

PYRROLOTRIAZINONE DERIVATIVES AS PI3K INHIBITORS

5 FIELD OF THE INVENTION

The present invention relates to novel compounds having PI3K activity. This invention also relates to pharmaceutical compositions containing them, processes for their preparation and their use in the treatment of several disorders.

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BACKGROUND OF THE INVENTION

When cells are activated by extracellular stimuli, intracellular signalling cascades involving the regulation of second messengers are initiated that eventually produce a response of the cell to the stimuli. Phosphoinositide 3-Kinases (PI3Ks) are among the enzymes involved in early signalling events to a plethora of different types of stimuli. PI3Ks phosphorylate the 3-hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns), PtdIns-4-phosphate (PtdIns4P), and PtdIns-4,5-bisphosphate (PtdIns(4,5)P₂). The resulting 3-phosphoinositides mediate correct localization and subsequent activation of a number of downstream effector proteins that bind to the lipids via specific lipid binding sequences such as the pleckstrin homology (PH) domain (*Vanhaesebroeck B, 2010, Nat Rev Mol Cell Biol 5:11381-6*).

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The PI3K family is divided into 3 different classes (PI3K class I, class II, and class III), depending on substrate preference and structural features.

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The best characterized is the PI3K class I with the preferential substrate PtdIns-(4,5)P₂. It englobes 4 different isoforms which originally were further subdivided into class IA (p110a, p110b, p110d), binding to a p85 type of regulatory subunit, and class IB (p110g) which is regulated by p101 and p87 subunits. Whereas p110a (PI3K α) and p110b (PI3K β) isoforms are expressed ubiquitously, p110g (PI3K γ) and especially p110d (PI3K δ) have a more restricted expression pattern and seem to play a major role in leukocytes (*Kok K, Trends Biochem Science 34:115-127, 2009*).

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Both, PI3Kd and PI3Kg are involved in activation of immune cells by a large variety of different stimuli. Pharmacological inhibition or genetic deficiency in active p110d has been shown to inhibit T cell proliferation and cytokine production in response to different stimuli such as anti-CD3, anti-CD3/CD28, superantigen or antigen in vitro (Ji H, Blood 2007; Okkenhaug K, Science 2002; Garcon F, 2009; Soond DR, Blood 2010; Herman SEM, Blood June 3, 2010; William O, Chemistry & Biology 17, 2010) and to suppress concanavalin A and anti-CD3 induced cytokine production as well as antigen-dependent tissue retention in vivo (Soond DR, Blood 2010; Jarmin SJ, JCI 2008). In addition, B cell function is critically dependent on functional PI3Kd activity as demonstrated by suppressed B cell proliferation and cytokine release in vitro in response to anti-IgM (Bilancio A, Blood 107, 2006), toll like receptor agonists such as LPS and oligodeoxynucleotides (Dil N, Mol Immunol 46, 2009) or impaired ability to stimulate antigen-specific T cells (Al-Alwan M, JI 2007) in the absence of functional p110d or pharmacological inhibition. In vivo, PI3Kg deficient mice display partially suppressed antibody production upon immunization (Garcon F, 2009; Durand CA, JI 2009). Further studies have demonstrated an important role of PI3Kd in inhibition of T cell apoptosis and in TH17 differentiation (Haylock-Jacobs S, J. Autoimmun 2010).

In addition, mast cell degranulation was reduced in cells from mice with inactivated PI3Kd or by pharmacological inhibition of PI3Kd (Ali K, Nature 431:1007-1011, 2004; Ali K, Journal of Immunology 180:2538-2544, 2008) and basophil activation via the FcE receptor is suppressed by pharmacological inhibition of PI3Kd (Lannutti BJ, Blood Oct. 2010).

In terms of neutrophil function, PI3Kd inhibition inhibits migration of mouse neutrophils to fMLP in an under-agarose migration assay by inhibiting cell polarization and directional movement (Sadhu C, JI 170, 2003) and mouse PI3Kd deficient or inhibitor treated neutrophils show slightly (25%) reduced in vitro chemotaxis to LTB₄, whereas in vivo accumulation in the lung in response to LPS was reduced by more than 80%, indicating an important role of PI3Kd in endothelial cells for mediating PMN transendothelial migration (Puri KD, Blood 103, 2004). Furthermore, TNF induced neutrophil infiltration to an air pouch in mice and elastase release is partially inhibited by a PI3Kd selective inhibitor (Sadhu C, Biochem Biophys Res Comm 308, 2003). In addition, TNF mediated priming of oxidative burst by human neutrophils depends on PI3Kd activity (Condliffe AM, Blood 106, 2005).

In contrast to the dominant role of PI3K δ in lymphocyte activation, PI3K γ seems to affect primarily chemotaxis of different immune cells induced by various mediators and chemokines (Martin AL, *JCI* 180, 2008; Thomas MS, *J Leukoc Biol* 84, 2008; Jarmin SJ, *JCI* 2008; Matthew T, *Immunology* 126, 2008), as well as degranulation and oxidative burst of innate immune cells induced by GPCR mediated stimuli such as fMLP, IL-8 or C5a (Condliffe AM, *Blood* 106, 2005; Yum HK, *JCI* 167, 2001; Pinho V, *JCI* 179, 2007

The above mentioned findings suggest that selective PI3K δ or dual PI3K δ /PI3K γ pharmacological inhibition represents a promising approach for treating a variety of diseases.

There is substantial experimental evidence supporting this view. In rodent models of allergic lung inflammation, genetic or pharmacological inactivation of PI3K δ or dual PI3K δ /PI3K γ dual inhibition reduces cell influx, mucus production, cytokine production and airway hyperreactivity (Nashed et al. 2007, *Eur J Immunol* 37:416; Lee et al. 2006, *FASEB J* 20:455 & Lee KS et al. 2006, *J Allergy Clin Immunol* 118:403; Doukas J, *JPET* 2009;328:758; Par SJ, *ERJ* 2010). Moreover, LPS induced lung neutrophil infiltration is blocked by PI3K δ inhibition (Puri KD, *Blood* 2004;103:3448) and inflammation in response to LPS or tobacco smoke exposure is suppressed by a dual PI3K δ /PI3K γ inhibitor (Doukas J, *JPET* 2009;328:758). Moreover, PI3K δ seems to be involved in the reduction of responsiveness to corticosteroid treatment associated with oxidative stress and chronic obstructive pulmonary disease (COPD). This notion is based on the findings that tobacco smoke induced inflammation remains responsive to treatment with budesonide, whereas wild type or PI3K γ deficient mice develop resistance to corticosteroid treatment (Marwick JA, *JRCCM* 179:542-548, 2009). Similar results were obtained with a PI3K δ selective inhibitor (To Y, *AJRCCM* 182:897-904, 2010). In addition, in vitro induction of corticosteroid resistance by oxidative stress is prevented by PI3K δ inhibition (To Y, *AJRCCM* 2010). In COPD patients, lung macrophages display increased expression of PI3K δ and phosphorylation of its downstream effector Akt and non-selective PI3K or PI3K δ -selective inhibition restored the impaired inhibitory efficacy of dexamethasone in PBMC from COPD patients (To Y, *AJRCCM* 182:897-904, 2010; Marwick JA, *JACI* 125:1146-53, 2010).

Furthermore, PI3K δ inhibition was effective in a model of contact hypersensitivity (Soond DR, *Blood* Jan 2010). In a model of experimental autoimmune encephalomyelitis, PI3K δ deficiency or pharmacological inhibition of PI3K δ attenuated T cell activation and function and reduced T cell numbers in the CNS, suggesting a

therapeutic benefit of PI3Kd inhibitor in multiple sclerosis and other Th17-mediated autoimmune diseases (Haylock-Jacobs S, J. Autoimmun 2010). In line with that, genetic deficiency or pharmacological inhibition of PI3Kd diminished joint erosion in a mouse model of inflammatory arthritis (Randis TM, Eur J Immunol 38, 2008).

5 Concerning metabolic diseases, PI3Kd overexpression seems to contribute to excessive vascular contraction and PI3Kd inhibition normalized vascular contractive responses in a mouse model of type I diabetes, suggesting a therapeutic potential of PI3Kd blockade to treat vascular dysfunction in diabetic patients (Pinho JF, Br. J. Pharmacol 161, 2010).

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There is also substantial experimental evidence supporting that genetic or pharmacological inactivation of PI3Kd or dual PI3Kd/g dual inhibition is effective in the treatment of cancers including but not restricted to leukemias, such as chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukaemia, non-hodgkins lymphoma, B-cell lymphoma, acute myeloid leukaemia, myelo-dysplastic syndrome or myelo-proliferative diseases. In this aspect, the selective PI3Kd inhibitor CAL-101 demonstrated anti-proliferative properties on different tumor cells in vitro and efficacy in cancer patients with a dysregulated PI3Kd activity, such as chronic lymphocytic leukemia (Hermann SE, Blood 116:2078-88, 2010; Lannutti BJ, Blood Oct. 2010).

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In view of the numerous conditions that are contemplated to benefit by treatment involving modulation of the PI3K pathway or modulation of the PI3 Kinases it is immediately apparent that new compounds that modulate PI3K pathways and use of these compounds should provide substantial therapeutic benefits to a wide variety of patients.

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Provided herein are novel pyrrolotriazinone derivatives for use in the treatment of conditions in which targeting of the PI3K pathway or inhibition of PI3 Kinases can be therapeutically useful.

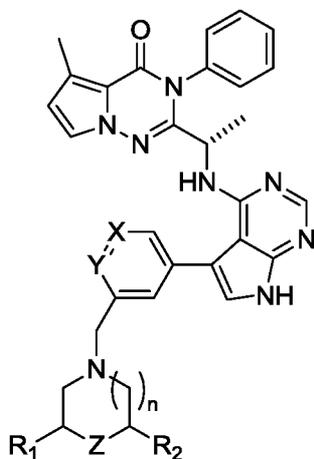
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It has now been found that certain pyrrolotriazinone derivatives are novel and potent PI3K inhibitors and can therefore be used in the treatment or prevention of these diseases. The introduction of a -CH₂- group linked to the tertiary amine (as described in the general Formula (I)) surprisingly increases the exposure in the lung for such compounds after i.t. administration in pre-clinical species.

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SUMMARY OF THE INVENTION

- 5 Thus the present invention is directed to compounds of formula (I), or a pharmaceutically acceptable salt, or N-oxide, or isotopically-labeled derivate thereof:



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Formula (I)

wherein,

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n represents an integer selected from 1 or 2;

X and Y each independently represent a nitrogen atom or CR₃ group;

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R₁ and R₂ each independently represent a hydrogen atom or a linear or branched C₁-C₄ alkyl group;

R₃ represents a hydrogen atom, a halogen atom, a hydroxyl, a linear or branched C₁-C₄ alkyl group, a C₁-C₄ alkoxy group or a C₁-C₄ haloalkyl group;

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Z represents a -CH((CH₂)₀₋₁-NR^aR^b)- group, a -NH- group or a -N(C₁-C₃ alkyl)- group;

R^a and R^b each independently represent a hydrogen atom or a linear or branched C₁-C₄ alkyl group; or R^a and R^b together with the nitrogen atom to which they are attached form a monocyclic 3- to 7-membered heterocyclyl group optionally containing at least one further heteroatom selected from O, S and N.

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

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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.

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

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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 Phosphoinositide 3-Kinases (PI3Ks), in particular wherein the pathological condition or disease is selected from respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; 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; more in particular wherein the pathological condition or disease is selected from leukemia, lymphomas and solid tumors, rheumatoid arthritis (RA), multiple sclerosis (MS), 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 (CF), idiopathic pulmonary fibrosis, sarcoidosis, atopic dermatitis, allergic rhinitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and actinic keratosis (AK). Preferably, the pathological condition or disease is selected from asthma and chronic obstructive pulmonary disease (COPD).

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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 Phosphoinositide 3-Kinases (PI3Ks), in particular wherein the pathological condition or disease is as defined above.

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The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinases (PI3Ks), in particular wherein the pathological condition or disease is as defined above.

10 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 respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; function disorders and neurological disorders; cardiovascular diseases; viral infection; metabolism/endocrine function
15 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; more in particular wherein the pathological condition or disease is selected from leukemia, lymphomas and solid tumors, rheumatoid arthritis (RA), multiple sclerosis (MS), amyotrophic lateral
20 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 (CF), idiopathic pulmonary
25 fibrosis, sarcoidosis, atopic dermatitis, allergic rhinitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and actinic keratosis (AK).

DETAILED DESCRIPTION OF THE INVENTION

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When describing the compounds, compositions, combinations and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

As used herein the term C₁-C₄ alkyl embraces linear or branched radicals having 1 to 4
35 carbon atoms, preferably 1 to 2 carbon atoms. Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl or t-butyl radicals.

As used herein, the term C₁-C₄ haloalkyl group is an alkyl group, for example a C₁-C₄ or C₁-C₂ alkyl group, which is bonded to one or more, preferably 1, 2 or 3 halogen atoms. Preferably, said haloalkyl group is chosen from -CCl₃, -CHF₂ and -CF₃.

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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.

As used herein, the term 3- to 7-membered heterocyclyl radical embraces typically a non-aromatic, saturated or unsaturated C₃-C₇ carbocyclic ring system, 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.

10 Examples of 3- to 7-membered heterocyclyl radicals include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl or thiomorpholinyl.

Where a 3- to 7-membered heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

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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.

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30 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.

Also included within the scope of the invention are the isomers, polymorphs, pharmaceutically acceptable salts, N-oxides, isotopes, solvates and prodrugs of the compounds of formula (I). Any reference to a compound of formula (I) throughout the

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present specification includes a reference to any isomer, polymorph, pharmaceutically acceptable salt, N-oxide, isotope, solvate or prodrug of such compound of formula (I).

Isomers

5 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 compounds of Formula (I) as described and claimed encompass the racemic forms of the compounds as well as the individual enantiomers, diastereomers, and stereoisomer-enriched mixtures.

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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
15 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 diastereoisomeric 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
20 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
25 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).

Atropisomers are stereoisomers resulting from hindered rotation about single bonds
30 where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. Oki (Oki, M; *Topics in Stereochemistry* 1983, 1) defined atropisomers as conformers that interconvert with a half-life of more than 1000 seconds at a given temperature. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual atropisomers (an atropisomer
35 "substantially free" of its corresponding enantiomer) and stereoisomer-enriched mixtures, i.e. mixtures of atropisomers.

Separation of atropisomers is possibly by chiral resolution methods such as selective crystallization. In an atropo-enantioselective or atroposelective synthesis one atropisomer is formed at the expense of the other. Atroposelective synthesis may be carried out by use of chiral auxiliaries like a Corey-Bakshi-Shibata (CBS) catalyst
5 (asymmetric catalyst derived from proline) in the total synthesis of knipholone or by approaches based on thermodynamic equilibration when an isomerization reaction favors one atropisomer over the other.

The compounds of Formula (I) may exhibit the phenomena of tautomerism and
10 structural isomerism. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of Formula (I).

15 Polymorphs

The compounds of formula (I) may exist in different physical forms, i.e. amorphous and crystalline forms.

Moreover, the compounds of the invention may have the ability to crystallize in more than one form, a characteristic which is known as polymorphism. Polymorphs can be
20 distinguished by various physical properties well known in the art such as X-ray diffraction pattern, melting point or solubility. All physical forms of the compounds of formula (I), including all polymorphic forms ("polymorphs") or amorphous forms thereof, are included within the scope of the invention.

25 Pharmaceutically acceptable salts

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.

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As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. 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,
35 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.

- 5 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.
- 10 Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including alkyl amines, arylalkyl amines, heterocycl
- 15 ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.
- 20 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 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,
- 25 mandelate, trifluoroacetate, methanesulphonate and p-toluenesulphonate. X- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X- is chloride, bromide, trifluoroacetate or methanesulphonate.

30 N-oxides

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

Isotopes

- 35 The invention also includes isotopically-labeled derivatives of the 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 derivatives of the 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 derivatives 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 %.

Solvates

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 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.

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 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.

10 Prodrugs

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).

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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).

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As used herein, the term PI3Kd inhibitor generally refers to a compound that inhibits the activity of the PI3Kd isoform more effectively than other isoforms of the PI3K family.

As used herein, the term PI3Kd/g inhibitor generally refers to a compound that inhibits the activity of both the PI3Kd isoform and the PI3Kg isoform more effectively than other isoforms of the PI3K family.

The relative efficacies of compounds as inhibitors of an enzyme activity (or other biological activity) can be established by determining the concentrations at which each compound inhibits the activity to a predefined extent and then comparing the results. Typically, the preferred determination is the concentration that inhibits 50% of the activity in a biochemical assay, i.e., the 50% inhibitory concentration or "IC₅₀." IC₅₀

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determinations can be accomplished using conventional techniques known in the art. In general, an IC_{50} can be determined by measuring the activity of a given enzyme in the presence of a range of concentrations of the inhibitor under study. The experimentally obtained values of enzyme activity then are plotted against the inhibitor concentrations used. The concentration of the inhibitor that shows 50% enzyme activity (as compared to the activity in the absence of any inhibitor) is taken as the IC_{50} value.

Accordingly, a PI3Kd inhibitor alternatively can be understood to refer to a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to PI3Kd that is at least of less than about 100 μ M, preferably of less than about 50 μ M, more preferably of less than about 20 μ M, even more preferably of less than about 10 μ M PI3K HTRF assay (as described in Gray et al. *Anal Biochem*, 2003; 313: 234–45).

Typically, n represents 1.

Typically, R_1 and R_2 represent a hydrogen atom.

In a particular embodiment of the invention X represents a CR^3 group and Y represents a nitrogen atom.

In a preferred embodiment R^3 represents a hydrogen atom.

In a particular embodiment of the invention Z represents a $-CH((CH_2)_{0-1}NR^aR^b)-$ group.

In a preferred embodiment R^a and R^b each independently represent a hydrogen atom or a methyl group.

In a more preferred embodiment,

n represents 1;

R_1 and R_2 represent a hydrogen atom;

X represents a CH group and Y represents a nitrogen atom;

Z represents a $-CH((CH_2)_{0-1}NR^aR^b)-$ group; and

R^a and R^b each independently represent a hydrogen atom or a methyl group.

In another preferred embodiment,
n represents 1 or 2;

R₁ and R₂ represent a hydrogen atom or a methyl group;

R₃ represents a hydrogen atom, a methoxy group, a methyl group, a -CF₃ group, a fluorine atom or a hydroxyl group; and

R^a and R^b each independently represent a hydrogen atom or a methyl group; or R^a and R^b together with the nitrogen atom to which they are attached form a pyrrolidinyl group.

Particular individual compounds of the invention include:

10 (S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-(trifluoromethyl)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

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(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-5-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-5-Methyl-2-(1-((5-(2-((4-(methylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

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(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methylpyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(2-((4-((Dimethylamino)methyl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

25

(S)-5-Methyl-3-phenyl-2-(1-((5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

2-((S)-1-((5-(2-(((3S,5R)-3,5-Dimethylpiperazin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

30

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one; or

(S)-5-Methyl-2-(1-((5-(2-((4-methyl-1,4-diazepan-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

10 or a pharmaceutically acceptable salt, or N-oxide, or isotopically-labeled derivate thereof.

Examples of the preferred compounds in this embodiment are:

(S)-5-Methyl-2-(1-((5-(2-((4-(methylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(2-((4-((Dimethylamino)methyl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one; or

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

20 or a pharmaceutically acceptable salt, or N-oxide, or isotopically-labeled derivate thereof.

As used herein, the term therapeutically effective amount refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

As used herein, the term treatment refers to the treatment of a disease or medical condition in a human patient which includes:

- (a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;
- (b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient;
- (c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or

(d) alleviating the symptoms of the disease or medical condition in a patient.

GENERAL SYNTHETIC METHODS

5

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.

15 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*
20 *Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

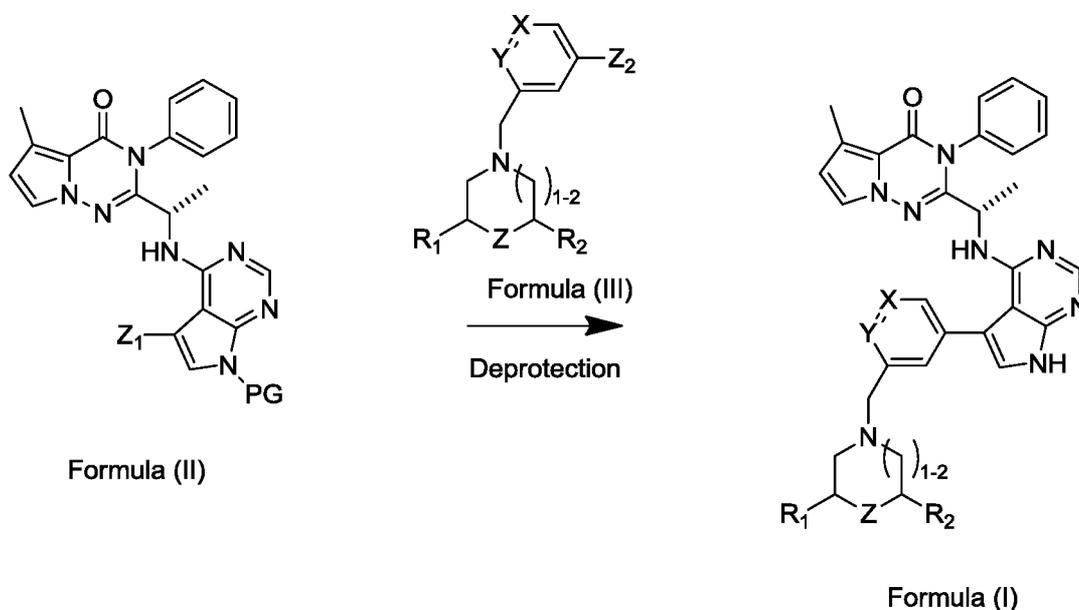
According to one embodiment of the present invention, compounds of general Formula (I) may be prepared by the synthetic route illustrated in Scheme 1, from compounds of general Formula (II) where Z_1 represents an halogen by treatment with compounds of
25 Formula (III) where Z_2 represents a boronic acid or ester using standard Suzuki coupling conditions.

Alternatively, compounds of Formula (I) can be obtained from compounds of general Formula (II) where Z_1 represents a boronic acid or ester by treatment with compounds
30 of Formula (III) where Z_2 represents an halogen using also standard Suzuki coupling conditions.

All boronic acids or esters can be prepared from the corresponding halogenated derivatives by treatment with standard reagents well known for those skilled in the art,
35 such as 4,4,5,5-tetramethyl-1,3,2-dioxaborolane or bis(pinacolato)diboron in the

presence of a palladium catalyst such as bis(diphenylphosphino)ferrocene-palladium (II)dichloromethane complex, an appropriate base such as potassium carbonate and in a suitable solvent such as dioxane at a temperature ranging from 60°C to 120°C.

5

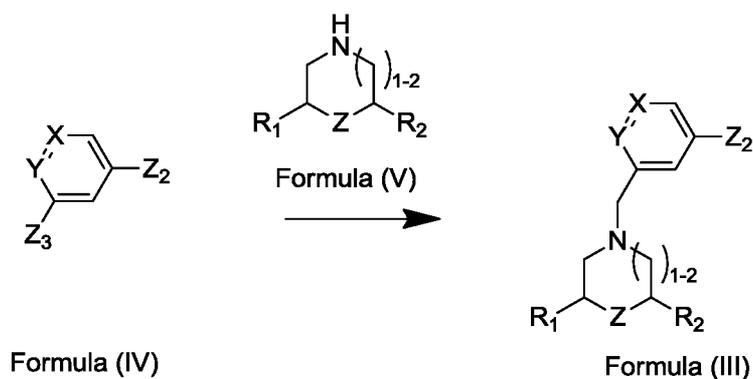


Scheme 1

10 In addition, compounds of general Formula (III) can be prepared by reductive amination from compounds of general Formula (IV) where Z_3 is a carboxaldehyde and the corresponding amines of general Formula (V) as is shown in Scheme 2, with the presence of a reducing agent such as sodium triacetoxyborohydride and in a solvent such as dichloroethane or methanol. Alternatively, compounds of general Formula (III)

15 can be prepared by nucleophilic substitution from compounds of general Formula (IV) where Z_3 is a methylene group attached to a leaving group by treatment with the corresponding amine of general Formula (V) with or without the presence of a base and in a solvent such as ethanol or methanol.

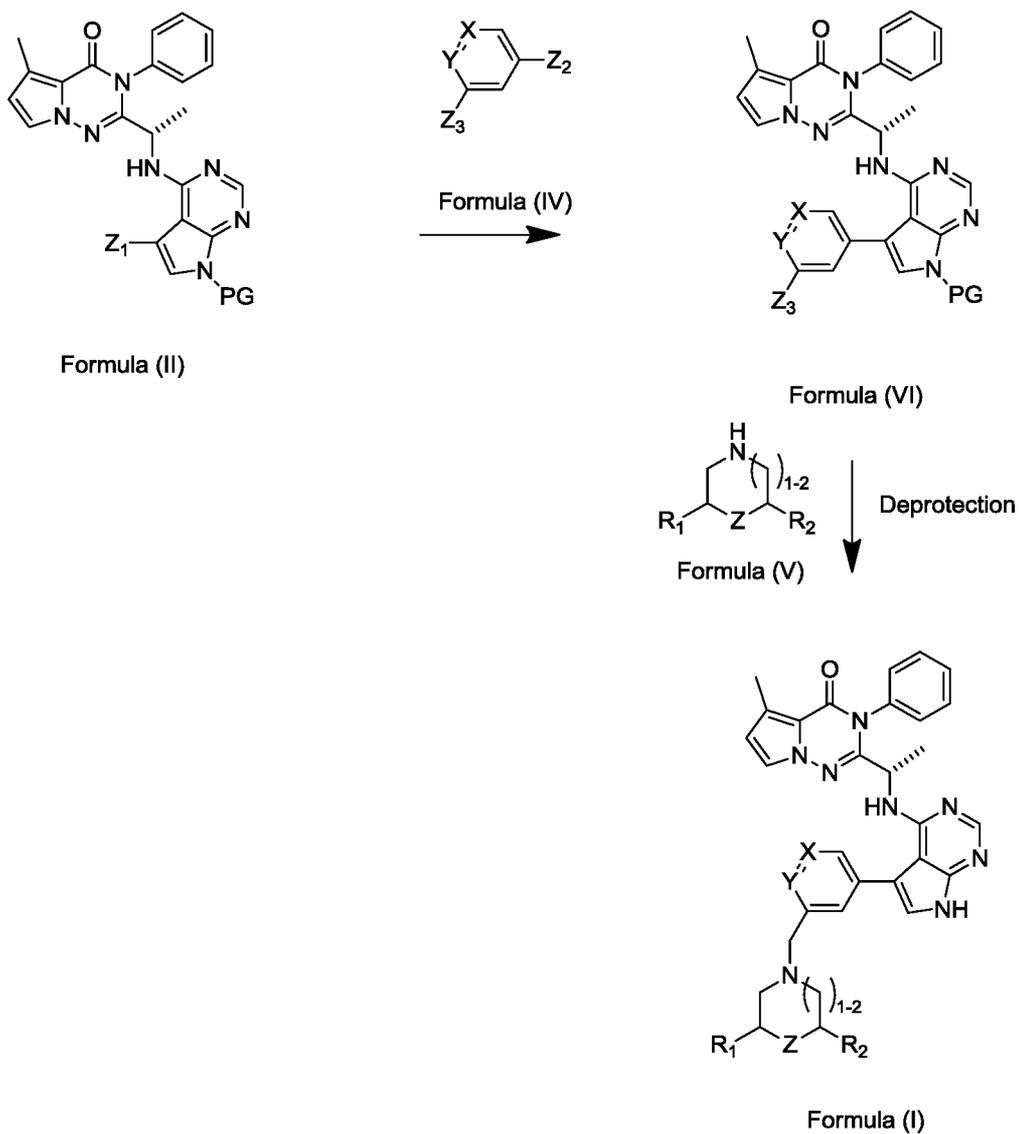
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Scheme 2

In another embodiment of the present invention, compounds of general Formula (I) may be prepared by the synthetic route illustrated in Scheme 3, from compounds of general Formula (VI) by treatment with compounds of general Formula (V) using the same general methods as described for compounds of Formula (III).

Finally, compounds of general Formula (VI) may be prepared by standard Suzuki conditions well known for those skilled in the art, from an halogenated derivative of general Formula (II) and a boronic acid or ester of general Formula (IV) or the other way around.



Scheme 3

5 EXAMPLES

General

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples (1-12) (including Preparation Examples (Preparations 1-41)) are given in order to provide a person skilled in the 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. As explained in the general description some

intermediates were prepared using the methods and procedures described in WO2014060432A1.

5 Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Concentration or evaporation refers to evaporation under vacuum using a Büchi rotatory evaporator.

10 Reaction products were purified, when necessary, in a Biotage SP1[®] automated purification system. Purifications in normal phase were made in the solvent system as indicated. Purifications in reverse phase were made using a C₁₈ column and two different methods depending on the compound. Method A consist of a gradient of water-acetonitrile/MeOH (1:1) (0.1% v/v ammonium formate both phases) from 0% to 100% acetonitrile/MeOH (1:1) in 40 column volumes. Method B consist of a gradient of water-acetonitrile (0.1% v/v formic acid both phases) from 0% to 100% acetonitrile in 15 40 column volumes. The appropriate fractions were collected and the solvents evaporated under reduced pressure and/or lyophilized.

Preparative HPLC-MS were performed on a Waters instrument equipped with a 2767 injector/collector, a 2525 binary gradient pump, a 2996 PDA detector, a 515 pump as a 20 make-up pump and a ZQ4000 Mass spectrometer detector or on a Agilent 1200 Series coupled to an Agilent 6120 Mass spectrometer detector. Both systems were equipped with a Symmetry Prep C₁₈ (19 x 300 mm, 7 µm) column or a XBridge Prep C₁₈ (19 x 100 mm, 5 µm) column. The mobile phase was formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) (B) and formic acid (0.5 mL), 25 ammonia (0.125 mL) and water (1000 mL) (A), the specific gradients used are specified in each particular case. The flow rate was 20 mL/min.

Purity and MS identification was performed in a Waters 2795 system coupled to a 2996 Diode array detector and to a Waters ZQ mass spectrometer detector or in a Waters 30 Acquity UPLC system coupled to a SQD mass spectrometer detector. The injection volume was 5 microliter on the HPLC and 0.5 microliter on the UPLC. Chromatograms were processed at 210 nM or 254 nM. Mass spectra of the chromatograms were acquired using positive and negative electrospray ionization. The mobile phase was formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) 35 (B) and formic acid (0.5 mL), ammonia (0.125 mL) and water (1000 mL) (A) and a gradient between 0 to 95% of B was used. Columns: HPLC: Waters Symmetry (2.1x50mm, 3.5 µm); UPLC: ACQUITY UPLC BEH C-18 (2.1x50mm, 1.7 µm)

¹H Nuclear Magnetic Resonance Spectra were recorded on a Varian Mercury plus operating at a frequency of 400 MHz for the ¹H spectra. Samples were dissolved in the specified deuterated solvent. Tetramethylsilane was used as reference.

5

Abbreviations:

	NH ₄ OH	Ammonium hydroxide
	DMSO	Dimethylsulfoxide
	CDCl ₃	Deuterated chloroform
10	NMR	Nuclear magnetic resonance
	s	Singlet
	d	Doublet
	dd	Doublet of doublets
	td	Triplet of doublets
15	br	Broad
	q	Quadret
	t	Triplet
	m	Multiplet
	LRMS	Low resolution mass spectrometry
20	h	hour
	min	minutes
	Celite®	diatomaceous earth
	HPLC	High-performance liquid chromatography
	UPLC	Ultra-performance liquid chromatography

25

PREPARATION 1

(S)-5-Methyl-3-phenyl-2-(1-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

30

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (500 mg, 0.84 mmol, described in WO2014060432A1) was dissolved in 8mL dioxane. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (0.474mL, 3.36 mmol) and triethylamine (0.468ml,

35

3.36 mmol) were added and the mixture was submitted to three vacuum-argon cycles. Tris(dibenzylideneacetone)dipalladium (0) (38.4 mg, 0.042 mmol) and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (40 mg, 0.084 mmol) were added and the mixture was heated at 95°C for 1h. The reaction mixture was partitioned
5 between ethyl acetate and water. The organic phase was washed twice with brine, dried and concentrated to give an oil. This residue was purified using SP1® Purification System (hexane-ether) to obtain 481 mg (68% yield) of the title compound.

LRMS (m/z): 642 (M+1)⁺.

PREPARATION 2

10 **4-Bromo-2-(bromomethyl)-6-methoxypyridine**

A solution of 4-bromo-2-methoxy-6-methylpyridine (1.1 g, 5.44 mmol), *N*-bromosuccinimide (1.07 g, 5.99 mmol) and benzoic peroxyanhydride (132 mg, 0.544 mmol) in carbon tetrachloride was stirred at 90°C for 20h. The reaction was cooled, diluted with dichloromethane and washed with sodium bisulfite and sodium
15 bicarbonate. The organic phase was dried, filtered and evaporated under reduced pressure. The crude was purified by SP1® Purification System (hexane-dichloromethane) to obtain 600 mg (94% yield) of the title compound.

LRMS (m/z): 280,282,284 (M+1)⁺.

PREPARATION 3

20 **1-((4-Bromo-6-methoxypyridin-2-yl)methyl)-*N,N*-dimethylpiperidin-4-amine**

4-Bromo-2-(bromomethyl)-6-methoxypyridine (200 mg, 0.714 mmol) was dissolved in 1 mL dimethylsulfoxide. *N,N*-Dimethylpiperidin-4-amine (458 mg, 3.57 mmol) was added and the reaction was stirred at room temperature for 1h. The residue was partitioned between water and ethyl acetate. The organic phase was dried, filtered and evaporated
25 under reduced pressure to obtain 165 mg (94% yield) of the title compound that was used in the following step without further purification.

LRMS (m/z): 328,330 (M+1)⁺.

PREPARATION 4

**(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-4-yl)-7-
30 ((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one**

(S)-5-Methyl-3-phenyl-2-(1-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (240 mg, 0.262 mmol) was dissolved in 4 mL dioxane. 1-((4-Bromo-6-methoxypyridin-2-yl)methyl)-N,N-dimethylpiperidin-4-amine (165 mg, 0.794 mmol), cesium carbonate (256 mg, 0.786 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (11 mg, 0.013 mmol) were added under argon atmosphere and the mixture was heated at 95°C for 1 h. The reaction was filtered and solvent evaporated. The crude was purified by reverse phase using SP1® Purification System to give 80 mg (90% yield) of the title compound.

LRMS (m/z): 763 (M+1)⁺.

PREPARATION 5

(5-Bromo-2-(trifluoromethyl)pyridin-3-yl)methanol

Ethyl 5-bromo-2-(trifluoromethyl)nicotinate (250 mg, 0.88 mmol) was dissolved in 3 mL tetrahydrofuran. Lithium aluminium hydride powder 95% (88 mg, 2.32 mmol) was added portionwise and the mixture was stirred at 0°C for 1 h. Water (0.2 mL), sodium hydroxide (2N, 0.2 mL) and brine (0.5 mL) were added and the mixture was stirred at room temperature for 1 h more. The crude was filtered through a pad of Celite® and then purified by SP1® Purification System (hexane-ether) to obtain 94 mg (44% yield) of desired compound.

LRMS (m/z): 256, 258 (M+1)⁺.

PREPARATION 6

(5-Bromo-2-(trifluoromethyl)pyridin-3-yl)methyl methanesulfonate

(5-Bromo-2-(trifluoromethyl)pyridin-3-yl)methanol (90 mg, 0.351 mmol) was dissolved in 5 mL dichloromethane. Triethylamine (0.098 ml, 0.702 mmol) was added and the reaction mixture was cooled at 0°C. Methanesulfonyl chloride (0.041 ml, 0.527 mmol) was added and the mixture was stirred at 0°C for 1h. The mixture was poured into a water and layers separated. The organic phase was further washed twice with saturated sodium bicarbonate solution, dried over sodium sulphate, filtered and evaporated under reduced pressure to afford 98 mg (84% yield) of a yellow oil pure enough to follow the next step.

LRMS (m/z): 334, 336 (M+1)⁺.

PREPARATION 7**1-((5-Bromo-2-(trifluoromethyl)pyridin-3-yl)methyl)-*N,N*-dimethylpiperidin-4-amine**

(5-Bromo-2-(trifluoromethyl)pyridin-3-yl)methyl methanesulfonate (98 mg, 0.293 mmol) was dissolved in 15 mL ethanol. *N,N*-Dimethylpiperidin-4-amine (188 mg, 1.47 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted twice with dichloromethane. The organics were washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure to obtain 86 mg (80% yield) of the title compound that was used in the next step without further purification.

LRMS (m/z): 336, 338 (M+1)⁺.

PREPARATION 8***N,N*-Dimethyl-1-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-amine**

1-((5-Bromo-2-(trifluoromethyl)pyridin-3-yl)methyl)-*N,N*-dimethylpiperidin-4-amine (80 mg, 0.218 mmol) was dissolved in 2 mL dioxane. Bis(pinacolato)diboron (66.5 mg, 0.248 mmol) and potassium carbonate (43 mg, 0.436 mmol) were added and the mixture was submitted to three vacuum-argon cycles. Bis(diphenylphosphino)ferrocene-palladium (II) dichloromethane complex (9 mg, 0.011 mmol) was added under argon conditions. The mixture was heated at 80°C for 18 h. The crude was filtered and evaporated under reduced pressure to obtain 82 mg (99% yield) as a boronic acid-boronate form mixture pure enough to be used in the next synthetic step.

LRMS (m/z): 414, 332 (M+1)⁺.

PREPARATION 9**(*S*)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-(trifluoromethyl)pyridin-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one**

(*S*)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (125 mg, 0.2

mmol, described in WO2014060432A1) was treated with *N,N*-dimethyl-1-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-4-amine (82 mg, 0.2 mmol), cesium carbonate (130 mg, 0.4 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (8.2 mg, 0.01 mmol) in 6 mL dioxane according to the method described in Preparation 4. The residue was purified by reverse phase using SP1® Purification System to give 46 mg (29% yield) of the title compound.

LRMS (m/z): 802 (M+1)⁺.

PREPARATION 10

10 **3-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde**

3-Bromo-5-fluorobenzaldehyde (526 mg, 2.6 mmol) was treated with bis(pinacolato)diboron (765 mg, 3 mmol) and potassium carbonate (736 mg, 7.5 mmol) and bis(diphenylphosphino)ferrocene-palladium (II) dichloromethane complex (100 mg, 0.125 mmol) in 8 mL dioxane according to the method described in Preparation 8. The crude was filtered and evaporated under reduced pressure. The brown oil obtained was triturated with hexane to give 630 mg (98% yield) of the title compound as a brown solid.

LRMS (m/z): 251 (M+1)⁺.

PREPARATION 11

20 **(S)-3-Fluoro-5-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)benzaldehyde**

(*S*)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (130 mg, 0.22 mmol, described in WO2014060432A1) was treated with 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (180 mg, 0.72 mmol), cesium carbonate (2M, 0.44 mL, 0.88 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (18 mg, 0.022 mmol) in 5 mL dioxane according to the method described in Preparation 4. The crude was purified using SP1® Purification System (hexane-ethyl acetate) to give 82 mg (58% yield) of the title compound.

LRMS (m/z): 638 (M+1)⁺.

PREPARATION 12**(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-5-fluorophenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one**

5 (S)-3-Fluoro-5-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzaldehyde (40 mg, 0.06 mmol) was dissolved in 5 mL dichloroethane. *N,N*-Dimethylpiperidin-4-amine (25 mg, 0.19 mmol) and sodium triacetoxyborohydride (45 mg, 0.21 mmol) were added and stirred at room temperature for 4 h. The reaction
10 mixture was diluted with dichloromethane and washed twice with water and brine. The organics were washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using SP1® Purification System (dichloromethane- dichloromethane/methanol/NH₄OH) to give 34 mg (75% yield) of the title compound.

15 LRMS (m/z): 750 (M+1)⁺.

PREPARATION 13***tert*-Butyl (1-((4-bromopyridin-2-yl)methyl)piperidin-4-yl)(methyl)carbamate**

4-Bromopicolinaldehyde (500 mg, 2.69 mmol) and *tert*-butyl methyl(piperidin-4-yl)carbamate (634 mg, 2.96 mmol) were dissolved in 50 mL methanol. Sodium cyanoborohydride (254 mg, 4.04 mmol) and four drops of acetic acid were added and
20 the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated and the crude was re-dissolved in dichloromethane, washed with sodium carbonate and sodium hydroxide. The organics were dried over sodium sulphate, filtered and concentrated under reduced pressure. The yellow oil obtained was purified
25 by reverse phase using SP1® Purification System to give 573 mg (56% yield) of the title compound.

LRMS (m/z): 385 (M+1)⁺.

PREPARATION 14

***tert*-Butyl methyl(1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)piperidin-4-yl)carbamate**

30

tert-Butyl (1-((4-bromopyridin-2-yl)methyl)piperidin-4-yl)(methyl)carbamate (570 mg, 1.483 mmol) was treated with bis(pinacolato)diboron (452 mg, 1.77 mmol), potassium carbonate (291 mg, 2.96 mmol) and bis(diphenylphosphino)ferrocene-palladium (II) dichloromethane complex (121 mg, 0.148 mmol) in 5 mL dioxane according to the method described in Preparation 8. The crude was filtered through a pad of Celite® and concentrated under reduced pressure to give 858 mg (100% yield) of the title compound as boronic acid form which was used in the next step without further purification.

LRMS (m/z): 350 (M+1)⁺.

10 PREPARATION 15

(S)-*tert*-Butyl methyl(1-((4-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-yl)methyl)piperidin-4-yl)carbamate

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (200 mg, 0.336 mmol, described in WO2014060432A1) was treated with *tert*-butyl methyl(1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)piperidin-4-yl)carbamate (435 mg, 1.01 mmol), cesium carbonate (2M, 0.505 mL, 1.0 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (27.5 mg, 0.033 mmol) in 10 mL dioxane according to the method described in Preparation 4. The crude was purified by reverse phase using SP1® Purification System to give 62.6 mg (23% yield) of the title compound.

LRMS (m/z): 820 (M+1)⁺.

PREPARATION 16

25 **(5-Bromo-2-methylpyridin-3-yl)methanol**

Ethyl 5-bromo-2-methylnicotinate (350 mg, 1.52 mmol) was treated with lithium aluminium hydride powder 95% (139 mg, 3.6 mmol) in 6 mL tetrahydrofuran according to the method described in Preparation 5 to give 212 mg (69% yield) of the title compound.

30 LRMS (m/z): 202, 204 (M+1)⁺.

PREPARATION 17

(5-Bromo-2-methylpyridin-3-yl)methyl methanesulfonate

(5-Bromo-2-methylpyridin-3-yl)methanol (204 mg, 1 mmol) was treated with methanesulfonyl chloride (85.3 μ l, mmol) and triethylamine (167 μ l, mmol) in 10 mL dichloromethane according to the method described in Preparation 6 to give 261 mg
5 (93% yield) of the title compound pure enough to be used in the next synthetic step.

LRMS (m/z): 280, 282 (M+1)⁺.

PREPARATION 18**1-((5-Bromo-2-methylpyridin-3-yl)methyl)-*N,N*-dimethylpiperidin-4-amine**

(5-Bromo-2-methylpyridin-3-yl)methyl methanesulfonate (261 mg, 0.931 mmol) was
10 treated with *N,N*-dimethylpiperidin-4-amine (659 μ l, 4.645 mmol) in 6 mL ethanol according to the method described in Preparation 7 to give 231 mg (79% yield) of the title compound as an oil.

LRMS (m/z): 312, 314 (M+1)⁺.

PREPARATION 19**15 *N,N*-Dimethyl-1-((2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methyl)piperidin-4-amine**

1-((5-Bromo-2-methylpyridin-3-yl)methyl)-*N,N*-dimethylpiperidin-4-amine (231 mg, 0.739 mmol) was treated with bis(pinacolato)diboron (187 mg, 0.739 mmol), potassium carbonate (218 mg, 2.217 mmol) and bis(diphenylphosphino)ferrocene-palladium (II)
20 dichloromethane complex (60.3 mg, 0.073 mmol) in 5 mL dioxane according to the method described in Preparation 8 to give 427 mg of the title compound as boronic acid form which was used in the next synthetic step without further purification.

LRMS (m/z): 278 (M+1)⁺.

PREPARATION 20**25 (S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methylpyridin-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one**

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (150 mg, 0.252
30 mmol, described in WO2014060432A1) was treated with *N,N*-dimethyl-1-((2-methyl-5-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methyl)piperidin-4-amine (226 mg, 0.63 mmol), cesium carbonate (2M, 378 μ L, 0.756 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (20.6 mg, 0.025 mmol) in 2.5 mL dioxane according to the method described in
5 Preparation 4. The crude was purified using SP1[®] Purification System (dichloromethane-dichloromethane/methanol) to give 76 mg (40% yield) of the title compound.

LRMS (m/z): 748 (M+1)⁺.

PREPARATION 21

10 **1-(1-((4-Bromopyridin-2-yl)methyl)piperidin-4-yl)-*N,N*-dimethylmethanamine**

4-Bromopicolinaldehyde (150 mg, 0.806 mmol) was treated with *N,N*-dimethyl-1-(piperidin-4-yl)methanamine (137.6 mg, 0.967 mmol) and sodium triacetoxymethylborohydride (0.513 mg, 2.4 mmol) in 16 mL dichloromethane according to the method described in
15 Preparation 12. The solvent was evaporated and the residue re-dissolved in ethyl acetate and washed with sodium carbonate, two drops of sodium hydroxide and brine. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by reverse phase using SP1[®] Purification System to obtain 185 mg (73% yield) of the title compound.

LRMS (m/z): 313 (M+1)⁺.

20 PREPARATION 22

***N,N*-Dimethyl-1-(1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)piperidin-4-yl)methanamine**

1-(1-((4-Bromopyridin-2-yl)methyl)piperidin-4-yl)-*N,N*-dimethylmethanamine (185 mg, 0.592 mmol) was treated with bis(pinacolato)diboron (180 mg, 0.71 mmol), potassium
25 carbonate (116.3 mg, 1.18 mmol) and bis(diphenylphosphino)ferrocene-palladium (II) dichloromethane complex (48.4 mg, 0.05 mmol) according to the method described in Preparation 8. The crude was filtered and hexane was added to the filtrate forming a yellow precipitate that was filtered again to give 184.6 mg (87% yield) of the title compound.

30 LRMS (m/z): 360 (M+1)⁺.

PREPARATION 23

(S)-2-(1-((5-(2-((4-((Dimethylamino)methyl)piperidin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (122 mg, 0.206 mmol, described in WO2014060432A1) was treated with *N,N*-dimethyl-1-(1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methyl)piperidin-4-yl)methanamine (185 mg, 0.515 mmol), cesium carbonate (2M, 0.309 mL, 0.618 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (16.8 mg, 0.020 mmol) in 6 mL dioxane according to the method described in Preparation 4. The crude was purified by reverse phase using SP1[®] Purification System to give 77 mg (49% yield) of the title compound.

LRMS (m/z): 748 (M+1)⁺.

PREPARATION 24

15 4-Bromo-2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridine

4-Bromopicolinaldehyde (500 mg, 2.68 mmol) was treated with 4-(pyrrolidin-1-yl)piperidine (465 mg, 2.95 mmol) and sodium triacetoxymethylborohydride (1704 mg, 8.04 mmol) in 30 mL dichloroethane according to the method described in Preparation 12. The reaction mixture was washed with saturated sodium carbonate solution, drops of sodium hydroxide 2N and brine. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by reverse phase using SP1[®] Purification System to give 685 mg (79% yield) of the title compound.

LRMS (m/z): 325 (M+1)⁺.

25 PREPARATION 25

2-((4-(Pyrrolidin-1-yl)piperidin-1-yl)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

4-Bromo-2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridine (680 mg, 2.09 mmol) was treated with bis(pinacolato)diboron (590 mg, 2.3 mmol), potassium carbonate (605 mg, 6.27 mmol) and bis(diphenylphosphino)ferrocene-palladium (II)dichloromethane complex (170 mg, 0.209 mmol) in 10 mL dioxane according to the method described in Preparation 8. The residue was filtered and washed with ethyl acetate and hexane. The

solid obtained was dried under vacuum to give 770 mg (100% yield) of the title compound that was used in the next step without further purification.

LRMS (m/z): 372 (M+1)⁺.

PREPARATION 26

5 **(S)-5-Methyl-3-phenyl-2-(1-((5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one**

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (200 mg, 0.33
10 mmol, described in WO2014060432A1) was treated with 2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (371 mg, 1 mmol), cesium carbonate (2M, 0.5 mL, 1 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane
15 Preparation 4. The residue was purified using SP1[®] Purification System (dichloromethane-dichloromethane/methanol/NH₄OH) to give 180 mg (72% yield) of the title compound.

LRMS (m/z): 760 (M+1)⁺.

PREPARATION 27

20 **(3S,5R)-1-((4-Bromopyridin-2-yl)methyl)-3,5-dimethylpiperazine**

4-Bromopicolinaldehyde (200 mg, 1.08 mmol) was treated with (2S,6R)-2,6-dimethylpiperazine (200 mg, 1.07 mmol), *N,N*-diisopropyletamine (600 µl, 3.44 mmol) and sodium triacetoxyborohydride (460 mg, 2.17 mmol) in 10 mL dichloromethane according to the method described in Preparation 12. The solvent was removed and
25 the crude was purified using SP1[®] Purification System (dichloromethane-methanol) to give 159 mg (52% yield) of the title compound as a yellow oil.

LRMS (m/z): 285 (M+1)⁺.

PREPARATION 28

(2-(((3S,5R)-3,5-Dimethylpiperazin-1-yl)methyl)pyridin-4-yl)boronic acid

(3*S*,5*R*)-1-((4-Bromopyridin-2-yl)methyl)-3,5-dimethylpiperazine (147 mg, 0.52 mmol) was treated with bis(pinacolato)diboron (190 mg, 0.75 mmol), potassium carbonate (105 mg, 1.07 mmol) and bis(diphenylphosphino)ferrocene-palladium (II)dichloromethane complex (21 mg, 0.03 mmol) in 2 mL dioxane according to the method described in Preparation 8. The reaction mixture was filtered through a pad of Celite® and evaporated to give 326 mg (quantitative yield) of the title compound pure enough to follow the next step.

LRMS (m/z): 250 (M+1)⁺.

PREPARATION 29

10 **2-((*S*)-1-((5-(2-(((3*S*,5*R*)-3,5-Dimethylpiperazin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one**

(*S*)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (125 mg, 0.21 mmol, described in WO2014060432A1) was treated with (2-(((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)methyl)pyridin-4-yl)boronic acid (326 mg, 0.82 mmol), sodium carbonate (70 mg, 0.66 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (20 mg, 0.02 mmol) in 10 mL dimethoxyethane and 3 mL water according to the method described in Preparation 4. The reaction mixture was filtered through a pad of Celite® and concentrated. The crude was re-dissolved in ethyl acetate and washed with water and brine, dried over sodium sulphate, filtered and evaporated. The residue was purified using SP1® Purification System (dichloromethane-methanol) to give 59 mg (39%) of the title compound as an oil.

25 LRMS (m/z): 720 (M+1)⁺.

PREPARATION 30

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

4-Bromopicolinaldehyde (300 mg, 1.61 mmol) was treated with *N,N*-dimethylpiperidin-4-amine (227 mg, 1.77 mmol) and sodium triacetoxyborohydride (1.02 g, 4.84 mmol) in 30 mL dichloroethane according to the method described in Preparation 12. The reaction mixture was poured into water and sodium hydroxide. The aqueous was extracted with dichloromethane, dried over sodium sulphate, filtered and evaporated

under reduced pressure to give 390 mg (81% yield) of the title compound as an orange oil.

LRMS (m/z): 299 (M+1)⁺.

PREPARATION 31

5 **(2-((4-(dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)boronic acid**

1-((4-Bromopyridin-2-yl)methyl)-*N,N*-dimethylpiperidin-4-amine (390 mg, 1.31 mmol) was treated with bis(pinacolato)diboron (400 mg, 1.58 mmol), potassium carbonate (256 mg, 2.61 mmol) and bis(diphenylphosphino)ferrocene-palladium (II) dichloromethane complex (107 mg, 0.13 mmol) in 4 mL dioxane according to the method described in Preparation 8 at 120°C for 30 min. The reaction mixture was filtered through a pad of Celite[®] and concentrated under reduced pressure to give 950 mg (quantitative yield) of the title compound. The dark oil was used in the next step without further purification.

LRMS (m/z): 346 (M+1)⁺.

15 PREPARATION 32

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (100 mg, 0.17 mmol, described in WO2014060432A1) was treated with (2-((4-(dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)boronic acid (147 mg, 0.34 mmol), cesium carbonate (168 mg, 0.34 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (13.7 mg, 0.02 mmol) in 5 mL dioxane according to the method described in Preparation 4. The reaction mixture was filtered through a pad of Celite[®] and poured into water and ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using SP1[®] Purification System (dichloromethane-dichloromethane/methanol/NH₄OH) to give 77 mg (63% yield) of the title compound as a white solid.

LRMS (m/z): 734 (M+1)⁺.

PREPARATION 33**2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinaldehyde**

5-Bromo-2-methoxynicotinaldehyde (500 mg, 2.31 mmol) was treated with treated with bis(pinacolato)diboron (1175 mg, 4.63 mmol), potassium carbonate (681 mg, 6.94 mmol), bis(diphenylphosphino)ferrocene-palladium (II)dichloromethane complex (189 mg, 0.231 mmol) and 1,1'-bis(diphenylphosphino)ferrocene in 40 mL dioxane according to the method described in Preparation 8 at 100°C for 16 h. The reaction mixture was filtered through a pad of Celite® and evaporated under reduced pressure. The crude was purified using SP1® Purification System (dichloromethane-dichloromethane/methanol) to give 760 mg (74% yield) of the title compound.

LRMS (m/z): 264 (M+1)⁺.

PREPARATION 34**(S)-2-Methoxy-5-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)nicotinaldehyde**

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (100 mg, 0.17 mmol, described in WO2014060432A1) was treated with 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinaldehyde (53 mg, 0.20 mmol), cesium carbonate (168 mg, 0.34 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (14 mg, 0.02 mmol) in 5 mL dioxane according to the method described in Preparation 4. The reaction mixture was filtered through a pad of Celite® and washed with water and brine. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to give 110 mg (99% yield) of the title compound as an orange oil that was used in the next step without further purification.

LRMS (m/z): 651 (M+1)⁺.

PREPARATION 35**(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one**

(S)-2-Methoxy-5-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)nicotinaldehyde (110 mg, 0.17 mmol) was treated with *N,N*-dimethylpiperidin-4-amine (54 mg, 0.42 mmol) and sodium triacetoxyborohydride (125 mg, 0.59 mmol) in 5 mL dichloromethane according to the method described in Preparation 12. The reaction mixture was diluted with more dichloromethane and washed with potassium carbonate and water. The organics were combined and washed with more water, brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified using SP1[®] Purification System (dichloromethane-dichloromethane/methanol/NH₄OH) to give 62 mg (48% yield) of the title desired compound as a white solid.

LRMS (m/z): 764 (M+1)⁺.

PREPARATION 36

2-Hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde

5-Bromo-2-hydroxybenzaldehyde (1 g, 4.97 mmol) was treated with treated with bis(pinacolato)diboron (1770 mg, 6.97 mmol), potassium carbonate (980 mg, 9.99 mmol), bis(diphenylphosphino)ferrocene-palladium (II) dichloromethane complex (200 mg, 0.24 mmol) in 9 mL dioxane according to the method described in Preparation 8. The reaction mixture was filtered through a pad of Celite[®] and concentrated under reduced pressure to give 3 g (quantitative yield) of the title compound used in the next step without further purification.

LRMS (m/z): 249 (M+1)⁺.

PREPARATION 37

(S)-2-Hydroxy-5-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)benzaldehyde

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (200 mg, 0.34 mmol, described in WO2014060432A1) was treated with 2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (251 mg, 0.74 mmol), sodium carbonate (89 mg, 0.94 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (82 mg, 0.10 mmol) in 8 mL dimethoxyethane and 2 mL water according to the method

described in Preparation 4. The reaction mixture was filtered through a pad of Celite® and re-dissolved with ethyl acetate. The organic was washed with a saturated solution of sodium carbonate, dried over sodium sulphate, filtered and evaporated under reduced pressure to obtain a dark oil. The residue was purified by SP1® Purification System (dichloromethane-dichloromethane/methanol) to give 166 mg (62% yield) of the title compound as a brown oil.

LRMS (m/z): 636 (M+1)⁺.

PREPARATION 38

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-4-hydroxyphenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-2-Hydroxy-5-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzaldehyde (75 mg, 0.09 mmol) was treated with *N,N*-dimethylpiperidin-4-amine (34 mg, 0.24 mmol) and sodium triacetoxyborohydride (70 mg, 0.33 mmol) in 8 mL dichloroethane according to the method described in Preparation 12. The reaction mixture was washed with a solution of saturated sodium bicarbonate and water. The organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure to obtain 66 mg (67% yield) of the title compound used in the next step without further purification.

LRMS (m/z): 749 (M+1)⁺.

PREPARATION 39

1-((4-Bromopyridin-2-yl)methyl)-4-methyl-1,4-diazepane

4-Bromopicolinaldehyde (500 mg, 2.69 mmol) was treated with 1-methyl-1,4-diazepane (767 mg, 6.72 mmol) and sodium triacetoxyborohydride (2000 mg, 9.4 mmol) in 20 mL dichloroethane according to the method described in Preparation 12. The crude was purified using SP1® Purification System (dichloromethane-dichloromethane/methanol/NH₄OH) to give 660 mg (82% yield) of the title compound.

LRMS (m/z): 285 (M+1)⁺.

PREPARATION 40

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

1-((4-Bromopyridin-2-yl)methyl)-4-methyl-1,4-diazepane (660 mg, 2.32 mmol) was treated with bis(pinacolato)diboron (710 mg, 2.8 mmol), potassium carbonate (460 mg, 4.69mmol) and bis(diphenylphosphino)ferrocene-palladium (II)dichloromethane complex (95 mg, 0.12 mmol) in 10 mL dioxane according to the method described in Preparation 8. The reaction mixture was evaporated under reduced pressure to give 1 g (65% yield) of the title compound that was used in the next step without further purification.

LRMS (m/z): 250 (M+1)⁺.

PREPARATION 41

10 **(S)-5-Methyl-2-(1-((5-(2-((4-methyl-1,4-diazepan-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one**

(S)-2-(1-((5-Bromo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (350 mg, 0.0.59 mmol, described in WO2014060432A1) was treated with (2-((4-methyl-1,4-diazepan-1-yl)methyl)pyridin-4-yl)boronic acid (300 mg, 0.60 mmol), sodium carbonate (120 mg, 1.13 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (55 mg, 0.07 mmol) in 10 mL dimethoxyethane and 2 mL water according to the method described in Preparation 4. The reaction mixture was poured into dichloromethane and water. The organic phase was washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure to obtain 500 mg (70% yield) of the title compound.

LRMS (m/z): 719 (M+1)⁺.

25 EXAMPLE 1

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (76 mg, 0.099 mmol) was dissolved in 2.5 mL trifluoroacetic acid under argon conditions and was stirred at room temperature for

45 min. The solvent was evaporated and the crude was re-dissolved in ammonia (7N in methanol, 5mL) and stirred at room temperature for 45 min more. The reaction mixture was evaporated to dryness and the residue was suspended in water and extracted twice with dichloromethane. The aqueous phase was basified to pH 9 with 1N sodium hydroxide and extracted twice with dichloromethane. The organics were washed with water and brine, dried over sodium sulphate, filtered and concentrated under pressure to give 57 mg (96% yield) of the title compound as a solid.

LRMS (m/z): 633 (M+1)⁺.

¹H NMR (400 MHz, CDCl₃) δ ppm 11.05 (br s, 1H), 8.31 (s, 1H), 7.58-7.50 (m, 4H), 7.36-7.31 (m, 1H), 7.23 (s, 1H), 7.19 (s, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.87 (s, 1H), 6.30 (d, 1H), 5.91 (d, 1H), 5.21-5.14 (m, 1H), 3.98 (s, 3H), 3.63 (s, 2H), 3.10-3.01 (m, 2H), 2.48 (s, 3H), 2.29 (s, 6H), 2.30-2.11 (m, 3H), 1.81 (d, 2H), 1.65-1.52 (m, 2H), 1.36 (d, 3H).

EXAMPLE 2

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-(trifluoromethyl)pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-(trifluoromethyl)pyridin-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (43 mg, 0.053 mmol) was treated with trifluoroacetic acid (0.5 mL) and ammonia (7N in methanol, 1 mL) according to the method described in Example 1 to give 36 mg (96%) of the title compound.

LRMS (m/z): 672 (M+1)⁺.

¹H NMR (400MHz, DMSO-*d*₆) δ ppm 12.2 (s, 1H), 8.81 (d, 1H), 8.13-8.11 (m, 2H), 7.56 (s, 1H), 7.54-7.50 (m, 3H), 7.46-7.40 (m, 1H), 7.38-7.34 (m, 1H), 7.26 (d, 1H), 6.37 (d, 1H), 6.29 (d, 1H), 5.01-4.93 (m, 1H), 3.58 (d, 1H), 2.78 (d, 1H), 2.71 (d, 1H), 2.36 (s, 3H), 2.16-2.05 (m, 7H), 2.01-1.92 (m, 2H), 1.68-1.58 (m, 2H), 1.92-1.82 (m, 2H), 1.36-1.28 (m, 5H).

EXAMPLE 3

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-5-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-5-fluorophenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (34 mg, 0.045 mmol) was treated with trifluoroacetic acid (0.6 mL) and ammonia (7N in methanol, 2 mL) according to the method described in Example 1. The crude was extracted with ethyl acetate and washed with water. The organic layer was washed with aqueous carbonate solution and brine, dried over sodium sulphate, filtered and evaporated under reduced pressure to give 25 mg (92% yield) of the pure desired compound.

LRMS (m/z): 621 (M+1)⁺.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.98 (s, 1H), 8.14 (s, 1H), 7.60 ? 7.53 (m, 3H), 7.52 (m, 2H), 7.38 (d, 1H), 7.31 (s, 1H), 7.29 (dd, 1H), 7.23 (d, 1H), 7.15 (d, 1H), 6.40 (d, 1H), 5.86 (d, 1H), 4.92 (q, 1H), 3.45 (d, 2H), 2.81 (d, 2H), 2.37 (s, 3H), 2.13 (s, 6H), 1.96 (m, 1H), 1.89 (q, 12.7 Hz, 2H), 1.64 (d, 2H), 1.42 (m, 2H), 1.30 (d, 3H).

15 EXAMPLE 4

(S)-5-Methyl-2-(1-((5-(2-((4-(methylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-*tert*-Butyl methyl(1-((4-(4-((1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-yl)methyl)piperidin-4-yl)carbamate (60 mg, 0.073 mmol) was treated with trifluoroacetic acid (0.90 mL) and ammonia (7N in methanol, 7.3 mL) according to the method described in Example 1. The crude was extracted with ethyl acetate and washed with water and saturated sodium bicarbonate solution. The organic layer was dried over sodium sulphate, filtered and evaporated under reduced pressure to give 38 mg (88% yield) of the title compound.

LRMS (m/z): 590 (M+1)⁺.

¹H NMR (400 MHz, MeOD) δ ppm 8.56 (d, 1H), 8.14 (s, 1H), 7.72 (d, 1H), 7.61-7.41 (m, 7H), 7.17 (d, 1H), 6.38 (d, 1H), 5.12 (q, 1H), 3.62 (m, 2H), 2.96-2.86 (m, 2H), 2.56-2.49 (m, 1H), 2.44 (s, 3H), 2.41 (s, 3H), 2.18-2.09 (m, 2H), 1.92-1.86 (m, 2H), 1.49-1.40 (m, 2H), 1.41 (d, 3H).

EXAMPLE 5

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methylpyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methylpyridin-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (70 mg, 0.093 mmol) was treated with trifluoroacetic acid (0.6 mL) and ammonia (7N in methanol, 1.2 mL) according to the method described in Example 1. The crude was basified with sodium hydroxide and extracted twice with dichloromethane. The organics were washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to give 40 mg (70% yield) of title compound as a brown oil.

LRMS (m/z): 618 (M+1)⁺.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.98 (s, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 7.70 (s, 1H), 7.51 (d, 5H), 7.35 (s, 1H), 7.25 (s, 1H), 6.41 (s, 1H), 5.89 (d, 1H), 4.97 – 4.85 (m, 1H), 3.37 (s, 3H), 2.86 – 2.77 (m, 2H), 2.58 (s, 3H), 2.37 (s, 3H), 2.12 (s, 6H), 1.95 (d, 2H), 1.64 (d, 2H), 1.33 – 1.23 (m, 5H).

EXAMPLE 6

(S)-2-(1-((5-(2-((4-((Dimethylamino)methyl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-2-(1-((5-(2-((4-((Dimethylamino)methyl)piperidin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (75 mg, 0.1 mmol) was treated with trifluoroacetic acid (1.23 mL) and ammonia (7N in methanol, 10 mL) according to the method described in Example 1. The solvent was concentrated under reduced pressure. The crude was dissolved in ethyl acetate and washed with water and saturated sodium bicarbonate, dried over reduced pressure, filtered and concentrated to give 45.4 mg (73% yield) of the title compound.

LRMS (m/z): 619 (M+1)⁺.

¹H NMR (400 MHz, MeOD) δ ppm 8.56 (d, 1H), 8.14 (s, 1H), 7.73 (d, 1H), 7.62-7.41 (m, 7H), 7.17 (d, 1H), 6.38 (d, 1H), 5.11 (q, 1H), 3.62 (m, 2H), 2.94-2.86

(m, 2H), 2.44 (s, 3H), 2.20 (s, 6H), 2.16 (d, 2H), 2.14-2.05 (m, 2H), 1.72-1.66 (m, 2H), 1.55-1.48 (m, 1H), 1.40 (d, 3H), 1.28-1.17 (m, 2H).

EXAMPLE 7

5 **(S)-5-Methyl-3-phenyl-2-(1-((5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one**

(S)-5-Methyl-3-phenyl-2-(1-((5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (180 mg, 0.23 mmol) was treated with trifluoroacetic acid (2.8 mL) and ammonia (7N in methanol, 5 mL) according to the method described in Example 1. The solvent was evaporated and re-dissolved in ethyl acetate. The organic phase was washed with saturated sodium carbonate solution, drops of sodium hydroxide 2N and brine and then dried over sodium sulphate, filtered and evaporated under reduced pressure to obtain 127 mg (89% yield) of the title compound as a solid.

LRMS (m/z): 629 (M+1)⁺.

¹H NMR (400 MHz, CDCl₃) δ ppm 10.71 (s, 1H), 8.67 (d, 1H), 8.32 (s, 1H), 7.70 (s, 1H), 7.60 – 7.48 (m, 5H), 7.42 (dd, 1H), 7.35 – 7.30 (m, 1H), 7.20 (s, 1H), 7.09 (d, 1H), 6.30 (d, 1H), 5.81 (d, 1H), 5.23 – 4.99 (m, 1H), 3.71 (s, 2H), 3.00 – 2.85 (m, 2H), 2.64 – 2.49 (m, 4H), 2.48 (s, 3H), 2.24 – 2.09 (m, 2H), 2.08 – 1.90 (m, 1H), 1.91 – 1.83 (m, 2H), 1.75 (d, 3H), 1.66 – 1.53 (m, 3H), 1.36 (d, 3H).

EXAMPLE 8

25 **2-((S)-1-((5-(2-(((3S,5R)-3,5-Dimethylpiperazin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one**

2-((S)-1-((5-(2-(((3S,5R)-3,5-Dimethylpiperazin-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (59 mg, 0.08 mmol) was treated with trifluoroacetic acid (1.5 mL) and ammonia (7N in methanol, 3 mL) according to the method described in Example 1. The solvent was evaporated and the residue re-dissolved in ethyl acetate. The organic phase was washed with saturated sodium

bicarbonate solution, dried over sodium sulphate, filtered and evaporated under reduced pressure to obtain 33 mg (68%) of the title compound as a solid.

LRMS (m/z): 589 (M+1)⁺.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.88 (d, 6H), 1.30 (d, 3H), 1.63 (bs, 2H),
5 2.35 (s, 3H), 2.57 - 2.73 (m, 2H), 2.80 (bs, 2H), 3.49 (s, 2H), 4.76 - 5.03 (m,
1H), 5.99 (d, , 1H), 6.37 (s, 1H), 7.22 (d, 1H), 7.32 - 7.66 (m, 9H), 8.12 (s, 1H),
8.53 (s, 1H), 12.11 (s, 1H).

EXAMPLE 9

**(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-
10 pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-
f][1,2,4]triazin-4(3H)-one**

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7-((2-
(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-
15 phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (77 mg, 0.11 mmol) was treated with
trifluoroacetic acid (2 mL) and ammonia (7N in methanol, mL) according to the method
described in Example 1. The solvent was evaporated and the residue poured into
water and ethyl acetate. The organic phase was washed with water, brine, dried over
sodium sulphate, filtered and concentrated under reduced pressure to give 38 mg (60%
yield) of the desired compound as a white solid.

20 LRMS (m/z): 603 (M+1)⁺.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.31 - 1.40 (m, 3H), 1.52 - 1.61 (m, 2H),
1.74 - 1.84 (m, 2H), 1.99 - 2.20 (m, 3H), 2.28 (s, 6H), 2.47 (s, 3H), 2.92 - 3.06
(m, 2H), 3.70 (s, 2H), 5.08 - 5.22 (m, 1H), 5.74 - 5.84 (m, 1H), 6.25 - 6.34 (m,
1H), 7.03 - 7.13 (m, 1H), 7.20 (s, 1H), 7.29 - 7.37 (m, 1H), 7.39 - 7.45 (m, 1H),
25 7.46 - 7.61 (m, 4H), 7.64 (s, 1H), 8.31 (s, 1H), 8.63 - 8.73 (m, 1H), 10.10 (s,
1H).

EXAMPLE 10

**(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-3-yl)-
7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-
30 f][1,2,4]triazin-4(3H)-one**

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-3-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (60 mg, 0.08 mmol) was treated with trifluoroacetic acid (2 mL) and ammonia (7N in methanol, 11 mL) according to the method described in Example 1. The solvent was concentrated and purified by reverse phase using SP1[®] Purification System to give 40 mg (80% yield) of the title compound as a white solid.

LRMS (m/z): 633 (M+1)⁺.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.25 (s, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.44 – 1.57 (m, 2H), 1.70 – 1.80 (m, 2H), 1.99 – 2.17 (m, 3H), 2.24 (s, 6H), 2.47 (s, 3H), 2.87 – 3.04 (m, 2H), 4.04 (s, 2H), 5.08 – 5.21 (m, 1H), 5.65 – 5.74 (m, 1H), 6.25 – 6.33 (m, 1H), 7.01 (s, 1H), 7.12 – 7.18 (m, 1H), 7.28 – 7.35 (m, 1H), 7.43 – 7.61 (m, 5H), 7.83 – 7.89 (m, 1H), 8.23 – 8.32 (m, 2H).

EXAMPLE 11

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-4-hydroxyphenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (66 mg, 0.06 mmol) was treated with trifluoroacetic acid (0.46 mL) and ammonia (7N in methanol, 8 mL) according to the method described in Example 1. The solvent was concentrated under reduced pressure. The residue was re-dissolved in dichloromethane, washed with a solution 4% of sodium bicarbonate and water. The organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure. The crude was purified using SP1[®] Purification System (dichloromethane-dichloromethane/methanol) to give 12.24 mg (66% yield) of the title compound.

LRMS (m/z): 618 (M+1)⁺.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.27 – 1.34 (m, 3H), 1.53 – 1.68 (m, 2H), 1.83 (s, 2H), 2.01 – 2.24 (m, 3H), 2.29 (s, 6H), 2.48 (s, 3H), 2.97 – 3.17 (m, 2H), 3.71 (s, 2H), 5.04 – 5.21 (m, 1H), 5.76 – 5.88 (m, 1H), 6.26 – 6.38 (m, 1H), 6.90 – 7.03 (m, 2H), 7.07 – 7.15 (m, 1H), 7.18 (s, 1H), 7.29 – 7.34 (m, 1H), 7.34 – 7.43 (m, 1H), 7.44 – 7.63 (m, 5H), 8.23 (s, 1H), 9.41 (s, 1H).

EXAMPLE 12**(S)-5-Methyl-2-(1-((5-(2-((4-methyl-1,4-diazepan-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one**

(S)-5-Methyl-2-(1-((5-(2-((4-methyl-1,4-diazepan-1-yl)methyl)pyridin-4-yl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (500 mg, 0.14 mmol) was treated with trifluoroacetic acid (2 mL) and ammonia (7N in methanol, 2 mL) according to the method described in Example 1. The solvent was concentrated under reduced pressure and purified by reverse phase using preparative HPLC-MS purification system to obtain 10 mg (13% yield) of the title compound as a white solid.

LRMS (m/z): 589 (M+1)⁺.

¹H NMR (400 MHz, CDCl₃) δ ppm 0.73 – 0.92 (m, 3H), 1.28 (s, 1H), 1.35 (t, 3H), 2.04 (m, 2H), 2.48 (s, 3H), 2.54 (s, 2H), 2.79 – 3.14 (m, 6H), 3.89 (s, 2H), 4.97 – 5.29 (m, 1H), 5.78 (d, 1H), 6.31 (s, 1H), 7.06 (d, 1H), 7.34 (d, 1H), 7.39 – 7.59 (m, 3H), 7.73 (s, 1H), 8.30 (s, 1H), 8.68 (d, 1H), 10.02 (s, 1H).

PHARMACOLOGICAL ACTIVITY**PI3K α , β , δ and γ Enzymatic Inhibition Assays**

Compounds were screened for their ability to inhibit PI3K α (PI3Ka), PI3K β (PI3Kb), PI3K δ (PI3Kd) and PI3K γ (PI3Kg) using a cell-free based PI3K HTRF™ assay (Millipore, ref. #33-017).

PI-3 Kinase HTRF kit (ref. #33-037) and the different PI3K recombinant isoforms (ref. #14-602, ref. #14-603, ref.#14-604, ref.#15-558 for Alpha, Beta, Delta and Gamma respectively) were purchased at Millipore (expressed in insect cells). ATP was purchased at Sigma Aldrich (ref. #A7699).

The compounds were pre-incubated with the enzyme for 30 min before starting of the catalytic reaction. [PIP2] was used at its K_m. [ATP] was used at 15 μ M for all isoforms for technical reasons (K_m values varied between 10 and 20 μ M depending on the

isoform). Time of assay and [Enzyme] were optimized to work in the linear range. Stop and Detection mixtures were used as specified in the Millipore PI-3 Kinase kit.

- Final Assay conditions

PI3K	Reaction Time (min)	[Enz] (nM)	[ATP] (μ M)	[PIP2] (μ M)	Preincubation Time (min)	Reading (hours)
ALPHA	6	0.30	15	2	30	1 - 18
BETA	6	0.75	15	5	30	1 - 18
DELTA	8	0.35	15	2	30	1 - 18
GAMMA	8	2.5	15	10	30	1 - 18

5 *Reaction time and enzyme concentration in the assay will depend of each batch.*

All experiments were analysed using Activity Base software from IDBS and the four-parameter log equation.

10 The results are shown in Table 1.

Example	IC ₅₀ PI3Kd HTRF (nM)
1	0,95
2	3,25
3	1,96
4	1,42
5	3,10
6	1,71
7	1,76
8	1,65
9	1,92
10	1,28
11	0,43
12	1,50

It can be seen from Table 1 that the compounds of formula (I) are potent inhibitors of Phosphoinositide 3-kinase delta (PI3kd). Preferred compounds of the invention possess an IC_{50} value for the inhibition of PI3Kd (determined as defined above) of less than 10 nM.

5

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
10 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.

15 **Combinations**

The pyrrolotriazinone derivatives defined herein may also be combined with other active compounds in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of PI3Ks.

20

The combinations of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; function disorders and neurological disorders; cardiovascular diseases; viral infection;
25 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.

30 Particularly, the combinations of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of neoplastic diseases (e.g. leukemia, lymphomas, solid tumors); transplant rejection, bone marrow transplant applications (e.g., graft- versus-host disease); autoimmune diseases (e.g. rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis,
35 Crohn's disease, ulcerative colitis, systemic lupus erythematosus, autoimmune hemolytic anemia, type I diabetes, cutaneous vasculitis, cutaneous lupus erythematosus, dermatomyositis and blistering diseases including but not limited to

pemphigus vulgaris, bullous pemphigoid and epidermolysis bullosa); respiratory inflammation diseases (e.g. asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis); skin inflammatory diseases (e.g., atopic dermatitis, contact dermatitis, eczema or psoriasis); premalignant and malignant skin conditions (e.g. basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or actinic keratosis (AK)); neurological disorders and pain (such as pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, inflammatory neuropathic pain, trigeminal neuralgia or central pain).

10 Preferably, the combinations of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of neoplastic diseases 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, type I
15 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, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma
20 and actinic keratosis.

In particular, the combinations of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of neoplastic diseases leukemia, lymphomas and solid tumors, rheumatoid arthritis,
25 multiple sclerosis, amyotrophic lateral sclerosis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, autoimmune hemolytic anemia, type I diabetes, type I diabetes, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic
30 keratosis

The combinations of the invention comprise (i) a compound of the invention as defined above; and (ii) another compound selected from the group consisting of an Adenoside A_{2A} agonist, an agent for treating cardiovascular disorders, an agent for treating
35 diabetes, and an agent for treating liver disease, an anti-allergic agent, an anti-cholinergic agent, an anti-inflammatory agent, an anti-infective agent, a β_2 -adrenergic agonist, a Chemoattractant receptor homologous molecule expressed on TH₂ cells

(CRTH2) inhibitor, a chemotherapeutic agent, a corticosteroid, an IKK β /IKBKB (I κ B kinase beta or IKK2) inhibitor, an immunosuppressant, a Janus kinase (JAK) inhibitor, a topically acting p38 Mitogen-Activated Protein Kinase (p38 MAPK) inhibitor, a Phosphodiesterase (PDE) IV inhibitor, and a Spleen tyrosine kinase (Syk) inhibitor,
5 for simultaneous, separate or sequential use in the treatment of the human or animal body.

In a particular embodiment, the combinations of the invention can optionally comprise one or more additional active substances selected from

- 10 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
15 WO2009/021696;
- c) Immunomodulators such as Glatiramer acetate (Copaxone), Laquinimod or Imiquimod;
- d) Inhibitors of DNA synthesis and repair, such as Mitoxantrone or Cladribine;
- 20 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, Finategrast or TMC-2003;
- 25 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) monoclonal
30 antibodies such as Infliximab, Adalimumab or Certolizumab pegol;
- k) Soluble Tumor necrosis factor-alpha (TNF-alpha) Antagonists such as Ethenerecept;
- l) Anti-CD20 (lymphocyte protein) monoclonal antibodies such as Rituximab, Ocrelizumab Ofatumumab or TRU-015;
- 35 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;
- q) Anti-Interleukin 12 Receptor (IL-12R) / Interleukin 23 Receptor (IL-23R), such as ustekinumab;
- 5 r) Calcineurin inhibitors such as cyclosporine A or tacrolimus;
- s) Inosine-monophosphate dehydrogenase (IMPDH) inhibitors, such as mycophenolate mophetyl, ribavirin, mizoribine or mycophenolic acid;
- 10 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;
- 15 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;
- 20 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 LAS100977 (abediterol);
- 25 ee) MABA (molecules with dual activity: beta-adrenergic agonists and muscarinic receptor antagonists)
- ff) Histamine 1 (H1) receptor antagonists, such as azelastine or ebastine;
- gg) Cysteinyl leukotriene (CysLT) receptor antagonists, such as montelukast;
- 30 hh) Mast cell stabilizers, such as nedocromil or chromoglycate;
- ii) 5-lipoxygenase-activating protein (FLAP) inhibitors, such as MK886 or BAY X 1005;
- jj) 5-lipoxygenase (5-LO) inhibitors, such as WY-50295T;
- 35 kk) Chemoattractant receptor homologous molecule expressed on TH₂ cells (CRTH2) inhibitors, such as OC-459, AZD-1981, ACT-129968, QAV-680;

- ll) Vitamin D derivatives like calcipotriol (Daivonex) ;
- mm) 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;
- 5
- nn) Anti-allergic agents;
- oo) Anti-viral agents;
- pp) Phosphodiesterase (PDE) III inhibitors;
- 10 qq) Phosphodiesterase (PDE) IV inhibitors such as roflumilast or GRC-4039;
- rr) Dual Phosphodiesterase (PDE) III/IV inhibitors;
- ss) Xanthine derivatives, such as theophylline or theobromine;
- tt) p38 Mitogen-Activated Protein Kinase (p38 MAPK) Inhibitors such as ARRY-797;
- 15 uu) Mitogen-activated extracellular signal regulated kinase (MEK) inhibitor, such as ARRY-142886 or ARRY-438162;
- vv) Janus kinase (JAK) inhibitors, such as tofacitinib (previously known as tasocitinib or CP-690,550) from Pfizer and INCB-18424 from Incyte;
- 20 ww) 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;
- 25 xx) Interferon alpha such as Sumiferon MP;
- yy) Epidermal Growth Factor Receptor (EGFR) inhibitors such as erlotinib, Trastuzumab, Herceptin, Avastin, Platins (cisplatin, carboplatin) or Temazolamide;
- zz) Antineoplastic agents such as Docetaxel, Estramustine, Anthracyclines, (doxorubicin (Adriamycin), epirubicin (Ellence), and liposomal doxorubicin (Doxil)), Taxanes (docetaxel (Taxotere), paclitaxel (Taxol), and protein-bound paclitaxel (Abraxane)), Cyclophosphamide (Cytoxan), Capecitabine (Xeloda), 5 fluorouracil (5 FU), Gemcitabine (Gemzar) or Vinorelbine (Navelbine).
- 30
- 35 The compounds of formula (I) and the combinations of the invention may be used in the treatment of respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; 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 such as polycythemia vera, essential thrombocythemia or mielofibrosis); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors, wherein the use of a PI3K inhibitor is expected to have a beneficial effect, for example 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, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

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In particular 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, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

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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.

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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.

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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 the above mentioned diseases.

5 The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinases (PI3Ks), in particular wherein the pathological condition or disease is selected from respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; function disorders and neurological disorders; cardiovascular diseases; viral infection;
10 metabolism/endocrine function disorders; neurological disorders and pain; bone marrow and organ transplant rejection; myelo-dysplastic syndrome; myeloproliferative disorders (MPDs such as polycythemia vera, essential thrombocythemia or mielofibrosis); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors; more in particular wherein the pathological condition or disease is selected
15 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,
20 chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

In particular the pathological condition or disease is selected from leukemia, lymphomas and solid tumors, rheumatoid arthritis, multiple sclerosis, amyotrophic
25 lateral sclerosis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, autoimmune hemolytic anemia, type I diabetes, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

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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,
35 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 pyrrolotriazinone 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 pyrrolotriazinone 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 respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; function disorders and neurological disorders; cardiovascular diseases; viral infection; metabolism/endocrine function disorders; neurological disorders and pain; bone marrow and organ transplant rejection; myelodysplastic syndrome; myeloproliferative disorders (MPDs such as polycythemia vera, essential thrombocythemia or myelofibrosis); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors; more in particular wherein 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, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

In particular 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, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

Another execution of the present invention consists of a package comprising a pyrrolotriazinone derivative of the invention and another active compound useful in the treatment of respiratory diseases; allergic diseases; inflammatory or autoimmune-

mediated diseases; 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 such as polycythemia vera, essential thrombocythemia or myelofibrosis); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors; more in particular wherein 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, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

In particular 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, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

25 **Pharmaceutical Compositions**

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

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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, or N-oxides, or isotopically-labeled derivative 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.

5 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 Phosphoinositide 3-Kinases (PI3Ks), such as the ones previously described.

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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 Phosphoinositide 3-Kinases (PI3Ks), in particular wherein the pathological condition or disease is selected from respiratory diseases; allergic diseases;

15 inflammatory or autoimmune-mediated diseases; 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 such as polycythemia vera, essential thrombocythemia or myelofibrosis); cancer and

20 hematologic malignancies, leukemia, lymphomas and solid tumors; more in particular wherein 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

25 erythematosus, dermatomyositis, blistering diseases including but not limited to pemphigus vulgaris, bullous pemphigoid and epidermolysis bullosa, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

30 In particular 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, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis,

35 atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis. 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 Phosphoinositide 3-Kinases (PI3Ks), in particular wherein the pathological condition or disease is selected from respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; 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 such as polycythemia vera, essential thrombocythemia or myelofibrosis); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors; more in particular wherein 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, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis; more in particular 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, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis; comprising administering a therapeutically effective amount of a pharmaceutical composition of the invention.

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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, or N-oxide, or isotopically-labeled derivative 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

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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 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 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.

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

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.

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 as a bolus, electuary or paste.

ii) Oral mucosal administration

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), and (c) local delivery, which is drug delivery into the oral cavity.

5 iii) Inhaled administration

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
10 pressurized container, pump, spray, atomizer (preferably an atomizer using 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.

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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
20 suitable powder base (carrier substance) such as lactose or starch. Use of lactose is 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.

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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.

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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
35 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.

- 5 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
10 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
15 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.

- 20 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
25 dose system, including the technique used to transport the strip and open the blister pockets.

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
30 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
35 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.

5

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

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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.

15

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.

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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.

30

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

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micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

5 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
10 will typically be present as milled lactose, preferably crystalline alpha lactose monohydrate.

iv) Nasal mucosal administration

The compounds of the invention may also be administered via the nasal mucosal.
15 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
25 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),
30 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 such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by
35 lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

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 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, phonophoresis, sonophoresis and microneedle or needle-free injection.

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.

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.

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

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.

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.

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)

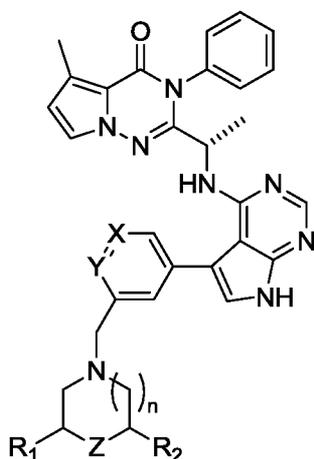
Ingredient	Amount
-------------------	---------------

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

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

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, or N-oxide, or
 5 isotopically-labeled derivate thereof:



Formula (I)

10

wherein,

n represents an integer selected from 1 or 2;

15 X and Y each independently represent a nitrogen atom or CR₃ group;

R₁ and R₂ each independently represent a hydrogen atom or a linear or branched C₁-C₄ alkyl group;

20 R₃ represents a hydrogen atom, a halogen atom, a hydroxyl, a linear or branched C₁-C₄ alkyl group, a C₁-C₄ alkoxy group or a C₁-C₄ haloalkyl group;

Z represents a -CH((CH₂)₀₋₁NR^aR^b)- group, a -NH- group or a -N(C₁-C₃ alkyl)- group;

25 R^a and R^b each independently represent a hydrogen atom or a linear or branched C₁-C₄ alkyl group; or R^a and R^b together with the nitrogen atom to which they are attached form a monocyclic 3- to 7-membered heterocyclyl group optionally containing at least one further heteroatom selected from O, S and N.

2. A compound according to claim 1, wherein n represents 1.
3. A compound according to claim 1 or 2 wherein R₁ and R₂ represent a hydrogen atom.
- 5
4. A compound according to any preceding claim wherein X represents a CR³ group and Y represents a nitrogen atom.
- 10
5. A compound according to any preceding claim wherein R³ represents a hydrogen atom.
6. A compound according to any preceding claim wherein Z represents a –CH((CH₂)₀₋₁NR^aR^b)- group.
- 15
7. A compound according to any preceding claim wherein R^a and R^b each independently represent a hydrogen atom or a methyl group.
8. A compound according to claim 1 wherein:
- 20
- n represents 1;
- R₁ and R₂ represent a hydrogen atom;
- X represents a CH group and Y represents a nitrogen atom;
- Z represents a –CH((CH₂)₀₋₁NR^aR^b) group; and
- R^a and R^b each independently represent a hydrogen atom or a methyl group.
- 25
9. A compound according to claim 1 wherein:
- n represents 1 or 2;
- R₁ and R₂ represent a hydrogen atom or a methyl group;
- R₃ represents a hydrogen atom, a methoxy group, a methyl group, a -CF₃ group, a
- 30
- fluorine atom or a hydroxyl group; and
- R^a and R^b each independently represent a hydrogen atom or a methyl group; or R^a and R^b together with the nitrogen atom to which they are attached form a pyrrolidiny group.
- 35
10. A compound according to claim 1, which is one of:

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

5 (S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-(trifluoromethyl)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-5-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

10 (S)-5-Methyl-2-(1-((5-(2-((4-(methylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methylpyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

15 (S)-2-(1-((5-(2-((4-((Dimethylamino)methyl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-5-Methyl-3-phenyl-2-(1-((5-(2-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

20 2-((S)-1-((5-(2-(((3S,5R)-3,5-Dimethylpiperazin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(2-((4-(Dimethylamino)piperidin-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

25 (S)-2-(1-((5-(5-((4-(Dimethylamino)piperidin-1-yl)methyl)-6-methoxypyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

(S)-2-(1-((5-(3-((4-(Dimethylamino)piperidin-1-yl)methyl)-4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-5-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one; or

30 (S)-5-Methyl-2-(1-((5-(2-((4-methyl-1,4-diazepan-1-yl)methyl)pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-3-phenylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one;

or a pharmaceutically acceptable salt, or N-oxide, or isotopically-labeled derivate thereof.

11. A compound according to any one of claims 1 to 10, for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K).

12. A compound for use according to claim 11, wherein the pathological condition or disease is selected from respiratory diseases; allergic diseases; inflammatory or autoimmune-mediated diseases; function disorders and neurological disorders; cardiovascular diseases; viral infection; metabolism/endocrine function disorders; neurological disorders and pain; bone marrow and organ transplant rejection; myelodysplastic syndrome; myeloproliferative disorders (MPDs); cancer and hematologic malignancies, leukemia, lymphomas and solid tumors.

13. A compound for use according to claims 11 or 12, wherein 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, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, allergic rhinitis, atopic dermatitis, contact dermatitis, eczema, psoriasis, basal cell carcinoma, squamous cell carcinoma and actinic keratosis.

14. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 10 in association with a pharmaceutically acceptable diluent or carrier.

15. Use of a compound as defined in any one of claims 1 to 10, for the manufacture of a medicament for the treatment of a pathological condition or disease as defined in any one of claims 11 to 13.

16. A method for treating a subject afflicted with a pathological condition or disease as defined in any one of claims 11 to 13 which comprises administering to said subject a therapeutically effective amount of a compound as defined in any one of claims 1 to 10, or a pharmaceutical composition as defined in claim 14.

17. A combination product comprising (i) a compound as defined in any one of claims 1 to 10; and (ii) another compound selected from the group consisting of an Adenoside A_{2A} agonist, an agent for treating cardiovascular disorders, an agent for treating diabetes, and an agent for treating liver disease, an anti-allergic agent, an anti-cholinergic agent, an anti-inflammatory agent, an anti-infective agent, a β 2-adrenergic agonist, a Chemoattractant receptor homologous molecule expressed on TH₂ cells (CRTH2) inhibitor, a chemotherapeutic agent, a corticosteroid, an IKK β /IKBKB (IKB kinase beta or IKK2) inhibitor, an immunosuppressant, a Janus kinase (JAK) inhibitor, a topically acting p38 Mitogen-Activated Protein Kinase (p38 MAPK) inhibitor, a Phosphodiesterase (PDE) IV inhibitor, and a Spleen tyrosine kinase (Syk) inhibitor, for simultaneous, separate or sequential use in the treatment of the human or animal body.

15

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063635

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D487/04 C07D519/00 A61K31/53 A61P11/00 A61P9/00
 A61P25/00 A61P35/00 A61P17/00 A61P37/00
 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.
A	WO 2014/060432 A1 (ALMIRALL SA [ES]) 24 April 2014 (2014-04-24) cited in the application the whole document -----	1-17

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 19 August 2016	Date of mailing of the international search report 05/09/2016
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Panday, Narendra
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/063635

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014060432	A1	24-04-2014	
		AR 093036 A1	13-05-2015
		AU 2013333938 A1	09-04-2015
		CA 2883426 A1	24-04-2014
		CN 104854108 A	19-08-2015
		CR 20150175 A	11-05-2015
		DO P2015000077 A	30-04-2015
		EA 201500426 A1	30-10-2015
		EP 2909207 A1	26-08-2015
		HK 1211027 A1	13-05-2016
		JP 2015533181 A	19-11-2015
		KR 20150068953 A	22-06-2015
		MD 20150048 A2	31-10-2015
		PE 06372015 A1	08-05-2015
		PH 12015500813 A1	08-06-2015
		SG 11201502032V A	28-05-2015
		TW 201429975 A	01-08-2014
		US 2015291595 A1	15-10-2015
		UY 35086 A	30-05-2014
		WO 2014060432 A1	24-04-2014
