58 - 9.66 (dd, 1H).

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EXAMPLE 16

3-((3*R*)-3-([5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-hydroxyphenyl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile

10% Palladium on carbon (0.03 g, 0.32 mmol) was added to a suspension of (*R*)-3-(3-((6-(4-(benzyloxy)phenyl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 19, 0.07 g, 0.11 mmol) in tetrahydrofuran (3 mL) and the resulting mixture was stirred under an hydrogen atmosphere at ambient temperature for 72h. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was evaporated. The residue was partitioned between water and dichloromethane. The organic layer was separated, washed with 4% aqueous solution of sodium hydrogencarbonate, dried by Phase Separator and the solvent was evaporated to dryness. The residue was purified by reverse phase chromatography to obtain the title compound (2 mg, 4%) as a monoformate salt.

LRMS (m/z): 490 (M+1)⁺

¹H NMR δ (300 MHz, DMSO-*d*₆): 1.60 - 1.80 (m, 4H), 4.00 - 4.22 (m, 6H), 4.25 (bs, 1H), 7.05 (d, 1H), 7.62 (q, 1H), 7.81 (dd, 1H), 7.90 (m, 1H) 7.98 (d, 2H), 8.59 - 8.65 (d, 1H), 9.95 - 9.99 (m, 1H).

EXAMPLE 17

3-[(3*R*)-3-([5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methoxybenzyl)piperazin-1-yl]pyrimidin-4-yl]amino)piperidin-1-yl]-3-oxopropanenitrile

Obtained as a yellow solid (94%) from 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropane nitrile and (*R*)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-(4-methoxybenzyl)piperazin-1-yl)-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 21) following the experimental procedure as described in Example 1.

LRMS (m/z): 602 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.70 - 1.90 (m, 4H), 2.57 (m, 6H), 3.38 - 3.41 (m, 1H), 3.52 - 3.58 (m, 4H), 3.73 - 3.80 (m, 5H), 3.83 (s, 3H), 4.18 (bs, 1H), 6.89 (s, 1H), 6.91 (s, 1H), 7.22 - 7.30 (m, 3H), 7.61 - 7.70 (m, 1H), 8.34 (d, 1H), 9.73 (dq, 1H).

EXAMPLE 18

3-[(3*R*)-3-([5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-hydroxybenzyl)piperazin-1-yl]pyrimidin-4-yl]amino)piperidin-1-yl]-3-oxopropanenitrile

Obtained as a yellow solid (23%) from 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropane nitrile and (*R*)-4-((4-(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(piperidin-3-ylamino)pyrimidin-4-yl)piperazin-1-yl)methyl)phenol (Preparation 22) following the

experimental procedure as described in Example 1 followed by purification of the crude product by flash chromatography (diethyl ether/ethanol).

LRMS (m/z): 588 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.50 - 1.80 (m, 4H), 2.54 - 2.64 (m, 6H), 3.38 - 3.41 (m, 1H), 3.48 - 3.57 (m, 4H), 3.70 - 3.81 (m, 7H), 4.20 (bs, 1H), 4.67 - 4.77 (m, 1H), 6.82 (d, 2H), 7.17 - 7.24 (m, 3H), 7.60 - 7.72 (m, 1H), 8.31 - 8.43 (m, 1H), 9.67 - 9.74 (m, 1H).

EXAMPLE 19

3-((3*R*)-3-((5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-{4-[(4-methylpiperazin-1-yl) methyl]phenyl}pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

A Schlenk tube was charged with (*R*)-3-(3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 23, 0.05 g, 0.12 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl) piperazine (0.04 g, 0.13 mmol), 2M aqueous cesium carbonate solution (0.18 mL, 0.35 mmol) and 1,4-dioxane (2 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then [1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloride (0.01 g, 0.01 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred overnight at 80 °C. The mixture was partitioned between 4% aqueous solution of sodium hydrogencarbonate and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulphate and the solvent was evaporated to dryness. The residue was purified by flash chromatography (dichloromethane to dichloromethane/methanol 95:5) to give the title compound (19 mg, 28%) as a light brown solid.

LRMS (m/z): 587 (M+1)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.75 - 2.00 (m, 4H), 2.31 (d, 3H), 2.42 - 2.62 (m, 4H), 3.42 - 3.50 (m, 6H), 3.58 (s, 2H), 3.60 - 3.64 (m, 4H), 4.25 - 4.38 (m, 1H), 5.20 - 5.30 (m, 1H), 6.73 (d, 1H), 7.13 (d, 1H), 7.52 (t, 2H), 7.66 - 7.76 (m, 1H), 8.03 (d, 1H), 8.53 (d, 1H), 9.95 (dq, 1H).

EXAMPLE 20

(*S*)-5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-*N*-(1-(5-fluoropyridin-2-yl) ethyl)-6-(4-((1-methyl-1*H*-imidazol-2-yl)methyl)piperazin-1-yl)pyrimidin-4-amine

Obtained as a yellow oil (67%) from (*S*)-6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-*N*-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidin-4-amine (Preparation 16) and 1-[(1-Methyl-1*H*-imidazol-2-yl)methyl]piperazine (Preparation 24) following the

experimental procedure as described in Preparation 16 (using *N,N*-dimethylacetamide as solvent and heating at 130 °C overnight) followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol 9:1).

LRMS (m/z): 549 (M+1)⁺.

- 5 ¹H NMR δ (300 MHz, CDCl₃): 1.64 (d, 3H), 2.53 - 2.65 (m, 4H), 3.65 - 3.68 (m, 2H), 3.69 - 3.74 (m, 4H), 3.74 - 3.77 (m, 3H), 5.31 - 5.43 (m, 1H), 5.75 (dd, 1H), 6.88 (d, 1H), 6.95 (d, 1H), 7.18 (ddd, 1H), 7.35 - 7.43 (m, 2H), 7.62 (ddd, 1H), 8.33 (s, 1H), 8.43 - 8.48 (m, 1H), 9.57 (ddd, 1H).

10 EXAMPLE 21

3-[(3*R*)-3-({5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-4-yl}amino)piperidin-1-yl]-3-oxopropanenitrile

- Obtained as a solid (38%) from (*R*)-3-(3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 23)
15 and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine following the experimental procedure as described in Example 19 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol 95:5).

LRMS (m/z): 573 (M+1)⁺

- 20 ¹H NMR δ (300 MHz, CDCl₃): 1.75 - 2.01 (m, 4H), 2.20 - 2.51 (m, 6H), 3.57 - 3.63 (m, 4H), 3.70 - 3.80 (m, 4H), 3.85 - 3.95 (m, 1H), 4.30 - 4.45 (m, 2H), 5.23 - 5.35 (m, 1H), 6.82 (d, 1H), 7.17 - 7.22 (m, 1H), 7.25 - 7.32 (m, 1H), 7.52 - 7.58 (m, 1H), 7.67 - 7.77 (m, 1H), 8.06 (d, 1H), 8.54 (d, 1H), 9.97 (qd, 1H).

25 EXAMPLE 22

3-[(3*R*)-3-({5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino)piperidin-1-yl]-3-oxopropanenitrile

- Obtained as a solid (25%) from (*R*)-3-(3-((6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 23)
30 and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine following the experimental procedure as described in Example 19 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol 95:5).

LRMS (m/z): 573 (M+1)⁺

- 35 ¹H NMR δ (300 MHz, CDCl₃): 1.70 - 1.99 (m, 4H), 2.37 (s, 3H), 2.61 (t, 4H), 3.35 - 3.41 (m, 4H), 3.47 - 3.60 (m, 6H), 4.29 (bs, 1H), 5.13 - 5.22 (m, 1H), 7.05 (m,

1H), 7.17 - 7.30 (m, 2H), 7.64 - 7.74 (m, 1H), 8.06 (d, 1H), 8.50 (d, 1H), 9.97 (qd, 1H).

EXAMPLE 23

5 ***N*-(1-Benzylpiperidin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-ylpyrimidin-4-amine**

Obtained as a solid (53%) from (*N*-(1-benzylpiperidin-4-yl))-6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-amine (Preparation 25) and morpholine following the experimental procedure as described in Example 15.

10 LRMS (m/z): 506 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 2.09 - 2.20 (d, 2H), 2.20 - 2.33 (t, 2H), 2.85 - 3.01 (m, 2H), 3.55 - 3.60 (s, 2H), 3.67 - 3.78 (m, 4H), 3.79 - 3.89 (m, 4H), 3.96 - 4.12 (m, 1H), 4.67 - 4.76 (d, 1H), 7.17 - 7.25 (m, 1H), 7.28 - 7.32 (m, 1H), 7.32 - 7.39 (m, 2H), 7.61 - 7.72 (dd, 1H), 8.35 - 8.41 (s, 1H), 9.78 - 9.85 (dd, 1H).

15

EXAMPLE 24

3-((3*R*)-3-{{[6-[4-{{1-[(2*R*)-2,3-Dihydroxypropyl]-1*H*-benzimidazol-2-yl)methyl]piperazin-1-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile and 3-((3*R*)-3-{{[6-[4-{{1-[(2*S*)-2,3-dihydroxypropyl]-1*H*-benzimidazol-2-yl)methyl]piperazin-1-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

To a solution of 3-((*R*)-3-((6-(4-((1-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)methyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl) amino)piperidin-1-yl)-3-oxopropanenitrile and 3-((*R*)-3-((6-(4-((1-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)methyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 27, 0.02 g, 0.03 mmol) in acetonitrile (0.5 mL) was added 2N hydrochloric acid and the reaction mixture was stirred at ambient temperature for 1h. The organic solvent was evaporated, water was added and the crude was basified by addition of solid sodium carbonate. Dichloromethane was added, the organic layer was separated by Phase Separator and the solvent was evaporated to dryness to give the title compound (17 mg, 76%) as a mixture of diastereoisomers.

LRMS (m/z): 687 (M+2)⁺

35

EXAMPLE 25***N*-[(1*S*,2*S*)-Bicyclo[2.2.1]hept-2-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(pyrrolidin-1-ylmethyl)piperidin-1-yl]pyrimidin-4-amine**

Prepared from 3-(4-chloro-5-fluoro-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-2-yl)-6-fluoroimidazo[1,2-*a*]pyridine (Preparation 28) and (1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-amine following the experimental procedure as described in Preparation 16 using *N,N'*-dimethyl acetamide as solvent and heating at 120 °C for 5h. The solid obtained was purified by flash chromatography (chloroform to chloroform/methanol 95:5) to obtain a yellow gum. The gum was dissolved in diisopropylether and 4M solution of hydrogen chloride in 1,4-dioxane was added. The yellow solid formed was filtered to yield the hydrochloride salt of the title compound (30%).

LRMS (m/z): 508 (M+1)+

EXAMPLE 26**4-({5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(pyrrolidin-1-ylmethyl)piperidin-1-yl]pyrimidin-4-yl}amino)bicyclo[2.2.2]octan-1-ol**

Prepared from 3-(4-chloro-5-fluoro-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-2-yl)-6-fluoroimidazo[1,2-*a*]pyridine (Preparation 28) and 4-aminobicyclo[2.2.2]octan-1-ol in *N,N'*-dimethylacetamide following the experimental procedure as described in Preparation 16. The solid obtained was purified by flash chromatography (chloroform to chloroform/methanol 94:6). The resulting gum was treated with diisopropylether and filtered to yield the title compound (11 mg, 11%) as a solid.

LRMS (m/z): 538 (M+1)+

¹H-NMR δ (300 MHz, CD₃OD): 1.19 - 1.38 (m, 3H), 1.38 - 1.51 (m, 2H), 1.51 - 1.73 (m, 3H), 1.79 - 1.98 (m, 2H), 2.00 - 2.24 (m, 4H), 2.31 - 2.47 (d, 2H), 3.01 - 3.21 (m, 4H), 3.64 - 3.77 (m, 2H), 3.86 - 3.96 (d, 1H), 4.46 - 4.58 (d, 2H), 8.03 - 8.11 (d, 2H), 8.67 - 8.72 (s, 1H), 10.41 - 10.48 (m, 1H).

EXAMPLE 27**3-((3*R*)-3-[(2-(Dimethylamino)ethyl][5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-yl]pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a solid (29%) from (*R*)-*N*1-(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)-*N*2,*N*2-dimethyl-*N*1-(piperidin-3-yl)ethane-1,2-diamine hydrochloride (Preparation 31) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile in *N,N'*-dimethyl formamide following the experimental procedure as described in Example 1 followed by purification of the crude product by reverse phase chromatography.

LRMS (m/z): 554 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 1.70 - 1.86 (m, 2H), 1.90 - 2.18 (m, 4H), 2.27 - 2.35 (s, 6H), 2.49 - 2.62 (m, 3H), 2.85 - 2.97 (m, 1H), 3.08 - 3.21 (m, 1H), 3.41 - 3.56 (m, 3H), 3.56 - 3.65 (m, 2H), 3.65 - 3.72 (m, 4H), 3.72 - 3.83 (m, 2H), 3.83 - 3.92 (m, 4H), 4.07 - 4.26 (m, 2H), 4.60 - 4.81 (m, 2H), 7.16 - 7.24 (m, 1H), 7.61 - 7.73 (m, 1H), 8.30 - 8.40 (ds, 1H), 9.62 - 9.72 (m, 1H).

EXAMPLE 28

N-[5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholin-4-ylpyrimidin-4-yl]-

N-[(1S)-1-(5-fluoropyridin-2-yl)ethyl]-N',N'-dimethylethane-1,2-diamine

Obtained as a gum (22%) from (S)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(1-(5-fluoropyridin-2-yl)ethyl)-6-morpholinopyrimidin-4-amine (Preparation 32) and (2-chloroethyl)dimethylamine hydrochloride following the experimental procedure as described in Preparation 30 followed by purification of the crude product by reverse phase chromatography.

LRMS (m/z): 527 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 1.72 - 1.82 (d, 3H), 2.15 - 2.24 (s, 6H), 2.44 - 2.58 (m, 1H), 3.42 - 3.64 (m, 2H), 3.64 - 3.73 (m, 4H), 3.82 - 3.91 (m, 4H), 5.77 - 5.88 (m, 1H), 7.14 - 7.24 (m, 1H), 7.30 - 7.46 (m, 2H), 7.60 - 7.69 (m, 1H), 8.31 - 8.39 (s, 1H), 8.42 - 8.50 (s, 1H), 9.62 - 9.69 (m, 1H).

EXAMPLE 29

3-[(3R)-3-({5-Fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-[2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl]pyrimidin-4-yl}amino)piperidin-1-yl]-3-

oxopropanenitrile

Obtained as a solid (8%) from 3-((3R)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl]amino]piperidin-1-yl)-3-oxopropanenitrile (Preparation 23) and (2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl)boronic acid (Preparation 33b) following the experimental procedure as described in Example 19 followed by purification of the crude product by flash chromatography (dichloromethane/methanol 98:2 to dichloromethane/methanol/ammonia 100:8:1).

LRMS (m/z): 587 (M+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.76 - 2.01 (m, 3H), 2.03 - 2.31 (m, 6H), 2.41 (s, 3H), 2.56 - 2.67 (m, 2H), 2.72 - 2.85 (m, 2H), 3.32 - 3.62 (m, 4H), 3.66 - 3.81 (m, 3H), 3.83 - 4.06 (m, 3H), 4.20 - 4.53 (m, 1H), 5.06 - 5.48 (m, 1H), 7.10 - 7.25 (m, 3H), 7.60 - 7.87 (m, 1H), 8.21 - 8.38 (m, 1H), 8.42 (d, 1H), 9.72 - 10.18 (m, 1H).

EXAMPLE 30

3-((3*R*)-3-[[6-{2-[4-(Dimethylamino)piperidin-1-yl]pyridin-4-yl]-5-fluoro-2-(6-fluoroimidazo [1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (35%) from 3-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile (Preparation 23) and {2-[4-(dimethyl amino)piperidin-1-yl]pyridin-4-yl}boronic acid (Preparation 34b) following the experimental procedure as described in Example 19 followed by purification of the crude product by reverse phase chromatography (water to methanol).

LRMS (m/z): 601 (M+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.58 - 1.72 (m, 3H), 1.98 (d, 4H), 2.17 - 2.29 (m, 1H), 2.34 (s, 6H), 2.39 - 2.53 (m, 1H), 2.87 - 3.05 (m, 2H), 3.36 - 3.70 (m, 5H), 3.82 - 3.98 (m, 1H), 4.29 - 4.41 (m, 1H), 4.43 - 4.60 (m, 2H), 5.20 - 5.40 (m, 1H), 7.16 - 7.18 (m, 1H), 7.24 - 7.31 (m, 1H), 7.43 (s, 1H), 7.61 - 7.82 (m, 1H), 8.30 - 8.35 (m, 1H), 8.52 (d, 1H), 9.86 - 10.07 (m, 1H).

EXAMPLE 31

3-((3*R*)-3-[[6-(4-{4-[2-(Dimethylamino)ethoxy]benzyl}piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (23%) from 3-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile (Preparation 23) and *N,N*-dimethyl-2-(4-(piperazin-1-ylmethyl)phenoxy)ethanamine hydrochloride (Preparation 35b) in *N,N*-dimethyl acetamide following the experimental procedure described in Preparation 16 followed by purification of the crude product by reverse phase chromatography (water/ammonia 1000:1 to methanol).

LRMS (m/z): 659 (M+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.74 - 1.98 (m, 4H), 2.08 - 2.25 (m, 1H), 2.35 (s, 6H), 2.51 - 2.66 (m, 4H), 2.75 (t, 2H), 3.12 - 3.32 (m, 2H), 3.57 - 3.59 (m, 4H), 3.69 - 3.87 (m, 5H), 4.17 - 4.27 (m, 1H), 4.31 - 4.45 (m, 1H), 4.65 - 4.89 (m, 1H), 6.91 (d, 2H), 7.14 - 7.37 (m, 3H), 7.59 - 7.79 (m, 1H), 8.38 (d, 1H), 9.35 - 9.93 (m, 1H).

EXAMPLE 32

3-((3*R*)-3-{{6-[2-(1,4-Diazepan-1-yl)pyridin-4-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl) pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as an orange solid (85%) from *tert*-butyl 4-{4-[6-{{(3*R*)-1-(cyanoacetyl)piperidin-3-yl]amino}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]

- 5 pyridin-2-yl]-1,4-diazepane-1-carboxylate (Preparation 37) following the experimental procedure as described in Preparation 31 followed by purification of the crude product using an SCX column (eluting with ammonia 7.0 M in methanol).

LRMS (*m/z*): 574 (*M*+1)⁺

- 10 ¹H-NMR δ (300 MHz, CDCl₃): 1.76 - 2.09 (m, 5H), 2.12 - 2.24 (m, 1H), 2.80 - 3.02 - 3.10 (m, 2H), 3.06 - 3.21 (m, 2H), 3.36 - 3.43 (m, 6H), 3.76 - 3.99 (m, 5H), 4.26 - 4.48 (m, 2H), 7.04 - 7.20 (m, 3H), 7.68 (s, 1H), 8.32 (t, 1H), 8.51 (d, 1H), 9.81 - 10.12 (m, 1H).

EXAMPLE 33

- 15 **3-[(3*R*)-3-{{5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[6-(4-methyl-1,4-diazepan-1-yl) pyridin-3-yl]pyrimidin-4-yl]amino}piperidin-1-yl]-3-oxopropanenitrile**

- A Schlenk tube was charged with 3-((3*R*)-3-{{6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile (Preparation 23, 0.1 g, 0.23 mmol), [6-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl]boronic acid (Preparation 38, 0.22 g, 0.93 mmol), 2M aqueous sodium carbonate solution (139 μL, 0.28 mmol) and 1,4-dimethoxyethane (4 mL). The Schlenk tube was subjected to three cycles of evacuation-backfilling with argon and then tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.02 mmol) was added. After three further cycles of evacuation-backfilling with argon, the Schlenk tube was sealed and the mixture was stirred and heated at 90 °C overnight. The solvent was removed and the residue was purified by reverse phase chromatography (water to methanol) to yield the title compound (42 mg, 28%) as a yellow solid.

LRMS (*m/z*): 587 (*M*+1)⁺

- 30 ¹H-NMR δ (300 MHz, CDCl₃): 1.76 - 2.30 (m, 6H), 2.41 (s, 3H), 2.54 - 2.81 (m, 4H), 3.24 - 4.00 (m, 8H), 4.18 - 4.52 (m, 2H), 5.05 - 5.34 (m, 2H), 6.59 - 6.73 (m, 1H), 7.43 - 7.78 (m, 1H), 8.02 - 8.32 (m, 1H), 8.51 (d, 1H), 8.97 (s, 1H), 9.81 - 10.00 (m, 1H).

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EXAMPLE 34

3-((3*R*)-3-((5-Fluoro-2-imidazo[1,2-*a*]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (75%) from 3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-oxopropanenitrile and (*R*)-5-fluoro-2-(imidazo[1,2-*a*]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 41b) following the experimental procedure as described in Example 1 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol/ammonia 40:4:0.2).

LRMS (*m/z*): 583 (*M*+2)⁺

¹H NMR δ (300 MHz, CDCl₃): 1.22 - 1.33 (m, 2H), 1.70 - 2.05 (m, 4H), 2.16 - 2.26 (m, 2H), 2.48 (s, 3H), 2.75 - 2.90 (m, 6H), 3.45 - 3.63 (m, 5H), 3.71 - 3.95 (m, 3H), 4.25 - 4.36 (m, 1H), 4.40 - 4.48 (m, 1H), 7.02 (t, 1H), 7.33 (q, 1H), 7.52 (t, 2H), 7.73 (t, 1H), 8.04 (d, 2H), 8.48 (d, 1H), 9.85 - 9.97 (m, 1H).

EXAMPLE 35**3-((3*R*)-3-((5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a solid (11%) from 3-((3*R*)-3-[[5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-formylphenyl)pyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 42b) and 1-methyl-1,4-diazepane following the experimental procedure as described in Preparation 40b followed by purification of the crude product by reverse phase chromatography.

LRMS (*m/z*): 601 (*M*+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.69 - 2.04 (m, 7H), 2.16 - 2.32 (m, 1H), 2.40 (s, 3H), 2.58 - 2.87 (m, 6H), 3.27 - 3.64 (m, 4H), 3.74 (s, 1H), 3.82 - 4.01 (m, 1H), 4.22 - 4.54 (m, 2H), 5.23 - 5.40 (m, 1H), 7.15 - 7.35 (m, 2H), 7.54 (t, 2H), 7.62 - 7.77 (m, 1H), 8.03 (d, 2H), 8.51 (d, 1H).

EXAMPLE 36**3-((3*R*)-3-[[6-{2-[4-(Dimethylamino)piperidin-1-yl]pyridin-4-yl}-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a solid (27%) from 3-((3*R*)-3-[[6-chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 43b) and {2-[4-(dimethylamino)piperidin-1-yl]pyridin-4-yl}boronic acid (Preparation 34b) following the experimental procedure as described in Example 19 followed by

purification of the crude product by reverse phase chromatography (gradient from water with 0.04% hydrochloric acid 37% to methanol).

LRMS (m/z): 598 (M+1)⁺.

¹H-NMR δ (300 MHz, CD₃OD): 1.46 - 1.59 (m, 2H), 1.72 - 1.85 (m, 2H), 1.93 - 2.01 (m, 2H), 2.09 (s, 3H), 2.16 - 2.27 (m, 1H), 2.34 (s, 6H), 2.45 - 2.60 (m, 2H), 2.77 (dd, 1H), 2.91 (t, 2H), 3.78 (d, 1H), 3.89 - 3.96 (m, 1H), 4.13 - 4.32 (m, 2H), 4.43 (d, 2H), 6.80 (d, 1H), 7.01 (s, 1H), 7.42 (dd, 1H), 7.64 - 7.72 (m, 1H), 8.21 (dd, 1H), 8.43 - 8.57 (m, 1H), 9.95 - 10.02 (m, 1H).

10 EXAMPLE 37

3-[(3*R*)-3-({2-(6-Fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methyl-6-[2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl]pyrimidin-4-yl)amino)piperidin-1-yl]-3-oxopropanenitrile

Obtained as a solid (33%) from 3-((3*R*)-3-[(6-chloro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 43b) and [2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl]boronic acid (Preparation 33b) following the experimental procedure as described in Example 19 followed by purification of the crude product by reverse phase chromatography (gradient from water with 0.04% hydrochloric acid 37% to methanol).

20 LRMS (m/z): 583 (M+1)⁺

¹H-NMR δ (300 MHz, CD₃OD): 1.69 - 2.00 (m, 3H), 2.05 - 2.25 (m, 4H), 2.39 (s, 3H), 2.64 (d, 2H), 2.73 - 2.84 (m, 2H), 3.32 - 3.62 (m, 4H), 3.71 (t, 2H), 3.85 - 3.88 (m, 3H), 4.20 - 4.29 (m, 2H), 6.76 (d, 1H), 6.83 (bs, 1H), 7.39 - 7.48 (m, 1H), 7.66 - 7.73 (m, 1H), 8.17 (d, 1H) 8.47 - 8.57 (m, 1H), 10.00 - 10.06 (m, 1H).

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EXAMPLE 38

3-[(3*R*)-3-[(6-{2-[4-(Dimethylamino)piperidin-1-yl]pyridin-4-yl}-2-imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino)piperidin-1-yl]-3-oxopropanenitrile

Obtained as a solid (11%) from (*R*)-3-(3-((6-chloro-2-(imidazo[1,2-*a*]pyridin-3-yl)-5-methyl pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (Preparation 48) and (2-(4-(dimethyl amino)piperidin-1-yl)pyridin-4-yl)boronic acid (Preparation 34b) following the experimental procedure as described in Example 33 followed by purification of the crude product by flash chromatography.

LRMS (m/z): 580 (M+2)⁺.

35 ¹H NMR δ (300 MHz, CDCl₃): 1.35 - 1.55 (m, 7H), 1.73 - 1.90 (m, 4H), 2.07 - 2.13 (m, 1H), 2.14 - 2.24 (m, 2H), 2.26 - 2.33 (m, 1H), 2.79 (s, 6H), 3.17 - 3.35 (m, 2H), 3.55 - 3.75 (m, 4H), 4.10 (bs, 1H), 4.38 (bs, 1H), 4.58 (d, 1H), 6.79 -

6.87 (m, 2H), 6.98 (q, 1H), 7.34 (t, 1H), 7.74 (d, 1H), 8.31 (t, 1H), 8.53 (d, 1H), 9.86 (d, 1H).

EXAMPLE 39

5 **3-((3*R*)-3-[[6-(4-{4-[2-(Dimethylamino)ethoxy]benzyl}piperazin-1-yl)-5-fluoro-2-imidazo[1,2-*a*]pyridin-3-yl]pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a beige solid (29%) from (*R*)-6-(4-(4-(2-(dimethylamino)ethoxy)-benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-*a*]pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 52) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure described in Example 1 followed by purification of the crude product by flash chromatography.

LRMS (*m/z*): 641 (*M*+2)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.71 - 2.00 (m, 4H), 2.06 - 2.23 (m, 2H), 2.26 - 2.42 (s, 6H), 2.51 - 2.62 (m, 4H), 2.69 - 2.78 (t, 2H), 3.09 - 3.20 (dd, 1H), 3.38 - 3.42 (s, 1H), 3.46 - 3.53 (m, 2H), 3.53 - 3.67 (m, 2H), 3.67 - 3.84 (m, 5H), 4.02 - 4.11 (t, 2H), 4.11 - 4.26 (bs, 2H), 4.42 - 4.53 (m, 1H), 4.63 - 4.76 (dd, 1H), 6.85 - 6.92 (d, 2H), 6.92 - 7.01 (m, 1H), 7.17 - 7.26 (d, 2H), 7.29 - 7.37 (m, 1H), 7.64 - 7.75 (dd, 1H), 8.26 - 8.41 (ds, 1H), 9.61 - 9.73 (dd, 1H).

20 EXAMPLE 40

3-((3*R*)-3-{[2-[4-(Dimethylamino)piperidin-1-yl]ethyl][5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-yl]pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (55%) from *N*-{2-[4-(dimethylamino)piperidin-1-yl]ethyl}-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-yl-*N*-[(3*R*)-piperidin-3-yl]pyrimidin-4-amine (Preparation 54b) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Example 1.

LRMS (*m/z*): 638 (*M*+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.54 (dd, 4H), 1.83 (d, 2H), 1.90 - 2.20 (m, 5H), 2.29 (s, 6H), 2.49 - 2.65 (m, 2H), 2.87 - 3.06 (m, 3H), 3.08 - 3.21 (m, 1H), 3.38 - 3.56 (m, 3H), 3.58 - 3.81 (m, 6H), 3.87 (s, 3H), 4.06 - 4.22 (m, 1H), 4.58 - 4.80 (m, 2H), 7.16 - 7.25 (m, 1H), 7.59 - 7.72 (m, 1H), 8.35 (d, 1H), 9.62 - 9.69 (m, 1H).

35 EXAMPLE 41

3-((3*R*)-3-[[6-(4-{4-[2-(Dimethylamino)ethoxy]benzyl}piperazin-1-yl)-2-imidazo[1,2-*a*]pyridin-3-yl)-5-methylpyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (75%) from 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile and (*R*)-6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-*a*]pyridin-3-yl)-5-methyl-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 56) following the experimental procedure as described in Example 1 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol/ammonia 80:8:0.2).

LRMS (*m/z*): 638 (*M*+2)⁺

EXAMPLE 42**3-((3*R*)-3-[[2-(Dimethylamino)ethyl][5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile**

Obtained as a solid from (36%) from 3-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl][2-(dimethylamino)ethyl]amino}piperidin-1-yl)-3-oxopropanenitrile (Preparation 59) and 1-methylpiperazine following the experimental procedure as described in Example 15 heating in a sealed tube at 100 °C for 3h. The crude product was purified by flash chromatography (dichloromethane to dichloromethane/methanol/ammonia 80:20:0.2).

LRMS (*m/z*): 568 (*M*+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.86 - 2.17 (m, 3H), 2.19 - 2.45 (m, 9H), 2.46 - 2.71 (m, 5H), 2.71 - 2.99 (m, 2H), 3.01 - 3.26 (m, 1H), 3.32 - 3.87 (m, 8H), 3.99 - 4.28 (m, 2H), 4.54 - 4.84 (m, 2H), 7.09 - 7.29 (m, 1H), 7.68 (dd, 1H), 8.21 - 8.49 (m, 2H), 9.69 (dd, 1H).

EXAMPLE 43**3-[(3*R*)-3-[[3-(Dimethylamino)propyl][5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl]amino}piperidin-1-yl]-3-oxopropanenitrile**

Obtained as a solid (8%) from *N*-{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}-*N,N'*-dimethyl-*N*-[(3*R*)-piperidin-3-yl]propane-1,3-diamine (Preparation 61) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Example 1 followed by purification by reverse phase chromatography.

LRMS (*m/z*): 657 (*M*+1)⁺

¹H-NMR δ (300 MHz, CDCl₃): 1.63 - 1.73 (m, 8H), 1.81 - 2.05 (m, 2H), 2.07 - 2.20 (m, 1H), 2.25 (s, 3H), 2.37 (s, 3H), 2.51 - 2.68 (m, 3H), 2.93 - 3.29 (m, 2H),

3.30 - 3.34 (m, 2H), 3.43 - 3.66 (m, 3H), 3.68 - 3.89 (m, 2H), 4.12 - 4.47 (m, 2H), 4.62 - 4.85 (m, 2H), 6.98 - 7.12 (m, 2H), 7.17 - 7.38 (m, 2H), 7.58 - 7.84 (m, 1H), 7.87 - 8.11 (m, 1H), 8.42 (d, 1H), 9.77 - 10.14 (m, 1H).

5 EXAMPLE 44

3-[(3*R*)-3-[(2-(Dimethylamino)ethyl){5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino]piperidin-1-yl]-3-oxopropanenitrile

Obtained as a solid (13%) from *N*-{5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}-*N,N'*-dimethyl-*N*-[(3*R*)-piperidin-3-yl]ethane-1,2-diamine (Preparation 63) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Example 1 followed by purification of the crude product by reverse phase chromatography.

LRMS (m/z): 643 (M+1)⁺

15 ¹H-NMR δ (300 MHz, CDCl₃): 1.26 (m, 3H), 1.52 (s, 4H), 1.94 - 2.19 (m, 3H), 2.36 (d, 6H), 2.61 (m, 4H), 2.92 - 3.27 (m, 2H), 3.40 (s, 3H), 3.50 - 3.61 (m, 2H), 3.65 - 3.92 (m, 2H), 4.18 - 4.46 (m, 1H), 4.58 - 4.89 (m, 1H), 7.06 (dd, 2H), 7.19 - 7.33 (m, 1H), 7.63 - 7.78 (m, 1H), 8.00 (dd, 2H), 8.43 (d, 1H), 9.86 - 10.04 (m, 1H).

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EXAMPLE 45

3-{(3*R*)-3-[(5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl)(2-pyrrolidin-1-ylethyl)amino]piperidin-1-yl}-3-oxopropanenitrile

25 Obtained as a solid (52%) from 5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]-*N*-[(3*R*)-piperidin-3-yl]-*N*-(2-pyrrolidin-1-ylethyl)pyrimidin-4-amine (Preparation 65) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropanenitrile following the experimental procedure as described in Example 1.

LRMS (m/z): 669 (M+1)⁺

30 ¹H-NMR δ (300 MHz, CDCl₃): 0.69 - 0.97 (m, 2H), 1.09 - 1.50 (m, 3H), 1.80 (s, 4H), 1.96 - 2.23 (m, 3H), 2.28 - 2.48 (m, 3H), 2.53 - 2.75 (m, 6H), 2.93 - 3.26 (m, 2H), 3.38 (s, 3H), 3.55 (d, 2H), 3.67 - 3.90 (m, 3H), 4.25 - 4.44 (m, 1H), 4.60 - 4.91 (m, 2H), 7.06 (dd, 2H), 7.18 - 7.39 (m, 1H), 7.63 - 7.77 (m, 1H), 8.01 (d, 2H), 8.43 (d, 1H), 9.84 - 10.05 (m, 1H).

35

EXAMPLE 46

3-((3*R*)-3-[[2-(Dimethylamino)ethyl][6-[4-(dimethylamino)piperidin-1-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (26%) from 3-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl][2-(dimethylamino)ethyl]amino}piperidin-1-yl)-3-oxopropane nitrile (Preparation 59) and *N,N*-dimethylpiperidin-4-amine in *N,N'*-dimethylacetamide following the experimental procedure as described in Preparation 16 followed by purification of the crude product by reverse phase chromatography.

LRMS (m/z): 596 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 1.87 - 2.17 (m, 5H), 2.21 - 2.50 (m, 13H), 2.52 - 2.54 (m, 3H), 2.80 - 3.28 (m, 5H), 3.37 - 3.67 (m, 5H), 3.69 - 3.83 (m, 1H), 4.11 (dd, 1H), 4.26 - 4.44 (m, 2H), 4.57 - 4.82 (m, 1H), 7.12 - 7.25 (m, 1H), 7.56 - 7.74 (m, 1H), 8.34 (d, 1H), 9.65 - 9.78 (m, 1H).

EXAMPLE 47

3-((3*R*)-3-[[2-(Dimethylamino)ethyl][6-[2-(dimethylamino)pyridin-4-yl]-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (47%) from 3-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl][2-(dimethylamino)ethyl]amino}piperidin-1-yl)-3-oxopropane nitrile (Preparation 59) and [2-(dimethylamino)pyridin-4-yl]boronic acid (Preparation 66b) following the experimental procedure as described in Example 19 followed by purification of the crude product by reverse phase chromatography.

LRMS (m/z): 590 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 1.91 - 2.21 (m, 3H), 2.34 (s, 6H), 2.51 - 2.72 (m, 3H), 3.04 (t, 1H), 3.20 (s, 6H), 3.45 - 3.59 (m, 2H), 3.60 - 3.91 (m, 3H), 4.21 - 4.41 (m, 1H), 4.60 - 4.88 (m, 2H), 7.07 (t, 1H), 7.15 (d, 1H), 7.71 (m, 2H), 8.34 (t, 1H), 8.38 - 8.49 (m, 1H), 9.96 (m, 1H).

EXAMPLE 48

3-((3*R*)-3-[[2-(Dimethylamino)ethyl][5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-3-oxopropanenitrile

Obtained as a solid (47%) from 3-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl][2-(dimethylamino)ethyl]amino}piperidin-1-yl)-3-oxopropane nitrile (Preparation 59) and 1-methyl-1,4-diazepane following the experimental

procedure as described in Example 15 followed by purification by reverse phase chromatography.

LRMS (m/z): 582 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 1.86 - 2.18 (m, 5H), 2.32 (s, 6H), 2.43 (s, 3H),
2.50 - 2.71 (m, 4H), 2.79 - 2.99 (m, 3H), 3.16 (t, 1H), 3.37 - 3.67 (m, 4H), 3.69 -
3.93 (m, 4H), 3.99 - 4.23 (m, 2H), 4.57 - 4.81 (m, 2H), 7.15 - 7.23 (m, 1H), 7.63
(dd, 1H), 8.33 (d, 1H), 9.72 (td, 1H).

EXAMPLE 49

3-[(3*R*)-3-[(2-(Dimethylamino)ethyl){5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[3-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl}amino]piperidin-1-yl]-3-oxopropanenitrile

Obtained as a solid (34%) from 3-[(3*R*)-3-{[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl][2-(dimethylamino)ethyl]amino}piperidin-1-yl]-3-oxopropane
nitrile (Preparation 59) and 1-methyl-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (Preparation 67b) following the experimental procedure as described
in Example 33 followed by purification of the crude product by reverse phase chromatography.

LRMS (m/z): 644 (M+1)+

¹H-NMR δ (300 MHz, CDCl₃): 1.93 - 2.25 (m, 5H), 2.28 - 2.51 (m, 7H), 2.54 -
2.82 (m, 5H), 2.98 - 3.43 (m, 6H), 3.48 - 3.67 (m, 2H), 3.70 - 3.92 (m, 3H), 4.17
- 4.47 (m, 2H), 4.60 - 4.86 (m, 2H), 7.10 (d, 1H), 7.17 - 7.27 (m, 1H), 7.34 - 7.53
(m, 2H), 7.61 - 7.76 (m, 2H), 8.42 (d, 1H), 9.91 - 10.09 (m, 1H).

EXAMPLE 50

3-[(3*R*)-3-{[5-Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-[4-(4-methylpiperazin-1-yl)phenyl]pyrimidin-4-yl][2-(4-methylpiperazin-1-yl)ethyl]amino}piperidin-1-yl]-3-oxopropanenitrile

Obtained as a solid (26%) from (*R*)-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)-6-(4-(4-methylpiperazin-1-yl)phenyl)-*N*-(piperidin-3-yl)pyrimidin-4-amine (Preparation 69) and 3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropane nitrile following the experimental procedure as described in Example 1 followed by purification of the crude product by flash chromatography (dichloromethane to dichloromethane/methanol/ammonia 40:8:1).

LRMS (m/z): 698 (M+1)⁺.

¹H-NMR δ (300 MHz, CDCl₃): 1.21 - 1.58 (m, 3H), 1.67 - 1.90 (m, 2H), 1.94 -
2.19 (m, 3H), 2.34 (d, 6H), 2.44 - 2.82 (m, 10H), 2.90 - 3.28 (m, 2H), 3.38 (s,

3H), 3.50 - 3.65 (m, 2H), 3.64 - 3.93 (m, 3H), 4.09 - 4.47 (m, 2H), 4.59 - 4.88 (m, 1H), 7.05 (dd, 2H), 7.16 - 7.37 (m, 1H), 7.60 - 7.81 (m, 1H), 7.99 (d, 2H), 8.42 (d, 1H), 9.81 - 10.09 (m, 1H).

5 EXAMPLE 51

2-((3*R*)-3-[[Fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)-6-morpholin-4-yl]pyrimidin-4-yl]amino}piperidin-1-yl)-2-oxoethanol

Obtained as an orange solid (48%) from 2-((3*R*)-3-[[6-chloro-5-fluoro-2-(6-fluoroimidazo[1,2-*a*]pyridin-3-yl)pyrimidin-4-yl]amino}piperidin-1-yl)-2-oxoethanol

10 (Preparation 70) and morpholine following the experimental procedure as described in Example 15.

LRMS (*m/z*): 474 (*M*+1)⁺.

¹H-NMR δ (300 MHz, CDCl₃): 1.51 - 1.99 (m, 5 H), 2.08 - 2.26 (m, 1 H), 3.00 - 3.51 (m, 3 H), 3.50 - 3.79 (m, 5 H), 3.81 - 3.90 (m, 3 H), 3.93 - 4.54 (m, 1 H),
15 4.09 - 4.30 (m, 2 H), 4.69 - 4.90 (m, 1 H), 7.10 - 7.37 (m, 1 H), 7.56 - 7.82 (m, 1 H), 8.42 (d, 1 H), 9.37 - 9.90 (m, 1 H).

PHARMACOLOGICAL ACTIVITY

20 **In vitro JAK kinase Assays**

Compounds were screened for their ability to inhibit JAK1, JAK2 and JAK3 using the assays as indicated below.

The catalytic domains of human JAK1 (aa 850-1154), JAK2 (aa 826-1132), JAK3 (aa
25 795-1124) and Tyk2 (aa 871-1187) were expressed as N-terminal GST-fusion proteins using a baculovirus expression system and were purchased from Carna Biosciences.

The enzymatic activity was assayed using as substrate a biotinylated peptide, poly (GT)-Biotin (CisBio). The peptide concentration in the reactions was 60 nM for JAK1, 20 nM for JAK2, 140 nM for JAK3 and 50 nM for Tyk2. The degree of phosphorylation
30 was detected by TR-FRET (time-resolved fluorescence energy transfer).

IC₅₀s of compounds were measured for each kinase in a reaction mixture containing the enzyme, ATP and the peptide in 8 mM MOPS (pH 7.0), 10 mM MgCl₂, 0.05% β-mercaptoethanol, 0.45 mg/ml BSA. The ATP concentration in the reactions was 3 μM for JAK1, 0.2 μM for JAK2, 0.6 μM for JAK3 and 1.8 μM for Tyk2. The enzymatic
35 reactions took place for 30 minutes at room temperature. Then, the reactions were stopped with 20 μL of quench detection buffer (50 mM HEPES, 0.5 M KF, EDTA 0.25 M, 0.1% (w/v) BSA, pH 7.5) containing 0.115 μg/mL of anti-phosphoTyr (PT66)-

Cryptate (CisBio) and a variable concentration of SA-XL665 (CisBio) to keep the SA-B ratio constant. Incubate for 3 h and read on Victor 2V spectrofluorometer (PerkinElmer) set to read fluorescence resonance energy transfer.

5 Some of the acronyms used above have the following meaning:

AA: aminoacids

GST: glutathione-S-transferase

MOPS: 3-(N-morpholino)propane sulfonic acid

BSA: bovine serum albumin

10 ATP: adenosine tri-phosphate

EDTA: ethylenediaminetetraacetic acid

HEPES: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

SA-XL665: Streptavidin (biotin-binding tetrameric protein isolated from *Streptomyces avidinii*) XL665

15

Table 1 depicts IC₅₀ values for certain exemplary compounds described in the invention. In Table 1, “A” represents an IC₅₀ value of less than 0.1 μM (100 nM), “B” represents an IC₅₀ value in the range of 0.1 μM (100 nM) to 1 μM (1000 nM), and C represents an IC₅₀ value higher than 1 μM (1000 nM).

20

Table 1

Example No.	IC ₅₀ JAK3 (μM)	IC ₅₀ JAK2 (μM)	IC ₅₀ JAK1 (μM)
11	A	A	A
13	A	A	B
15	A	A	A
25	A	A	C
28	A	A	A
34	A	A	A
35	A	A	A
38	A	A	A
40	B	A	B
45	A	A	A
48	B	A	A
51	A	A	A

It can be seen from the Table 1 that compounds of formula (I) are potent inhibitors of JAK1, JAK2 and JAK3 kinases. Preferred compounds of the invention possess an IC₅₀ value for the inhibition of JAK1, JAK2 and JAK3 kinases (determined as defined above) of less than 1 μ M (1000 nM), preferably of less than 0.5 μ M (500 nM), more preferably of less than 0.2 μ M (200 nM) for each Janus Kinase

The invention is also directed to a compound of the invention as described herein for use in the treatment of the human or animal body by therapy. Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, or mixtures thereof. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

Combinations

The compounds of the present invention may also be combined with other active compounds in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases.

The combinations of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of myeloproliferative disorders (such as polycythemia vera, essential thrombocythemia or myelofibrosis), leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory, more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis, such as (a) Dihydrofolate reductase inhibitors, such as Methotrexate or CH-1504; (b) Dihydroorotate dehydrogenase (DHODH) inhibitors such as leflunomide, teriflunomide, or the compounds described in the International Patent Application Nos. WO2008/077639 and WO2009/021696; (c) Immunomodulators such as Glatiramer acetate (Copaxone), Laquinimod or Imiquimod; (d) Inhibitors of DNA synthesis and repair, such as Mitoxantrone or Cladribine; (e) Immunosuppressants, such as Imuran (azathioprine) or Purinethol (6-mercaptopurine or 6-MP); (f) Anti-alpha 4 integrin antibodies, such as Natalizumab (Tysabri); (g) Alpha 4 integrin antagonists such as R-

1295, TBC-4746, CDP-323, ELND-002, Firategrast or TMC-2003; (h) Corticoids and glucocorticoids such as prednisone or methylprednisolone, fluticasone, mometasone, budesonide, ciclesonide or beta-metasone; (i) Fumaric acid esters, such as BG-12; (j) Anti-tumor necrosis factor-alpha (Anti-TNF-alpha), such as Infliximab, Adalimumab, or
5 Certolizumab pegol; (k) Soluble Tumor necrosis factor-alpha (TNF-alpha) receptors such as Etanercept; (l) Anti-CD20 (lymphocyte protein) monoclonal antibodies such as Rituximab, Ocrelizumab, Ofatumumab or TRU-015; (m) Anti-CD52 (lymphocyte protein) monoclonal antibodies such as alemtuzumab; (n) Anti-CD25 (lymphocyte protein) such as daclizumab; (o) Anti-CD88 (lymphocyte protein), such as eculizumab or
10 pexelizumab; (p) Anti-Interleukin 6 Receptor (IL-6R), such as tocilizumab; (q) Anti-Interleukin 12 Receptor (IL-12R) / Interleukin 23 Receptor (IL-23R), such as ustekinumab; (r) Calcineurin inhibitors such as cyclosporine A, pimecrolimus or tacrolimus; (s) Inosine-monophosphate dehydrogenase (IMPDH) inhibitors, such as mycophenolate mophetyl, ribavirin, mizoribine or mycophenolic acid; (t) Cannabinoid
15 receptor agonists such as Sativex; (u) Chemokine CCR1 antagonists such as MLN-3897 or PS-031291; (v) Chemokine CCR2 antagonists such as INCB-8696; (w) Necrosis factor-kappaB (NF-kappaB or NFkB) Activation Inhibitors such as Sulfasalazine, Igaratimod or MLN-0415; (x) Adenosine A_{2A} agonists, such as ATL-313, ATL-146e, CGS-21680, Regadenoson or UK-432,097; (y) Sphingosine-1 (S1P)
20 phosphate receptor agonists such as fingolimod, BAF-312, or ACT128800; (z) Sphingosine-1 (S1P) liase inhibitors such as LX2931; (aa) Spleen tyrosine kinase (Syk) inhibitors, such as R-112; (bb) Protein Kinase Inhibitors (PKC) inhibitors, such as NVP-AEB071; (cc) Anti-cholinergic agents such as tiotropium or aclidinium; (dd) Beta adrenergic agonists such as formoterol, indacaterol or abediterol (LAS100977); (ee)
25 Compounds having bifunctional Muscarinic Antagonist-Beta2 Agonist activity (MABAs); (ff) Histamine 1 (H1) receptor antagonists, such as azelastine or ebastine; (gg) Chemoattractant receptor homologous molecule expressed on TH₂ cells (CRTH2) inhibitors, such as OC-459, AZD-1981, ACT-129968, QAV-680; (hh) Vitamin D derivatives like calcipotriol (Daivonex); (ii) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2)
30 inhibitors such as aceclofenac, diclofenac, ibuprofen, naproxen, apricoxib, celecoxib, cimicoxib, deracoxib, etoricoxib, lumiracoxib, parecoxib sodium, rofecoxib, selenocoxib-1 or valdecoxib; (jj) Anti-allergic agents; (kk) Anti-viral agents; (ll) Phosphodiesterase (PDE) III inhibitors; (mm) Phosphodiesterase (PDE) IV inhibitors such as roflumilast or
35 GRC-4039; (nn) Dual Phosphodiesterase (PDE) III/IV inhibitors; (oo) Xanthine derivatives, such as theophylline or theobromine; (pp) p38 Mitogen-Activated Protein Kinase (p38 MAPK) Inhibitors such as ARRY-797; (qq) Mitogen-activated extracellular

signal regulated kinase kinase (MEK) inhibitor, such as ARRY-142886 or ARRY-438162; (rr) Phosphoinositide 3-Kinases (PI3Ks) inhibitors; (ss) Interferons comprising Interferon beta 1a such as Avonex from Biogen Idec, CinnoVex from CinnaGen and Rebif from EMD Serono, and Interferon beta 1b such as Betaferon from Schering and Betaseron from Berlex; and (tt) Interferon alpha such as Sumiferon MP.

Specific examples of suitable corticoids and glucocorticoids that can be combined with the JAK inhibitors of the present invention are prednisolone, methylprednisolone, dexamethasone, dexamethasone cipeclate, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, flucinolone acetonide, flucinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, RPR-106541, deprodone propionate, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate, hydrocortisone probutate, clobetasol propionate, clobetasol butyrate, clobetasol, desonide, desoximethasone, diflorasone, difluprednate, flucinonide, fluocortin butyl, fluocortolone, halometasone, hydrocortisone-17-butyrate, hydrocortisone acetate, hydrocortisone probutate, prednicarbate, triamcinolone, ulobetasol.

In a preferred embodiment of the present invention, the specific examples of suitable corticoids and glucocorticoids that can be combined with the JAK inhibitors of the present invention are prednisolone, methylprednisolone, dexamethasone, dexamethasone cipeclate, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, flucinolone acetonide, flucinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, RPR-106541, deprodone propionate, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone,

betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate and hydrocortisone probutate.

- 5 Specific examples of suitable Syk kinase inhibitors that can be combined with the JAK inhibitors of the present invention are fosfaminib (from Rigel), R-348 (from Rigel), R-343 (from Rigel), R-112 (from Rigel), piceatannol, 2-(2-Aminoethylamino)-4-[3-(trifluoromethyl)phenylamino] pyrimidine-5-carboxamide, R-091 (from Rigel), 6-[5-Fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino]-2,2-dimethyl-3,4-dihydro-
 10 2H-pyrido[3,2-b][1,4]oxazin-3-one benzenesulfonate (R-406 from Rigel), 1-(2,4,6-Trihydroxyphenyl)-2-(4-methoxyphenyl)ethan-1-one, N-[4-[6-(Cyclobutylamino)-9H-purin-2-ylamino]phenyl]-N-methylacetamide (QAB-205 from Novartis), 2-[7-(3,4-Dimethoxyphenyl)imidazo[1,2-c]pyrimidin-5-ylamino]pyridine-3-carboxamide dihydrochloride (BAY-61-3606 from Bayer) and AVE-0950 (from Sanofi-Aventis).

15

- Specific examples of suitable M3 antagonists (anticholinergics) that can be combined with the JAK inhibitors of the present invention are tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, zamifenacin, revatropate, espatropate, darotropium bromide, CI-923, NPC-14695, BEA-2108, 3-[2-
 20 Hydroxy-2,2-bis(2-thienyl)acetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane salts (in particular acridinium salts, more preferably acridinium bromide), 1-(2-Phenylethyl)-3-(9H-xanthen-9-ylcarbonyloxy)-1-azoniabicyclo[2.2.2]octane salts, 2-oxo-1,2,3,4-tetrahydroquinazoline-3-carboxylic acid endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester salts (DAU-5884), 3-(4-Benzylpiperazin-1-yl)-1-cyclobutyl-1-hydroxy-1-
 25 phenylpropan-2-one (NPC-14695), N-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2(R)-[3,3-difluoro-1(R)-cyclopentyl]-2-hydroxy-2-phenylacetamide (J-104135), 2(R)-Cyclopentyl-2-hydroxy-N-[1-[4(S)-methylhexyl]piperidin-4-yl]-2-phenylacetamide (J-106366), 2(R)-Cyclopentyl-2-hydroxy-N-[1-(4-methyl-3-pentenyl)-4-piperidyl]-2-phenylacetamide (J-104129), 1-[4-(2-Aminoethyl)piperidin-1-yl]-2(R)-[3,3-
 30 difluorocyclopent-1(R)-yl]-2-hydroxy-2-phenylethan-1-one (Banyu-280634), N-[N-[2-[N-[1-(Cyclohexylmethyl)piperidin-3(R)-ylmethyl]carbamoyl]ethyl]carbamoylmethyl]-3,3,3-triphenylpropionamide (Banyu CPTP), 2(R)-Cyclopentyl-2-hydroxy-2-phenylacetic acid 4-(3-azabicyclo[3.1.0]hex-3-yl)-2-butynyl ester (Ranbaxy 364057), 3(R)-[4,4-Bis(4-fluorophenyl)-2-oxoimidazolidin-1-yl]-1-methyl-1-[2-oxo-2-(3-thienyl)ethyl]pyrrolidinium
 35 iodide, N-[1-(3-Hydroxybenzyl)-1-methylpiperidinium-3(S)-yl]-N-[N-[4-(isopropoxycarbonyl)phenyl]carbamoyl]-L-tyrosinamide trifluoroacetate, UCB-101333, Merck's OrM3, 7-endo-(2-hydroxy-2,2-diphenylacetoxy)-9,9-dimethyl-3-oxa-9-

azoniatricyclo[3.3.1.0(2,4)]nonane salts, 3(R)-[4,4-Bis(4-fluorophenyl)-2-oxoimidazolidin-1-yl]-1-methyl-1-(2-phenylethyl)pyrrolidinium iodide, trans-4-[2-[Hydroxy-2,2-(dithien-2-yl)acetoxy]-1-methyl-1-(2-phenoxyethyl)piperidinium bromide from Novartis (412682), 7-(2,2-diphenylpropionyloxy)-7,9,9-trimethyl-3-oxa-9-
5 azoniatricyclo[3.3.1.0*2,4*]nonane salts, 7-hydroxy-7,9,9-trimethyl-3-oxa-9-azoniatricyclo[3.3.1.0*2,4*]nonane 9-methyl-9H-fluorene-9-carboxylic acid ester salts, all of them optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally in the form of their pharmacologically-compatible acid addition salts. Among the salts chlorides, bromides,
10 iodides and methanesulphonates are preferred.

Specific examples of suitable beta adrenergic agonists (β 2-agonists) that can be combined with the JAK inhibitors of the present invention are are terbutaline sulphate, eformoterol fumarate, formoterol fumarate, bambuterol, ibuterol, isoprenaline
15 hydrochloride, dopexamine, metaprotenerol, tulobuterol, procaterol hydrochloride, sibenadet hydrochloride, mabuterol hydrochloride, albuterol sulphate, salbutamol sulphate, salmefamol, salmeterol xinafoate, carmoterol hydrochloride, (R)-albuterol hydrochloride, Levalbuterol hydrochloride; Levosalbutamol hydrochloride; (-)-Salbutamol hydrochloride, formoterol, (R,R)-Formoterol tartrate; Arformoterol tartrate,
20 sulfoneterol, Bedoradrine sulphate, Indacaterol, Trantinterol hydrochloride, Milveterol hydrochloride, Olodaterol, fenoterol hydrobromide, rimoterol hydrobromide, riproterol hydrochloride, Vilanterol broxaterol, pirbuterol hydrochloride, bitolterol mesylate, clenbuterol hydrochloride, AZD-3199, GSK-159802; GSK-597901, GSK-678007, GSK-961081; 4-[2-[3-(1H-Benzimidazol-1-yl)-1,1-dimethylpropylamino]-1-hydroxyethyl]-2-(4-methoxybenzylamino)phenol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-domethoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, KUL-1248, HOKU-81, SM-110444, RP-58802B, abediterol (LAS
25 100977) and compounds described in PCT patent applications Nos. WO 2007/124898, WO 2006/122788A1, WO 2008/046598, WO 2008095720, WO 2009/068177 and WO 2010/072354.

Specific examples of suitable Phosphodiesterase IV (PDE IV) inhibitors that can be
35 combined with the JAK inhibitors of the present invention are benafentrine dimaleate, etazolate, denbufylline, rolipram, cipamfylline, zardaverine, arofylline, filaminast, tielukast, tofomilast, piclamilast, tolafentrine, mesopram, drotaverine hydrochloride,

lirimilast, roflumilast, cilomilast, oglemilast, apremilast, tetomilast, filaminast, (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine (NCS-613), N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide (D-4418), 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride (V-11294A), 6-[3-(N,N-Dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methylquinoline-3-carboxamide hydrochloride (GSK-256066), 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one (T-440), (-)-trans-2-[3'-[3-(N-Cyclopropylcarbamoyl)-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]-3-fluorobiphenyl-4-yl]cyclopropanecarboxylic acid, AN2728, E-6005, DRM02, MK-0873, CDC-801, UK-500001, BLX-914, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one (IPL-455903), ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the compounds claimed in the PCT patent applications number WO 03/097613, WO 2004/058729, WO 2005/049581, WO 2005/123693, WO 2005/123692, and WO 2010/069504.

Examples of suitable Phosphoinositide 3-Kinases (PI3Ks) inhibitors that can be combined with the JAK inhibitors of the present invention are 2-Methyl-2-[4-[3-methyl-2-oxo-8-(3-quinolinyl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl]phenyl]propanenitrile (BEZ-235 from Novartis), CAL-101 (from Calistoga Pharmaceuticals) and N-Ethyl-N'-[3-(3,4,5-trimethoxyphenylamino)pyrido[2,3-b]pyrazin-6-yl]thiourea (AEZS-126 from Aeterna Zentaris).

The compounds of formula (I) and the combinations of the invention may be used in the treatment of myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, wherein the use of a JAK inhibitor is expected to have a beneficial effect, for example rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (such as ulcerative colitis or Crohn's disease), dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

The active compounds in the combination product may be administered together in the same pharmaceutical composition or in different compositions intended for separate,

simultaneous, concomitant or sequential administration by the same or a different route.

It is contemplated that all active agents would be administered at the same time, or very close in time. Alternatively, one or two actives could be administered in the morning and the other (s) later in the day. Or in another scenario, one or two actives could be administered twice daily and the other (s) once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably at least two, and more preferably all, of the actives would be administered together at the same time.

Preferably, at least two, and more preferably all actives would be administered as an admixture.

The invention is also directed to a combination product of the compounds of the invention together with one or more other therapeutic agents for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

In another embodiment of the present invention, the pathological condition or disease is selected from respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated; function disorders and neurological disorders; cardiovascular diseases; viral infection; metabolism/endocrine function disorders; neurological disorders and pain; bone marrow and organ transplant rejection; myelo-dysplastic syndrome; myeloproliferative disorders (MPDs); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors.

In a preferred embodiment, the pathological condition or disease is selected from leukemia, lymphomas and solid tumors, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, autoimmune hemolytic anemia, type I diabetes, cutaneous vasculitis, cutaneous lupus erythematosus, dermatomyositis, blistering diseases including but not

limited to pemphigus vulgaris, bullous pemphigoid and epidermolysis bullosa, asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, cough, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

The invention also encompasses the use of a combination of the compounds of the invention together with one or more other therapeutic agents for the manufacture of a formulation or medicament for treating these diseases.

The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis; comprising administering a therapeutically effective amount of a combination of the compounds of the invention together with one or more other therapeutic agents.

The active compounds in the combinations of the invention may be administered by any suitable route, depending on the nature of the disorder to be treated, e.g. orally (as syrups, tablets, capsules, lozenges, controlled-release preparations, fast-dissolving preparations, etc); topically (as creams, ointments, lotions, nasal sprays or aerosols, etc); by injection (subcutaneous, intradermic, intramuscular, intravenous, etc.) or by inhalation (as a dry powder, a solution, a dispersion, etc).

The active compounds in the combination, i.e. the pyridin-2(1H)-one derivatives of the invention, and the other optional active compounds may be administered together in the same pharmaceutical composition or in different compositions intended for separate, simultaneous, concomitant or sequential administration by the same or a different route.

One execution of the present invention consists of a kit of parts comprising a pyridin-2(1H)-one derivative of the invention together with instructions for simultaneous, concurrent, separate or sequential use in combination with another active compound useful in the treatment of myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular useful in the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

Another execution of the present invention consists of a package comprising a pyridin-2(1H)-one derivative of the invention and another active compound useful in the treatment of myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular useful in the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

Pharmaceutical Compositions

Pharmaceutical compositions according to the present invention comprise the compounds of the invention in association with a pharmaceutically acceptable diluent or carrier.

As used herein, the term pharmaceutical composition refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts, solvates, N-oxides, stereoisomers, deuterated derivatives thereof or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

As used herein, a physiologically/pharmaceutically acceptable diluent or carrier refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

The invention further provides pharmaceutical compositions comprising the compounds of the invention in association with a pharmaceutically acceptable diluent or carrier together with one or more other therapeutic agents for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), such as the ones previously described.

The invention is also directed to pharmaceutical compositions of the invention for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory , more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis. The invention also encompasses the use of a pharmaceutical composition of the invention for the manufacture of a medicament for treating these diseases.

The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases (JAK), in particular wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases, more in particular wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis, comprising administering a therapeutically effective amount of a pharmaceutical composition of the invention.

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight, of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, inhalation, topical, nasal, rectal, percutaneous or injectable administration.

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art.

Such compositions and methods for their preparation can be found, for example, in

- 5 Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, Philadelphia, Pa., 2001.

The pharmaceutically acceptable excipients which are admixed with the active compound or salts of such compound, to form the compositions of this invention are
10 well-known per se and the actual excipients used depend inter alia on the intended method of administering the compositions. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

- 15 Additional suitable carriers for formulations of the compounds of the present invention can be found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, Philadelphia, Pa., 2001.

i) Oral Administration

- 20 The compounds of the invention may be administered orally (peroral administration; *per os* (latin)). Oral administration involve swallowing, so that the compound is absorbed from the gut and delivered to the liver via the portal circulation (hepatic first pass metabolism) and finally enters the gastrointestinal (GI) tract.

- 25 Compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, solutions, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art. The active ingredient may also be presented
30 as a bolus, electuary or paste.

Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, talc, gelatine, acacia, stearic acid, starch, lactose and sucrose.

35

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a

suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent.

- 5 Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.
- 10 For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium
- 15 carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl- substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.
- 20 Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol,
- 25 xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate. Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% of the tablet.
- 30 Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet. Other conventional
- 35 ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may include one or more layers and may be coated or uncoated; or encapsulated.

The formulation of tablets is discussed in detail in "Pharmaceutical Dosage Forms: Tablets, Vol. 1 ", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., 1980.

Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatine capsule. Where the composition is in the form of a soft gelatine capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatine capsule.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can be found in Verma et al, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298. The disclosures of these references are incorporated herein by reference in their entireties.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a

suspending agent or flavouring agent. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

ii) Oral mucosal administration

- 5 The compounds of the invention can also be administered via the oral mucosal. Within the oral mucosal cavity, delivery of drugs is classified into three categories: (a) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (b) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa),
10 and (c) local delivery, which is drug delivery into the oral cavity. Pharmaceutical products to be administered via the oral mucosal can be designed using mucoadhesive, quick dissolve tablets and solid lozenge formulations, which are formulated with one or more mucoadhesive (bioadhesive) polymers (such as hydroxy propyl cellulose, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, hydroxy propyl
15 methyl cellulose, hydroxy ethyl cellulose, polyvinyl alcohol, polyisobutylene or polyisoprene); and oral mucosal permeation enhancers (such as butanol, butyric acid, propranolol, sodium lauryl sulphate and others)

iii) Inhaled administration

- 20 The compounds of the invention can also be administered by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using
25 electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may include a bioadhesive agent, for example, chitosan or cyclodextrin.
- 30 Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is
35 preferred. Each capsule or cartridge may generally contain between 0.001-50 mg, more preferably 0.01-5 mg of active ingredient or the equivalent amount of a

pharmaceutically acceptable salt thereof. Alternatively, the active ingredient (s) may be presented without excipients.

Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

For inhalers of the first type, single doses have been weighed by the manufacturer into small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler. Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centrifugal force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients.

Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b) problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or indenture, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has been reported (e. g. Nielsen et al, 1997).

Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with capsule chambers that can be brought in line with the air conduit for dose discharge (e. g. WO91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister foil, or by peeling off the cover foil. When a blister strip is used instead of a disk,

the number of doses can be increased, but it is inconvenient for the patient to replace an empty strip. Therefore, such devices are often disposable with the incorporated dose system, including the technique used to transport the strip and open the blister pockets.

5

Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (Ex. EP0069715) or disks (Ex. GB 2041763; EP 0424790; DE 4239402 and EP 0674533), rotatable cylinders (Ex. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (Ex. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices have measuring slides (Ex. US 5201308 and WO 97/00703) or measuring plungers with a local or circumferential recess to displace a certain volume of powder from the container to a delivery chamber or an air conduit (Ex. EP 0505321, WO 92/04068 and WO 92/04928), or measuring slides such as the Genuair® (formerly known as Novolizer SD2FL), which is described the following patent applications Nos: WO97/000703, WO03/000325 and WO2006/008027.

20

Reproducible dose measuring is one of the major concerns for multi dose inhaler devices.

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The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity.

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For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand, can contain a much higher number of doses, whereas the number of handlings to prime a dose is generally lower.

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Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi dose inhalers can not be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high number of doses in multi-dose devices, powder adhesion onto the inner walls of the air conduits and the de-agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses has been taken (Ex. WO 97/000703). For such semi-permanent multi dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even stricter.

Apart from applications through dry powder inhalers the compositions of the invention can be administered in aerosols which operate via propellant gases or by means of so-called atomisers, via which solutions of pharmacologically-active substances can be sprayed under high pressure so that a mist of inhalable particles results. The advantage of these atomisers is that the use of propellant gases can be completely dispensed with. Such atomiser is the Respimat® which is described, for example, in PCT Patent Applications Nos. W0 91/14468 and WO 97/12687, reference here is being made to the contents thereof.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the active ingredient (s) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1, 1, 2-tetrafluoroethane, 1,1, 1,2, 3,3, 3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant.

The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants (eg. oleic acid or lecithin) and cosolvents (eg. ethanol). Pressurised formulations will generally be retained in a canister (eg. an aluminium canister) closed with a valve (eg. a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μm , preferably 2-5 μm . Particles having a size above 20 μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

Achieving high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient such as lactose or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, preferably crystalline alpha lactose monohydrate.

Pressurized aerosol compositions will generally be filled into canisters fitted with a valve, especially a metering valve. Canisters may optionally be coated with a plastics material e. g. a fluorocarbon polymer as described in W096/32150. Canisters will be fitted into an actuator adapted for buccal delivery.

iv) Nasal mucosal administration

The compounds of the invention may also be administered via the nasal mucosal. Typical compositions for nasal mucosa administration are typically applied by a metering, atomizing spray pump and are in the form of a solution or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents.

v) Parenteral Administration

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle
5 such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. The solubility of compounds of the invention used
10 in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-,
15 controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

20 vi) Topical Administration

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and
25 microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis,
30 phonophoresis, sonophoresis and microneedle or needle-free injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

35 vii) Rectal/Intravaginal Administration

Compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

viii) Ocular Administration

Compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and nonbiodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

ix) Other Technologies

Compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is typically in the range of 0.01-3000 mg, more preferably 0.5-1000 mg of active ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

Preferably, the the pharmaceutical compositions of the invention are made up in a form suitable for oral, inhalation or topical administration, being particularly preferred oral or inhalation administration.

5

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

10

The amount of each active which is required to achieve a therapeutic effect will, of course, vary with the particular active, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

15 The following preparations forms are cited as formulation examples:

Formulation Examples

Formulation Example 1 (Oral suspension)

Ingredient	Amount
Active Compound	3 mg
Citric acid	0,5 g
Sodium chloride	2,0 g
Methyl paraben	0,1 g
Granulated sugar	25 g
Sorbitol (70% solution)	11 g
Veegum K	1,0 g
Flavoring	0,02 g
Dye	0,5 mg
Distilled water	q.s. to 100 mL

Formulation Example 2 (Hard gelatine capsule for oral administration)

Ingredient	Amount
Active Compound	1 mg
Lactose	150 mg
Magnesium stearate	3 mg

5 Formulation Example 3 (Gelatin cartridge for inhalation)

Ingredient	Amount
Active Compound (micronized)	0,2 mg
Lactose	25 mg

Formulation Example 4 (Formulation for inhalation with a DPI)

Ingredient	Amount
Active Compound (micronized)	15 mg
Lactose	3000 mg

10

Formulation Example 5 (Formulation for a MDI)

Ingredient	Amount
Active Compound (micronized)	10 g
1,1,1,2,3,3,3-heptafluoro-n-propane	q.s. to 200 mL

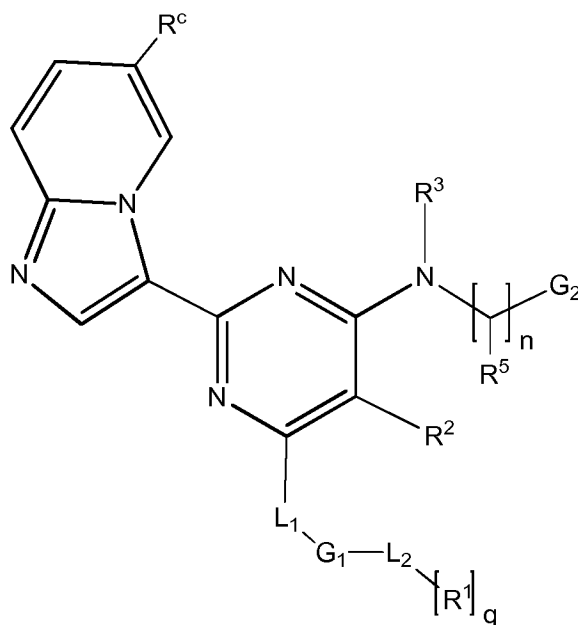
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Modifications, which do not affect, alter, change or modify the essential aspects of the compounds, combinations or pharmaceutical compositions described, are included within the scope of the present invention.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer or deuterated derivative thereof:

5



Formula (I)

wherein

G₁ is selected from the group consisting of a linear or branched C₁₋₄ alkyl group, a
 10 monocyclic C₅₋₈ aryl group, a monocyclic C₃₋₈ cycloalkyl group, a monocyclic 5- to 8-
 membered heteroaryl group containing at least one heteroatom selected from O, S and
 N and a saturated or non-saturated monocyclic 4- to 8- membered heterocyclyl group
 containing at least one heteroatom selected from O, S and N, wherein the alkyl, aryl,
 cycloalkyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted with one
 15 or more substituents selected from a halogen atom, a hydroxyl group, -CHO group, a
 C₁₋₂ alkyl group, a C₁₋₂ hydroxyalkyl group, a di (C₁₋₂ alkyl)amino-C₁₋₄ alkyl group, a C₁₋₂
 carboxyalkyl group, oxo group, and -NR'-SO₂-R'' group,

L₁ is selected from the group consisting of a -(CH₂)₍₀₋₁₎-, -(CH₂)₍₀₋₁₎-O-, -NR^x-(CH₂)₍₀₋₁₎-
 20 group, wherein R^x is selected from a group consisting of a hydrogen atom and a C₁₋₂
 alkyl group optionally substituted with -(CH₂)₍₀₋₂₎NR'R''- group,

L₂ is selected from the group consisting of a -(CH₂)_p-, -(CH₂)-NR-, -O-(CH₂)₍₀₋₂₎-, -(CH₂)₍₀₋₁₎-
 1)-C(O)-(CH₂)₍₀₋₁₎-O-(CH₂)₍₀₋₁₎-, -C(O)-, -S- and -NR- group, wherein R represents a
 25 hydrogen atom or a C₁₋₄ alkyl group optionally substituted with a group selected from -

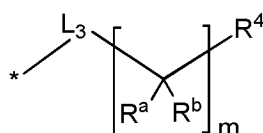
NR'R''- group and a phenyl group wherein said phenyl group is optionally substituted with a hydroxyl group,

R¹ is selected from the group consisting of a hydrogen atom, a linear or branched C₁₋₄ alkyl group optionally substituted with a –NR'R'' group or with –OH group, a monocyclic C₅₋₈ aryl group, a monocyclic C₃₋₈ cycloalkyl group, a mono- or bicyclic 5- to 14-membered heteroaryl group containing at least one heteroatom selected from O, S and N and a mono- or bicyclic 5- to 14- membered heterocyclyl group containing at least one heteroatom selected from O, S and N, wherein the aryl, cycloalkyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a linear or branched C₁₋₆ alkyl group, a linear or branched C₁₋₆ hydroxyalkyl group, a linear or branched C₁₋₄ alkoxy group, a –(O)₍₀₋₁₎(CH₂)₍₀₋₃₎–NR'R'' group, a –CO–O–R^d group, a –CH₂–R^e group, a monocyclic 5-to 8-membered heterocyclyl group containing at least one heteroatom selected from O, S and N and a monocyclic 5-to 8-membered heteroaryl group containing at least one heteroatom selected from O, S and N wherein said heterocyclyl and heteroaryl group independently are optionally substituted with one or more substituents selected from the group consisting of a C₁₋₂ alkyl group and a –NR'R'' group;

R² is selected from the group consisting of a halogen atom and a linear or branched, non-substituted C₁₋₄ alkyl group and a NH₂ group,

R³ is selected from the group consisting of a hydrogen atom, a C₁₋₄ alkyl group and a –(CH₂)₍₂₋₄₎NR'R''- group,

G₂ is selected from the group consisting of a monocyclic C₅₋₈ aryl group, a mono or a bicyclic C₃₋₁₀ cycloalkyl group, a monocyclic 5- to 8- membered heteroaryl group containing at least one heteroatom selected from O, S and N and a monocyclic 5- to 8- membered heterocyclyl group containing at least one heteroatom selected from O, S and N, wherein the aryl, cycloalkyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from a halogen atom, a hydroxyl group, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a C₁₋₂ hydroxyalkyl group, –NR'R'' group and a group of formula (a):



wherein

L₃ represents a direct bond, –CO– group, –S(O)₂–(CH₂)₍₀₋₁₎– group, or a –C(O)O– group, a –NH–CO– group,

- 5 R⁴ is selected from the group consisting of a hydroxyl group, a –(CH₂)₍₀₋₁₎–CN group, a –CF₃ group, a mono cyclic 3 to 8-membered heterocyclyl group containing at least one heteroatom selected from N, O and S, a monocyclic C₅₋₈ aryl group, a linear or branched C₁₋₄ alkyl group, a linear or branched C₁₋₄ alkoxy group, a linear or branched C₁₋₄ hydroxyalkyl group, a C₁₋₂ haloalkyl and a C₁₋₄ aminoalkyl group wherein the alkyl and the hydroxyalkyl groups are optionally substituted with one or more methyl groups,

- R^a and R^b are independently selected from the group consisting of a hydrogen atom, a hydroxyl, a C₁₋₄ alkyl group or R^a and R^b together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl group or a 3- to 5-membered heterocyclic group containing at least one heteroatom selected from N, O and S,

R⁵ is selected from the group consisting of a hydrogen atom and a linear or branched C₁₋₄ alkyl group,

- 20 R^c is selected from the group consisting of a hydrogen atom, a halogen atom, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a C₅₋₈ aryl group, a 5- to 8- membered heteroaryl group containing at least one heteroatom selected from O, S and N and a –NR'R'' group, wherein the heteroaryl group is optionally substituted with one or more substituents selected from the group consisting of a halogen atom and a C₁₋₄ alkyl group,

R^d represents a linear or branched C₁₋₄ alkyl group optionally substituted with one or more substituents selected from a phenyl group, a methyl group and a –NR'R'',

- R^e is selected from the group consisting of a monocyclic C₅₋₈ aryl group and a monocyclic 5- to 8- membered heteroaryl group containing at least one heteroatom selected from O, S and N, which cyclic ring are optionally substituted with one or more substituents selected from a hydroxyl group, a linear or branched C₁₋₄ alkyl group and a –CF₃ group,

- R' and R'' independently represents a hydrogen atom, a C₁₋₄ alkyl group or a C₃₋₆ cycloalkyl group, or R' and R'' together with the nitrogen atom to which they are attached form a 4 to 6 membered N-containing heterocyclic group optionally containing one or more additional heteroatom selected from N, S and O, and optionally substituted with a dimethylamino group,

n, m and q independently have a value of 0 or 1,

p has a value of 0, 1 or 2,

with the proviso that the compound is not any one of the following compounds:

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-

5 yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-1-((R)-3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-
yl)amino)piperidin-1-yl)-2,3-dihydroxypropan-1-one,

(R)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholino-N-(piperidin-3-
yl)pyrimidin-4-amine, and

10 (R)-tert-butyl 3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-
4-yl)amino)piperidine-1-carboxylate.

2. A compound according to claim 1, wherein R^c is selected from the group consisting
of a hydrogen atom, a halogen atom and a methyl group, preferably, a hydrogen atom
15 or a fluorine atom.

3. A compound according to claim 1 or 2, wherein G₁ is selected from the group
consisting of a monocyclic C₅₋₈ aryl group, a monocyclic 5- to 8- membered heteroaryl
group containing at least one heteroatom selected from O, S and N and a monocyclic
20 5- to 8- membered heterocyclyl group containing at least one heteroatom selected from
O, S and N, wherein the aryl, heteroaryl and heterocyclyl groups are unsubstituted or
substituted by one or two substituents selected from a halogen atom, a hydroxyl group,
a C₁₋₄ alkyl group and a C₁₋₂ hydroxyalkyl group.

25 4. A compound according to claim 3, wherein G₁ is selected from the group consisting
of a phenyl group, a pyridyl group and a monocyclic 6- membered heterocyclyl group
containing at least one heteroatom selected from O and N, wherein the phenyl, pyridyl
and heterocyclyl groups are unsubstituted or substituted by one or two substituents
selected from a halogen atom, and a C₁₋₂ alkyl group.

30

5. A compound according to claim 4, wherein G₁ is selected from the group consisting
of a phenyl group, a pyridyl group, a morpholinyl and a piperazinyl group.

6. A compound according to any one of the preceding claims, wherein L₁ is selected
35 from the group consisting of a -(CH₂)₍₀₋₁₎-, -NR^x-(CH₂)₍₁₎- group, wherein R^x is selected
from a group consisting of a hydrogen atom and a C₁₋₂ alkyl group optionally
substituted with -(CH₂)₍₀₋₂₎NR'R''- group, wherein R' and R'' independently represents a

hydrogen atom or a methyl group, preferably, L_1 is selected from the group consisting of direct bond and $-NR^x-(CH_2)_{(1)}$ - group, wherein R^x is selected from a group consisting of a hydrogen atom and a methyl group.

5 7. A compound according to claim 6, wherein L_1 represents a direct bond.

8. A compound according to any one of the preceding claims, wherein L_2 is selected from the group consisting of a $-(CH_2)_p-$, $-(CH_2)_{(0-1)}-C(O)-(CH_2)_{(0-1)}-O-(CH_2)_{(0-1)}-$, and $-NR-$ group, wherein R represents a hydrogen atom or a methyl group, wherein p has a value of 0 or 1, preferably, L_2 is selected from the group consisting of a $-(CH_2)_p-$,
10 $-N(CH_3)-$, $-(CH_2)-C(O)-O-(CH_2)-$, and $-(CH_2)-C(O)-O-$, wherein p has a value of 0 or 1.

9. A compound according to claim 8, wherein L_2 is selected from the group consisting of $-(CH_2)_p-$, wherein p has a value of 0 or 1
15

10. A compound according to any one of the preceding claims, wherein R^1 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group, a monocyclic C_{5-8} aryl group, a mono- or bicyclic 5- to 14- membered heteroaryl group containing at least one heteroatom selected from N and a monocyclic 5- to 8-
20 membered heterocyclyl group containing at least one heteroatom selected from N, wherein the aryl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a linear or branched C_{1-5} alkyl group, a linear C_{1-2} alkoxy group, and $-(O)_{(0-1)}(CH_2)_{(0-3)}-NR'R''$ group, wherein R' and R'' independently represents a hydrogen
25 atom or a methyl group, and q has a value of 0 or 1

11. A compound according to claim 10, wherein R^1 is selected from the group consisting of a hydrogen atom, a branched C_{3-4} alkyl group a monocyclic C_{5-8} aryl group and a monocyclic 5- to 7- membered heterocyclyl group containing one or two nitrogen
30 atom as heteroatom, wherein the aryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a linear or branched C_{1-5} alkyl group, a $-(O)(CH_2)_2-NR'R''$ group and a $-NR'R''-$ group, wherein R' and R'' independently represents a hydrogen atom or a methyl group, and q has a value of 0 or 1.

12. A compound according to claim 11, wherein R^1 is selected from the group consisting of a hydrogen atom, a phenyl group and a monocyclic 6- to 7- membered
35

heterocyclyl group containing one or two nitrogen atom as heteroatom, wherein the phenyl and heterocyclyl groups are substituted by one substituent selected from the group consisting of a methyl group, $-(O)(CH_2)_2-NR'R''$ group and a $-NR'R''$ - group, wherein both R' and R'' represents a methyl group, and q has a value of 0 or 1.

5

13. A compound according to any one of the preceding claims, wherein R^2 is selected from the group consisting of a halogen atom and a C_{1-2} alkyl group, preferably a fluorine atom and a methyl group, more preferably, a fluorine atom.

10

14. A compound according to any one of the preceding claims, wherein R^3 is selected from the group consisting of a hydrogen atom, a C_{1-2} alkyl group and $-(CH_2)_{(2-4)}NR'R''$ - group, wherein R' and R'' are as defined in claim 1, preferably, R^3 is selected from a hydrogen atom and a $-(CH_2)_{(2)}NR'R''$ - group, wherein both R' and R'' represent a methyl group.

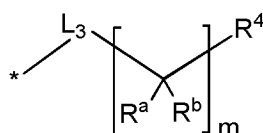
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15. A compound according to any one of the preceding claims, wherein R^5 is selected from the group consisting of a hydrogen atom and a methyl group, and n has a value of 0 or 1, preferably n has a value of 0.

20

16. A compound according to any one of the preceding claims, wherein G_2 is selected from the group consisting of a monocyclic N-containing 6- to 8- membered heteroaryl group and a monocyclic 5- to 8- membered heterocyclyl group containing at least one heteroatom selected from O, S and N, wherein the heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from a halogen atom, a hydroxyl group, a methyl group and a group of formula (a):

25



wherein

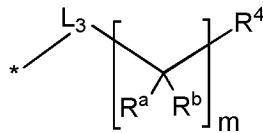
L_3 represents $-CO-$ group, or a $-C(O)O-$ group,

R^4 is selected from the group consisting of a cyano group, a $-CF_3$ group, a methyl group,

30

R^a and R^b are independently selected from the group consisting of a hydrogen atom, a hydroxyl, a methyl group and, m has a value of 0 or 1.

17. A compound according to claim 16, wherein G_2 represents a monocyclic N-containing 6-membered heterocyclyl group which is substituted by a group of formula (a):



5 wherein

L_3 represents $-\text{CO}-$ group, both R^a and R^b represent a hydrogen atom, m has a value of 1 and R^4 represents a ciano group..

18. A compound according to any one of the preceding claims, wherein

10 R^c represents a hydrogen atom or a fluorine atom,

G_1 is selected from the group consisting of a phenyl group, a pyridyl group, a morpholinyl group and a piperazinyl group,

L_1 represents a direct bond,

L_2 is selected from the group consisting of a $-(\text{CH}_2)_p-$, wherein p has a value of 0 or 1,

15 R^1 is selected from the group consisting of a hydrogen atom, a phenyl group and a monocyclic 6- to 7-membered heterocyclyl group containing one or two nitrogen atom as heteroatom, wherein the phenyl and heterocyclyl groups are substituted by one substituent selected from the group consisting of a methyl group, $-(\text{O})(\text{CH}_2)_2-\text{NR}'\text{R}''$ group and a $-\text{NR}'\text{R}''$ - group, wherein both R' and R'' represents a methyl group, and q

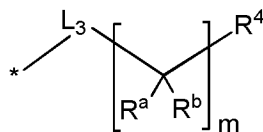
20 has a value of 0 or 1,

R^2 is a fluorine atom,

R^3 is selected from a hydrogen atom and a $-(\text{CH}_2)_{(2)}\text{NR}'\text{R}''$ - group, wherein both R' and R'' represent a methyl group,

R^5 represents a hydrogen atom and n has a value of 1.

25 G_2 represents a monocyclic N-containing 6-membered heterocyclyl group which is substituted by a group of formula (a):



wherein

L_3 represents $-\text{CO}-$ group,

30 both R^a and R^b represent a hydrogen atom, m has a value of 1, and

R^4 represents a cyano group.

19. A compound according to claim 1, wherein

R^c is selected from the group consisting of a hydrogen atom and a fluorine group,

G_1 is selected from the group consisting of a phenyl group, a monocyclic N-containing 6- membered heteroaryl group and a monocyclic 4-8- membered heterocyclyl group

5 containing at least one heteroatom selected from O and N, wherein the aryl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one substituent selected from a fluorine atom, a hydroxyl group, a methyl group, a hydroxymethyl group, a carboxymethyl group, an oxo group, and a hydroxyethyl group,

L_1 is selected from the group consisting of a direct bond and -NH- group,

10 L_2 is selected from the group consisting of a $-(CH_2)_p-$, $-O-(CH_2)_{(0-2)}-$, $-C(O)-O-(CH_2)-$, $-(CH_2)-C(O)-O-(CH_2)-$, $-C(O)-(CH_2)-O-(CH_2)-$, $-(CH_2)-C(O)-O-$, $-C(O)-$ and $-N(CH_3)-$ group, wherein p has a value of 0 or 1.

R^1 is selected from the group consisting of a hydrogen atom, a t-butyl group, a

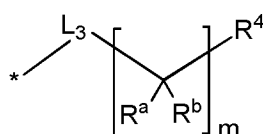
15 hydroxymethyl group, a phenyl group, a mono- or bicyclic 5- to 9- membered heteroaryl group containing at least one N as heteroatom and a monocyclic 5-7- membered heterocyclyl group containing at least one heteroatom selected from O and N, wherein the phenyl, heteroaryl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a fluoroine atom, a hydroxyl group, a methyl group, a dihydroxypropyl group, a methoxy group, a dimethylamino group, $-(O)-(CH_2)_2-N(CH_3)_2$ group;

R^2 is selected from the group consisting of a fluorine atom and a methyl group,

R^3 is selected from the group consisting of a hydrogen atom and a $-(CH_2)_{(2-3)}NR'R''-$ group,

25

G_2 is selected from the group consisting of a pyridyl group substituted with a fluorine atom, and a piperidinyI substituted with a group of formula (a):



wherein

30 L_3 represents a direct bond, $-CO-$ group, or a $-C(O)O-$ group,

R^4 is selected from the group consisting of a phenyl group, hydroxyl group, $-(CH_2)_{(0-1)}-CN$, a $-CF_3$ group, an methyl group, an ethyl group, a methoxy group, a hydroxypropyl group, a hydroxymethyl group optionally substituted with one or two methyl groups,

35 Both R^a and R^b are a hydrogen atom

R⁵ is selected from the group consisting of a hydrogen atom and a methyl group,
R' and R'' independently represents a hydrogen atom or a methyl group, or R' and R''
together with the nitrogen atom to which they are attached form a 5 to 6 membered N-
containing heterocyclic group optionally containing one or more additional heteroatom
5 selected from N, and O, and optionally substituted with a methyl group or a
dimethylamino group,
n, m and q independently have a value of 0 or 1.
p has a value of 0, 1 or 2.

- 10 20. A compound according to claim 1 which is one of:
- (R)-benzyl 4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-
fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazine-1-carboxylate,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(piperazin-1-yl)pyrimidin-
4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
- 15 (R)-benzyl 2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-
fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetate,
(R)-3-(3-((6-(4-(benzyloxy)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-
yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(R)-3-(3-((6-(4-(2-(benzyloxy)acetyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-
20 a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(2-
hydroxyacetyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-
oxopropanenitrile,
(R)-2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-fluoroimidazo[1,2-
25 a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetic acid,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-hydroxypiperidin-1-
yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(R)-tert-butyl 2-(4-(6-((1-(2-cyanoacetyl)piperidin-3-yl)amino)-5-fluoro-2-(6-
fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)piperazin-1-yl)acetate,
- 30 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-
(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-
oxopropanenitrile,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((1-methyl-1H-
imidazol-2-yl)methyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-
35 oxopropanenitrile,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(3-hydroxyazetidin-1-
yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(benzyloxy)piperidin-1-yl)-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
5 (S)-(1-(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-((1-(5-fluoropyridin-2-yl)ethyl)amino)pyrimidin-4-yl)piperidin-4-yl)methanol,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-hydroxyphenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methoxybenzyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
10 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-hydroxybenzyl)piperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
15 5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-N-(1-(5-fluoropyridin-2-yl)ethyl)-6-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)pyrimidin-4-amine,
(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(morpholinomethyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
20 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
N-(1-benzylpiperidin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-amine,
25 3-((3R)-3-((6-(4-((1-(2,3-dihydroxypropyl)-1H-benzo[d]imidazol-2-yl)methyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
N-((1S,2S,4R)-bicyclo[2.2.1]heptan-2-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-4-amine,
30 4-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octan-1-ol,
(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,
(S)-N1-(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)-N1-(1-(5-fluoropyridin-2-yl)ethyl)-N2,N2-dimethylethane-1,2-diamine,
35 (R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(1,4-diazepan-1-yl)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(6-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-5-methyl-6-(2-(4-methyl-1,4-diazepan-1-yl)pyridin-4-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(2-(4-(dimethylamino)piperidin-1-yl)pyridin-4-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-5-fluoro-2-(imidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(4-(dimethylamino)piperidin-1-yl)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholinopyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((6-(4-(4-(2-(dimethylamino)ethoxy)benzyl)piperazin-1-yl)-2-(imidazo[1,2-a]pyridin-3-yl)-5-methylpyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((3-(dimethylamino)propyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)(2-(pyrrolidin-1-yl)ethyl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(6-(4-(dimethylamino)piperidin-1-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(6-(2-(dimethylamino)pyridin-4-yl)-5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((2-(dimethylamino)ethyl)(5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(3-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile,

(R)-3-(3-((5-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-4-yl)(2-(4-methylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)-3-oxopropanenitrile,

2-((3R)-3-([F-fluoro-2-(6-fluoroimidazo[1,2-a]pyridin-3-yl)-6-morpholin-4-yl]pyrimidin-4-yl)amino)piperidin-1-yl)-2-oxoethanol,

or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer or deuterated derivative thereof.

21. A compound as defined in any one of claims 1 to 20, for use in the treatment of the human or animal body by therapy.

22. A compound as defined in any one of claims 1 to 20, for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Janus Kinases.

23. A compound for use according to claim 22, wherein the pathological condition or disease is selected from myeloproliferative disorders, leukemia, lymphoid malignancies and solid tumors; bone marrow and organ transplant rejection; immune-mediated diseases and inflammatory diseases.

24. A compound for use according to claim 22 or 23, wherein the pathological condition or disease is selected from rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, dry eye, uveitis, allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and psoriasis.

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25. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 20 in association with a pharmaceutically acceptable diluent or carrier.

26. Use of a compound as defined in any one of claims 1 to 20, for the manufacture of a medicament for the treatment of a pathological condition or disease as defined in any one of claims 22 to 24.

27. A method for treating a subject afflicted with a pathological condition or disease as defined in any one of claims 22 to 24, which comprises administering to said subject a therapeutically effective amount of a compound as defined in any one of claims 1 to 20, or a pharmaceutical composition as defined in claim 25.

28. A combination product comprising (i) a compound as defined in any one of claims 1 to 20; and (ii) another compound selected from:

- 20 a) Dyhydrofolate reductase inhibitors, such as Methotrexate or CH-1504;
- b) Dihydroorotate dehydrogenase (DHODH) inhibitors such as leflunomide, teriflunomide, or the compounds described in the International Patent Application Nos. WO2008/077639 and WO2009/021696;
- c) Immunomodulators such as Glatiramer acetate (Copaxone), Laquinimod or Imiquimod;
- 25 d) Inhibitors of DNA synthesis and repair, such as Mitoxantrone or Cladribine;
- e) Immunosuppressants, such as Imuran (azathioprine) or Purinethol (6-mercaptopurine or 6-MP);
- f) Anti-alpha 4 integrin antibodies, such as Natalizumab (Tysabri) ;
- 30 g) Alpha 4 integrin antagonists such as R-1295 , TBC-4746, CDP-323, ELND-002, Finategrast or TMC-2003;
- h) Corticoids and glucocorticoids such as prednisone or methylprednisolone, fluticasone, mometasone, budesonide, ciclesonide or beta-metasone;
- i) Fumaric acid esters, such as BG-12;
- 35 j) Anti-tumor necrosis factor-alpha (Anti-TNF-alpha), such as Infliximab, Adalimumab, or Certolizumab pegol,

- k) Soluble Tumor necrosis factor-alpha (TNF-alpha) receptors such as Etanercept,
- l) Anti-CD20 (lymphocyte protein) monoclonal antibodies such as Rituximab, Ocrelizumab Ofatumumab or TRU-015,
- 5 m) Anti-CD52 (lymphocyte protein) monoclonal antibodies such as alemtuzumab;
- n) Anti-CD25 (lymphocyte protein) such as daclizumab;
- o) Anti-CD88 (lymphocyte protein), such as eculizumab or pexelizumab;
- p) Anti-Interleukin 6 Receptor (IL-6R), such as tocilizumab;
- 10 q) Anti-Interleukin 12 Receptor (IL-12R) / Interleukin 23 Receptor (IL-23R), such as ustekinumab;
- r) Calcineurin inhibitors such as cyclosporine A, pimecrolimus or tacrolimus;
- s) Inosine-monophosphate dehydrogenase (IMPDH) inhibitors, such as mycophenolate mophetyl, ribavirin, mizoribine or mycophenolic acid;
- 15 t) Cannabinoid receptor agonists such as Sativex;
- u) Chemokine CCR1 antagonists such as MLN-3897 or PS-031291;
- v) Chemokine CCR2 antagonists such as INCB-8696;
- w) Necrosis factor-kappaB (NF-kappaB or NFkB) Activation Inhibitors such as Sulfasalazine, Iguratimod or MLN-0415;
- 20 x) Adenosine A_{2A} agonists, such as ATL-313, ATL-146e, CGS-21680, Regadenoson or UK-432,097;
- y) Sphingosine-1 (S1P) phosphate receptor agonists such as fingolimod, BAF-312, or ACT128800;
- z) Sphingosine-1 (S1P) liase inhibitors such as LX2931;
- 25 aa) Spleen tyrosine kinase (Syk) inhibitors, such as R-112;
- bb) Protein Kinase Inhibitors (PKC) inhibitors, such as NVP-AEB071;
- cc) Anti-cholinergic agents such as tiotropium or acclidinium;
- dd) Beta adrenergic agonists such as formoterol, indacaterol or abediterol (LAS100977);
- 30 ee) Compounds having bifunctional Muscarinic Antagonist-Beta2 Agonist activity (MABAs);
- ff) Histamine 1 (H1) receptor antagonists, such as azelastine or ebastine;
- gg) Chemoattractant receptor homologous molecule expressed on TH₂ cells (CRTH2) inhibitors, such as OC-459, AZD-1981, ACT-129968, QAV-680;
- 35 hh) Vitamin D derivatives like calcipotriol (Daivonex) ;
- ii) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors such as

aceclofenac, diclofenac, ibuprofen, naproxen, apricoxib, celecoxib, cimicoxib, deracoxib, etoricoxib, lumiracoxib, parecoxib sodium, rofecoxib, selenocoxib-1 or valdecoxib;

jj) Anti-allergic agents;

5 kk) Anti-viral agents;

ll) Phosphodiesterase (PDE) III inhibitors;

mm) Phosphodiesterase (PDE) IV inhibitors such as roflumilast or GRC-4039;

nn) Dual Phosphodiesterase (PDE) III/IV inhibitors;

oo) Xanthine derivatives, such as theophylline or theobromine;

10 pp) p38 Mitogen-Activated Protein Kinase (p38 MAPK) Inhibitors such as ARRY-797;

qq) Mitogen-activated extracellular signal regulated kinase kinase (MEK) inhibitor, such as ARRY-142886 or ARRY-438162;

rr) Phosphoinositide 3-Kinases (PI3Ks) inhibitors;

15 ss) Interferons comprising Interferon beta 1a such as Avonex from Biogen Idec, CinnoVex from CinnaGen and Rebif from EMD Serono, and Interferon beta 1b such as Betaferon from Schering and Betaseron from Berlex; and

tt) Interferon alpha such as Sumiferon MP;

20 29. A combination as defined in claim 28 which is for simultaneous, separate or sequential use in the treatment of the human or animal body.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/078037

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00 A61P37/00 A61P29/00
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, 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 2011/076419 A1 (ALMIRALL SA [ES]; EASTWOOD PAUL ROBERT [ES]; GONZALEZ RODRIGUEZ JACOB) 30 June 2011 (2011-06-30) claims 1, 25-30, 35-37 compounds 184, 185 preparation 95b), 95c) -----	1-29



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

12 March 2015

Date of mailing of the international search report

24/03/2015

Name and mailing address of the ISA/

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/078037

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-29

subject-matter related to the compounds of claim 1

1.1. claims: 1, 2, 6-17, 21-29(all partially)

subject-matter related to the compounds of claim 1 wherein
G1 is alkyl

1.2. claims: 1-29(partially)

subject-matter related to the compounds of claim 1 wherein
G1 is aryl or heteroaryl

1.3. claims: 1, 2, 6-17, 21-29(all partially)

subject-matter related to the compounds of claim 1 wherein
G1 is cycloalkyl

1.4. claims: 1-29(partially)

subject-matter related to the compounds of claim 1 wherein
G1 is aryl or heterocyclyl

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/078037

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