

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 August 2010 (19.08.2010)

PCT

(10) International Publication Number  
**WO 2010/092015 A1**

(51) International Patent Classification:

C07D 471/04 (2006.01) A61P 35/00 (2006.01)  
A61K 31/437 (2006.01) A61P 31/00 (2006.01)  
A61P 29/00 (2006.01) A61P 25/00 (2006.01)  
A61P 9/00 (2006.01)

(21) International Application Number:

PCT/EP2010/051462

(22) International Filing Date:

8 February 2010 (08.02.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

09152430.6 10 February 2009 (10.02.2009) EP

(71) Applicant (for all designated States except US): **CELL-ZOME LIMITED** [—/GB]; Chesterford Research Park, Little Chesterford, Cambridge CB10 1XL (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **RAMSDEN, Nigel** [GB/GB]; Sparrows Lodge, Green Lane, Fowlmere, Royston, Herts SG8 7QP (GB). **BELL, Kathryn** [GB/GB]; 6 Malvern Road, London E8 3LT (GB). **TAYLOR, Jess** [GB/GB]; 22 Downs View, Dorking, Surrey, RH4 1PX (GB). **SUNOSE, Mihiro** [JP/GB]; 18 Old Forge Way, Sawston, Cambridge CB22 3BD (GB). **MIDDLEMISS, David** [GB/GB]; 61 Thorley Hill, Bishops Stortford, Hertfordshire CM23 3NF (GB). **ELLARD, Katie**

[GB/GB]; 19 Barnack Grove, Royston, Herts SG8 5HQ (GB).

(74) Agent: **BÜCHEL, Edwin**; Eastsite One, Seckenenheimer Landstraße 4, 68163 Mannheim (DE).

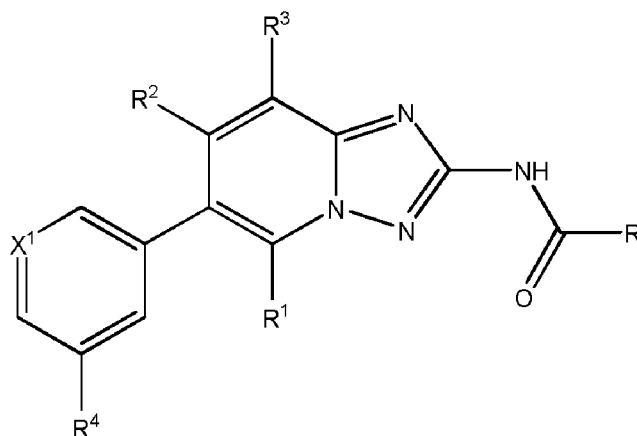
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: UREA TRIAZOLOLO [1, 5-A] PYRIDINE DERIVATIVES AS PI3K INHIBITORS



(I)

(57) Abstract: The invention relates to compounds of formula (I) wherein X<sup>1</sup>, R and R<sup>1</sup> to R<sup>4</sup> have the meaning as cited in the description and the claims. Said compounds are useful as protein kinase inhibitors, especially inhibitors of PI3K, for the treatment or prophylaxis of immunological, inflammatory, autoimmune, or allergic disorders. The invention also relates to pharmaceutical compositions including said compounds, the preparation of such compounds as well as the production of and use as medicaments.

WO 2010/092015 A1

---

UREA TRIAZOLOLO [1,5-A] PYRIDINE DERIVATIVES AS PI3K INHIBITORS

---

The present invention relates to a novel class of kinase inhibitors, including pharmaceutically acceptable salts, prodrugs and metabolites thereof, which are useful for modulating protein kinase activity for modulating cellular activities such as signal transduction, proliferation, differentiation, programmed cell death, migration and cytokine secretion. More specifically the invention provides compounds which inhibit, regulate and/or modulate kinase activity, in particular PI3K activity, and signal transduction pathways relating to cellular activities as mentioned above. Furthermore, the present invention relates to pharmaceutical compositions comprising said compounds, e.g. for the treatment of diseases such as immunological, inflammatory, autoimmune and allergic disorders, and processes for preparing said compounds.

Protein and lipid kinases participate in the signaling events which control the activation, growth, differentiation and survival of cells in response to extracellular mediators or stimuli such as growth factors, cytokines or chemokines. In general, protein kinases are classified in two groups, those that preferentially phosphorylate tyrosine residues and those that preferentially phosphorylate serine and/or threonine residues in their protein substrates. By contrast, lipid kinases phosphorylate a variety of lipid substrates.

Inappropriately high protein or lipid kinase activity is involved in many diseases including cancer, metabolic diseases, immunological diseases and inflammatory disorders. This can be caused either directly or indirectly by the failure of control mechanisms due to mutation, overexpression or inappropriate activation of the enzyme. In all of these instances, selective inhibition of the kinase is expected to have a beneficial therapeutic effect.

Phosphoinositide 3-kinases (also called Phosphatidylinositol 3-kinases, PI3Ks) represent a group of lipid kinases that play pivotal roles in numerous intracellular

signaling events, for example in T-cell receptor signaling. Some members of the PI3K family also display protein kinase activity (Vanhaesebroeck et al., 2001, *Annu. Rev. Biochem.* 70:535-602).

PI3Ks belong to a superfamily of signaling lipid kinases that catalyse the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P<sub>2</sub>) or phosphatidylinositol (PtdIns) at the 3'-OH group, giving rise to the second messengers phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P<sub>3</sub>) or phosphatidylinositol-3-phosphate (PtdIns(3)P). PtdIns(3,4,5)P<sub>3</sub> can be converted into PtdIns(3,4)P<sub>2</sub> by SH2-containing inositol phosphatase (SHIP), or can be dephosphorylated by phosphatase and tensin homologue (PTEN) phosphatase to regenerate PtdIns(4,5)P<sub>2</sub>. The 3'-phosphorylated phosphoinositides, PtdIns(3,4,5)P<sub>3</sub>, PtdIns(3,4)P<sub>2</sub>, PtdIns(4,5)P<sub>2</sub>, PtdIns(5)P and PtdIns(3)P, recruit and activate various signaling proteins (PtdIns-binding proteins; PtdIns-BPs) through direct lipid-protein interactions (Hawkins et al., 2006, *Biochem. Soc. Trans.* 34:647-62).

Phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P<sub>3</sub>) has an important role as second messenger by working as a docking platform for lipid-binding domains, such as the pleckstrin homology (PH) domains of various cellular proteins. These include kinases (such as 3-phosphoinositide-dependent protein kinase 1 (PDK1) and protein kinase B (PKB)/Akt) that trigger downstream kinase cascades, and guanine-nucleotide exchange factors (such as Vav and P-Rex) that control the activity of small GTPases (Wymann et al., 2005, *Curr. Opin. Cell Biol.* 17(2):141-9; Wymann et al., 2003, *Trends Pharmacol. Sci.* 24(7):366-76).

PI3-kinase activation is believed to be involved in a variety of signal transduction pathways, including those essential to cell proliferation, cell differentiation, cell growth, cell survival, apoptosis, adhesion, chemotaxis, invasion, cytoskeletal rearrangement, contraction, phagocytosis vesicle trafficking, receptor internalization, secretion, protein synthesis and metabolic pathways. PI3K gamma ( $\gamma$ ) and delta ( $\delta$ ) isoforms appear to be involved in a number of aspects of leukocyte activation (Rommel et al., 2007, *Nat. Rev. Immunol.* 7(3):191-201; Rückle et al., 2006, *Nat. Rev. Drug Discov.* 5(11):903-18).

Different types of PI3K have been identified and grouped into three classes according to their primary and secondary structures, mode of regulation and substrate specificity. Class I PI3K has been the most extensively studied so far, and includes heterodimeric proteins that consist of a catalytic and a regulatory adaptor subunit, the nature of which determines a further subdivision into class IA and IB PI3K. Class II PI3K uses PtdIns as *in vivo* substrate, yielding phosphatidylinositol-3-phosphate (PtdIns(3)P). Some evidence has been presented that class II enzymes, similarly to class I can be activated by external stimuli via receptor tyrosine kinases (RTKs), cytokine receptors and integrins, suggesting roles in cancer, wound healing and insulin signaling. By contrast, the class III PI3K, represented by a single species (hVps34) in humans, has relatively high activity even in resting cells. The class III represents the most ancient form of PI3K and it uses exclusively PtdIns as a substrate to produce PtdIns(3)P. This class of PI3Ks is involved in endocytic membrane traffic, phagosome maturation and autophagy (Falasca et al., 2007, Biochem. Soc. Trans. 35:211-4; Lindmo et al., 2006, J. Cell Sci. 119:605-14).

The class IA PI3Ks - PI3K $\alpha$ ,  $\beta$  and  $\delta$  (PIK3CA, PIK3CB and PIK3CD) - consist of a SH2-domain-containing regulatory subunit (p85; five distinct isoforms of which have been identified) that forms a complex with one of three catalytic subunits, p110 $\alpha$ , p110 $\beta$  or p110 $\delta$  (Bader et al., 2005, Nat. Rev. Cancer 5(12):921-9).

Genetic polymorphisms within the PI3K pathway are also associated with an increased risk of type 2 diabetes. Downstream of the insulin-like growth factor 1 (IGF1) receptor, signaling through class I PI3K controls growth and development. Amplification and point mutations of the gene encoding PI3K $\alpha$  that increase the enzymatic activity of the protein have been frequently found in human cancers (Bader et al., 2005, Nat. Rev. Cancer 5(12):921-9).

PI3K activation and PIP3 production are fundamental for most biological responses exerted by insulin. Activated insulin receptor (IR) triggers PI3K activity by binding and phosphorylating adaptor proteins of the insulin receptor substrate (IRS) family. Upon phosphorylation IRS serves as a docking site for p85 regulatory subunits that

consequently recruit p110 enzymes (mainly  $\alpha$  and  $\beta$  isoforms). PIP3 production in turn activates downstream effectors that control various metabolic processes such as glucose uptake, triglyceride formation, glycogen synthesis, lipolysis and hepatic gluconeogenesis inhibition (Knight et al., 2006, Cell 125(4): 733-747; Foukas et al., 2006, Nature, 441(7091):366-70).

PI3K $\beta$  has been implicated in regulating the formation and stability of integrin  $\alpha$ (IIb) $\beta$ (3), which is necessary for the activation and aggregation of platelets. Isoform-selective PI3K p110 $\beta$  inhibitors have been developed which *in vivo* eliminate occlusive thrombus formation but do not prolong bleeding time. These studies define PI3K p110 $\beta$  as an important new target for antithrombotic therapy (Jackson et al., 2005, Nat. Med. 11 (5):507-14).

PI3K $\delta$  is predominantly expressed in the haematopoietic system and PI3K $\delta$ -deficient mice are viable, fertile, apparently healthy and have a normal life span (Vanhaesebroeck et al., 2005. Trends in Biochemical Sciences 30, 194-204). PI3K $\delta$  has important roles in T- and B-cell signaling, mast-cell-mediated allergic responses, the neutrophils oxidative burst and, possibly, extravasation. PI3K inhibitors selective for PI3K $\delta$  were reported to block neutrophil activation in an animal model for neutrophil activation, thus pointing to PI3K $\delta$  as a target for the development of anti-inflammatory drugs (Sadhu et al., 2003, Biochem. Biophys. Res. Communications 308, 764-769).

PI3K $\gamma$ , the only member of class IB (PIK3CG), associates with either of two regulatory subunits, p101 and p84, that control its activation and subcellular location. PI3K $\gamma$  activation is driven by the direct association of its catalytic domain with the  $\beta\gamma$  subunits of G proteins following activation of pertussis-toxin-sensitive G $\alpha$ i-coupled G-protein-coupled receptors (GPCRs). In addition, PI3K $\gamma$  can be activated by Ras by a direct interaction with the catalytic subunit. Beside its lipid kinase activity, PI3K $\gamma$  has a protein kinase activity. It uses the regulatory subunits as well as itself as substrate and both events result in an increase of the lipid kinase activity (Leopoldt et al., 1998, J. Biol. Chem. 273(12):7024-9).

Other proteins, for example phosphodiesterases (PDEs) can bind to PI3K $\gamma$ , indicating a protein-scaffold function in addition to its enzymatic activity. PI3K $\gamma$  was also shown to activate MEK kinase as well as to mediate shear-sensitive triggering of the JNK kinase pathway in endothelial cells (Patrucco et al., 2004, *Cell* 118(3):375-87; Voigt et al., 2006, *J. Biol. Chem.* 281(15):9977-86).

The mouse PI3K $\gamma$  protein is encoded by the *Pik3cg* locus. Mice lacking functional PI3K $\gamma$  (PI3K $\gamma$ <sup>-/-</sup> mice) were viable, fertile, and displayed a normal life span in a conventional mouse facility. Further studies revealed that neutrophils of these mice were unable to produce PtdIns (3,4,5) P<sub>3</sub> when stimulated with GPCR agonists such as formylated bacterial peptides (N-formyl-Met-Leu-Phe, fMLP), complement C5a or interleukin 8 (IL-8). This observation demonstrates that PI3K $\gamma$  is the sole PI3K isoform that is coupled to these GPCRs in neutrophils (Vanhaesebroeck et al., 2005. *Trends in Biochemical Sciences* 30, 194-204).

Moreover, PtdIns (3, 4, 5) P<sub>3</sub>-dependent activation of protein kinase B (PKB) was also absent in those neutrophils, while PKB could still be activated by GM-CSF or IgG/C3b-coated zymosan. *Pi3kcg*<sup>-/-</sup> mice showed impaired thymocyte development and increases in neutrophil, monocyte, and eosinophil populations. Furthermore, neutrophils and macrophages isolated from *Pi3kcg*<sup>-/-</sup>-mice exhibited severe defects in migration and respiratory burst in response to GPCR agonists and chemotactic agents. Work with knockout mice also established that PI3K $\gamma$  is required for the homing of dendritic cells to lymph nodes and in the development and activation of T lymphocytes (together with PI3K $\delta$ ). In concert with IgE-dependent activation of PI3K $\delta$ , PI3K $\gamma$  also contributes to the activation of mast cell secretion by adenosine. Its involvement in the stimulation of autocrine and paracrine regulatory loops by purines has also been observed in other cell types. PI3K $\gamma$  also contributes to the activation of platelet aggregation by ADP in concert with PI3K $\beta$  (Ferguson et al., 2007, *Nat. Cell Biol.* 9(1):86-91).

Collectively, the class IB phosphoinositide 3-kinase PI3K $\gamma$  seems to be pivotal in the control of leukocyte trafficking and accordingly the development of isotype-selective inhibitors of PI3K $\gamma$  should be an attractive anti-inflammatory therapeutic strategy (Rommel et al., 2007, *Nat. Rev. Immunol.* 7(3):191-201; Rückle et al., 2006, *Nat. Rev. Drug Discov.* 5(11):903-18).

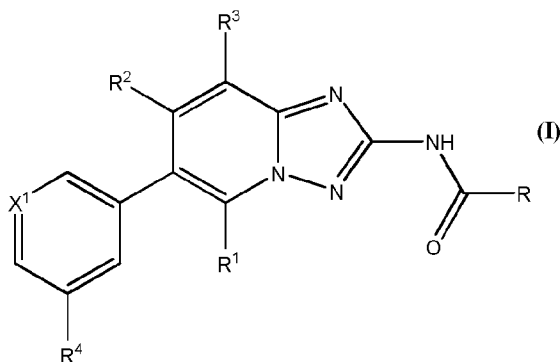
PI3K $\gamma$  plays a crucial role in both vascular cells and white blood cells. It controls diverse immune modulatory and vascular functions like respiratory burst, cell recruitment, mast cell reactivity, platelet aggregation, endothelial activation as well as smooth muscle contractility. The relative specificity of these events suggests that blocking PI3K $\gamma$  function might turn out beneficial for diseases like inflammation, allergy, autoimmunity, thrombosis, and major cardiovascular disorders like hypertension and atherosclerosis (Hirsch et al., 2006, *Thromb. Haemost.* 95(1):29-35). In addition, it was demonstrated that PI3K $\gamma$  plays a role in a mouse model for pancreatitis. The lethality of the choline-deficient/ethionine-supplemented diet-induced pancreatitis was significantly reduced in mice lacking PI3K $\gamma$  (Lupia et al., 2004. *Am. J. Pathol.* 165(6):2003-2011).

Recently, the development of potent and selective PI3K $\gamma$  inhibitors was reported (Pomel et al., 2006, *J. Med. Chem.* 49(13):3857-71; Palanki et al., 2007. *J. Med. Chem.* 50(18):4279-4294).

PI-3 Kinase inhibitors are described in WO-A 2007/095588 and WO-A 2008/025821. Triazolopyridine derivatives are described WO-A 2006/038116 as antibacterial agents.

Thus, an object of the present invention is to provide a new class of compounds as kinase inhibitors, especially as PI3K inhibitors, which may be effective in the treatment or prophylaxis of immunological, inflammatory, autoimmune, allergic disorders or other diseases or disorders associated with PI3K. Furthermore, another object of the present invention is to provide said compounds, which may be effective in the treatment or prophylaxis of cancer or cardiovascular disorders associated with PI3K.

Accordingly, the present invention provides compounds of formula (I)



or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein

R is  $N(R^{5a}R^5)$ ;

$R^5$  is  $(CH_2)_n-C(O)N(R^{6a}R^6)$ ;

n is 1; 2; or 3;

$R^{5a}$ ,  $R^{6a}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more halogen, which are the same or different;

$R^6$  is T; or  $CH_2T$ ;

Optionally,  $R^6$ ,  $R^{6a}$  are joined together with the nitrogen atom to which they are attached to form a ring  $T^1$ .

T is  $C_{3-7}$  cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T is optionally substituted with one or more  $R^7$ , which are the same or different;

$T^1$  is an at least the nitrogen atom as ring heteroatom containing at least partially saturated 4 to 7 membered heterocycle; or an at least the nitrogen atom as ring

heteroatom containing at least partially saturated 7 to 11 membered heterobicycle, wherein T<sup>1</sup> is optionally substituted with one or more R<sup>7</sup>, which are the same or different;

R<sup>7</sup> is halogen; CN; C(O)OR<sup>8</sup>; OR<sup>8</sup>; oxo (=O), where the ring is at least partially saturated; C(O)R<sup>8</sup>; C(O)N(R<sup>8</sup>R<sup>8a</sup>); S(O)<sub>2</sub>N(R<sup>8</sup>R<sup>8a</sup>); S(O)N(R<sup>8</sup>R<sup>8a</sup>); S(O)<sub>2</sub>R<sup>8</sup>; S(O)R<sup>8</sup>; N(R<sup>8</sup>)S(O)<sub>2</sub>N(R<sup>8a</sup>R<sup>8b</sup>); SR<sup>8</sup>; N(R<sup>8</sup>R<sup>8a</sup>); OC(O)R<sup>8</sup>; N(R<sup>8</sup>)C(O)R<sup>8a</sup>; N(R<sup>8</sup>)S(O)<sub>2</sub>R<sup>8a</sup>; N(R<sup>8</sup>)S(O)R<sup>8a</sup>; N(R<sup>8</sup>)C(O)N(R<sup>8a</sup>R<sup>8b</sup>); N(R<sup>8</sup>)C(O)OR<sup>8a</sup>; OC(O)N(R<sup>8</sup>R<sup>8a</sup>); or C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more R<sup>9</sup>, which are the same or different;

R<sup>8</sup>, R<sup>8a</sup>, R<sup>8b</sup> are independently selected from the group consisting of H; and C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more R<sup>9</sup>, which are the same or different;

R<sup>9</sup> is halogen; CN; C(O)OR<sup>10</sup>; OR<sup>10</sup>; C(O)R<sup>10</sup>; C(O)N(R<sup>10</sup>R<sup>10a</sup>); S(O)<sub>2</sub>N(R<sup>10</sup>R<sup>10a</sup>); S(O)N(R<sup>10</sup>R<sup>10a</sup>); S(O)<sub>2</sub>R<sup>10</sup>; S(O)R<sup>10</sup>; N(R<sup>10</sup>)S(O)<sub>2</sub>N(R<sup>10a</sup>R<sup>10b</sup>); SR<sup>10</sup>; N(R<sup>10</sup>R<sup>10a</sup>); OC(O)R<sup>10</sup>; N(R<sup>10</sup>)C(O)R<sup>10a</sup>; N(R<sup>10</sup>)S(O)<sub>2</sub>R<sup>10a</sup>; N(R<sup>10</sup>)S(O)R<sup>10a</sup>; N(R<sup>10</sup>)C(O)N(R<sup>10a</sup>R<sup>10b</sup>); N(R<sup>10</sup>)C(O)OR<sup>10a</sup>; or OC(O)N(R<sup>10</sup>R<sup>10a</sup>);

R<sup>10</sup>, R<sup>10a</sup>, R<sup>10b</sup> are independently selected from the group consisting of H; and C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more halogen, which are the same or different;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> are independently selected from the group consisting of H; halogen; CN; C(O)OR<sup>11</sup>; OR<sup>11</sup>; C(O)R<sup>11</sup>; C(O)N(R<sup>11</sup>R<sup>11a</sup>); S(O)<sub>2</sub>N(R<sup>11</sup>R<sup>11a</sup>); S(O)N(R<sup>11</sup>R<sup>11a</sup>); S(O)<sub>2</sub>R<sup>11</sup>; S(O)R<sup>11</sup>; N(R<sup>11</sup>)S(O)<sub>2</sub>N(R<sup>11a</sup>R<sup>11b</sup>); N(R<sup>11</sup>)S(O)N(R<sup>11a</sup>R<sup>11b</sup>); SR<sup>11</sup>; N(R<sup>11</sup>R<sup>11a</sup>); OC(O)R<sup>11</sup>; N(R<sup>11</sup>)C(O)R<sup>11a</sup>; N(R<sup>11</sup>)S(O)<sub>2</sub>R<sup>11a</sup>; N(R<sup>11</sup>)S(O)R<sup>11a</sup>; N(R<sup>11</sup>)C(O)N(R<sup>11a</sup>R<sup>11b</sup>); N(R<sup>11</sup>)C(O)OR<sup>11a</sup>; OC(O)N(R<sup>11</sup>R<sup>11a</sup>); and C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more halogen, which are the same or different;

$R^{11}$ ,  $R^{11a}$ ,  $R^{11b}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more halogen, which are the same or different;

$X^1$  is N; or  $C(R^{12})$ ;

$R^4$  is H; or  $R^{13}$ ;

$R^{12}$  is H; or  $R^{14}$ ;

$R^{13}$ ,  $R^{14}$  are independently selected from the group consisting of halogen; CN;  $C(O)OR^{15}$ ;  $OR^{15}$ ;  $C(O)R^{15}$ ;  $C(O)N(R^{15}R^{15a})$ ;  $S(O)_2N(R^{15}R^{15a})$ ;  $S(O)N(R^{15}R^{15a})$ ;  $S(O)_2R^{15}$ ;  $S(O)R^{15}$ ;  $N(R^{15})S(O)_2N(R^{15a}R^{15b})$ ;  $N(R^{15})S(O)N(R^{15a}R^{15b})$ ;  $SR^{15}$ ;  $N(R^{15}R^{15a})$ ;  $OC(O)R^{15}$ ;  $N(R^{15})C(O)R^{15a}$ ;  $N(R^{15})S(O)_2R^{15a}$ ;  $N(R^{15})S(O)R^{15a}$ ;  $N(R^{15})C(O)N(R^{15a}R^{15b})$ ;  $N(R^{15})C(O)OR^{15a}$ ;  $OC(O)N(R^{15}R^{15a})$ ; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more  $R^{16}$ ;

$R^{15}$ ,  $R^{15a}$ ,  $R^{15b}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more  $R^{16}$ ;

$R^{16}$  is halogen; CN;  $C(O)OR^{17}$ ;  $OR^{17}$ ;  $C(O)R^{17}$ ;  $C(O)N(R^{17}R^{17a})$ ;  $S(O)_2N(R^{17}R^{17a})$ ;  $S(O)N(R^{17}R^{17a})$ ;  $S(O)_2R^{17}$ ;  $S(O)R^{17}$ ;  $N(R^{17})S(O)_2N(R^{17a}R^{17b})$ ;  $N(R^{17})S(O)N(R^{17a}R^{17b})$ ;  $SR^{17}$ ;  $N(R^{17}R^{17a})$ ;  $OC(O)R^{17}$ ;  $N(R^{17})C(O)R^{17a}$ ;  $N(R^{17})S(O)_2R^{17a}$ ;  $N(R^{17})S(O)R^{17a}$ ;  $N(R^{17})C(O)N(R^{17a}R^{17b})$ ;  $N(R^{17})C(O)OR^{17a}$ ; or  $OC(O)N(R^{17}R^{17a})$ ;

$R^{17}$ ,  $R^{17a}$ ,  $R^{17b}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more halogen, which are the same or different.

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

Within the meaning of the present invention the terms are used as follows:

“Alkyl” means a straight-chain or branched hydrocarbon chain. Each hydrogen of an alkyl carbon may be replaced by a substituent.

“C<sub>1-4</sub> alkyl” means an alkyl chain having 1 to 4 carbon atoms, e.g. if present at the end of a molecule: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, or e.g. -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH(C<sub>2</sub>H<sub>5</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C<sub>1-4</sub> alkyl carbon may be replaced by a substituent.

“C<sub>1-6</sub> alkyl” means an alkyl chain having 1 to 6 carbon atoms, e.g. if present at the end of a molecule: C<sub>1-4</sub> alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl; tert-butyl, n-pentyl, n-hexyl, or e.g. -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH(C<sub>2</sub>H<sub>5</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C<sub>1-6</sub> alkyl carbon may be replaced by a substituent.

“C<sub>3-7</sub> cycloalkyl” or “C<sub>3-7</sub> cycloalkyl ring” means a cyclic alkyl chain having 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

“Halogen” means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

“4 to 7 membered heterocyclyl” or “4 to 7 membered heterocycle” means a ring with 4, 5, 6 or 7 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)<sub>2</sub>-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 4 to 7 membered heterocycles are azetidine, oxetane, thietane, furan,

thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine or homopiperazine.

“saturated 4 to 7 membered heterocyclyl” or “saturated 4 to 7 membered heterocycle” means a ring with 4, 5, 6 or 7 ring atoms that does not contain double bonds, wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)<sub>2</sub>-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a saturated 4 to 7 membered heterocycles are azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, tetrahydropyran, imidazolidine, piperidine, morpholine, triazolidine, tetrazolidine, diazepane, or homopiperazine.

“7 to 11 membered heterobicyclyl” or “7 to 11 membered heterobicycle” means a heterocyclic system of two rings with 7 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)<sub>2</sub>-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 7 to 11 membered heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, quinoline, dihydroquinoline, tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine. The term 7 to 11 membered heterobicycle also includes spiro structures of two rings like 1,4-dioxo-8-azaspiro[4.5]decane or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane.

“saturated 7 to 11 membered heterobicycyl” or “saturated 7 to 11 membered heterobicycle” means a heterocyclic system of two rings with 7 to 11 ring atoms, where at least one ring atom is shared by both rings and that does not contain double bonds, wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)<sub>2</sub>-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a saturated 7 to 11 membered heterobicycle are decahydroquinoline, or decahydroisoquinoline. The term saturated 7 to 11 membered heterobicycle also includes saturated spiro structures of two rings like 1,4-dioxa-8-azaspiro[4.5]decane or bridged saturated heterocycles like 8-aza-bicyclo[3.2.1]octane.

Preferred compounds of formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents mentioned below independently have the following meaning. Hence, one or more of these substituents can have the preferred or more preferred meanings given below.

Preferably, R<sup>5a</sup> is H.

Preferably, n is 1; or 2.

Preferably, R<sup>6a</sup> is H; or CH<sub>3</sub>.

Preferably, R<sup>6</sup> is T.

Preferably, T is C<sub>3-7</sub> cycloalkyl; or saturated 4 to 7 membered heterocyclyl, wherein T is unsubstituted or substituted with one or more R<sup>7</sup>, which are the same or different.

Preferably, T is cyclopropyl; pyrrolidiny; piperidiny; or morpholinyl, wherein T is unsubstituted or substituted with one or more R<sup>7</sup>, which are the same or different.

Preferably, R<sup>6</sup>, R<sup>6a</sup> are joined together with the nitrogen atom to which they are attached to form a ring T<sup>1</sup>.

Preferably, T<sup>1</sup> is an at least the nitrogen atom as ring heteroatom containing saturated 4 to 7 membered heterocycle and wherein T<sup>1</sup> is unsubstituted or substituted with one or more R<sup>7</sup>, which are the same or different.

Preferably, T<sup>1</sup> is pyrrolidine; morpholine; piperidine; or piperazine, and wherein T<sup>1</sup> is unsubstituted or substituted with one or more R<sup>7</sup>, which are the same or different.

Preferably, R<sup>7</sup> is OC<sub>1-6</sub> alkyl; N(C<sub>1-6</sub> alkyl)<sub>2</sub>; or C<sub>1-6</sub> alkyl, which is unsubstituted or substituted with one or more R<sup>9</sup>, which are the same or different and selected from the group consisting of halogen; OC<sub>1-6</sub> alkyl; and N(C<sub>1-6</sub> alkyl)<sub>2</sub>.

Preferably, R<sup>3</sup> is H; CH<sub>3</sub>; or halogen. Even more preferably, R<sup>3</sup> is H; or F.

Preferably, R<sup>2</sup> is H.

Preferably, R<sup>1</sup> is H.

Preferably, R<sup>4</sup> is R<sup>13</sup>.

Preferably, R<sup>13</sup> is SO<sub>2</sub>N(R<sup>15</sup>R<sup>15a</sup>); SO<sub>2</sub>R<sup>15</sup>; or C<sub>1-6</sub> alkyl, optionally substituted with one or more halogen, which are the same or different.

Preferably, R<sup>15a</sup> is H; or CH<sub>3</sub>.

Preferably, R<sup>15</sup> is C<sub>1-6</sub> alkyl.

Preferably, X<sup>1</sup> is N. In case X<sup>1</sup> is C(R<sup>12</sup>) it is preferred that R<sup>12</sup> is H.

Compounds of formula (I) in which some or all of the above-mentioned groups have the preferred meanings are also an aspect of the present invention.

Further preferred compounds of the present invention are those which are selected from the group consisting of

N-tert-butyl-5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(3-oxo-3-(piperidin-1-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-isopropyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-oxo-2-(piperidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-isopropyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

1-(6-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-3-(2-morpholino-2-oxoethyl)urea;

1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-3-(6-(5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)urea;

N-tert-butyl-5-(8-fluoro-2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(8-fluoro-2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-cyclopropyl-N-methylacetamide;

2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-cyclopropylacetamide;

N-tert-butyl-5-(2-(3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-(4-(2-methoxyethyl)piperazin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

(S)-N-tert-butyl-5-(2-(3-(2-(3-(dimethylamino)pyrrolidin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-(piperidin-4-yl)acetamide; and

5-(2-(3-(2-(4-aminopiperidin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide.

Prodrugs of the compounds of the present invention are also within the scope of the present invention.

"Prodrug" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of a prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.

Metabolites of compounds of formula (I) are also within the scope of the present invention.

The term "metabolites" refers to all molecules derived from any of the compounds according to the present invention in a cell or organism, preferably mammal.

Preferably the term relates to molecules which differ from any molecule which is present in any such cell or organism under physiological conditions.

The structure of the metabolites of the compounds according to the present invention will be obvious to any person skilled in the art, using the various appropriate methods.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) may occur, the individual forms, like e.g. the keto and enol form, are comprised separately and together as mixtures in any ratio. Same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) may be obtained from stereoselective synthesis using optically pure starting materials.

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion

exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The term “pharmaceutically acceptable” means approved by a regulatory agency such as the EMEA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, preferably in humans.

The present invention furthermore includes all solvates of the compounds according to the invention.

The present invention provides compounds of formula (I) as kinase inhibitors, especially as PI3K inhibitors.

Accordingly, the compounds of the present invention are useful for the prevention or treatment of immunological disorders (e.g. immune or autoimmune diseases), inflammatory disorders or allergic disorders.

Thus, another aspect of the present invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use as a medicament.

Another aspect of the present invention is a compound or a pharmaceutically acceptable salt thereof according to the present invention for use in a method of treating or preventing diseases and disorders associated with PI3K.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of diseases and disorders associated with PI3K, preferably PI3K $\gamma$  and/or PI3K $\delta$ .

Compounds of the invention may be selective for one PI3 kinase isoform (for example gamma or delta) over a different isoform. Such compounds may preferentially inhibit one isoform. For example, a compound may preferentially inhibit the gamma isoform over the alpha isoform. As an option to determine a compound's selectivity, the compound's activity can be determined according to the Biological Assays as described herein. For example, the IC<sub>50</sub> value of a compound is determined for four PI3 kinase isoforms (e.g. alpha, beta, gamma, delta). The obtained values should then be compared to determine the selectivity of the tested compound.

In addition, the IC<sub>50</sub> value for other PI3K-like kinases (PIKK) such as DNA-dependent kinase (DNA-PK) may be determined, said kinase may be considered as an unwanted target because inhibition may lead to toxic or other unwanted side effects. The obtained value should then be compared to the value of the target of interest, for example PI3K gamma, to determine the selectivity of the tested compound.

According to the present invention "PI3K" or "PI3 kinase" includes all members of the PI3K family comprising class IA (e.g. PI3K alpha, beta and delta), class IB (e.g. PI3K gamma), class II (e.g. PI3KC2 alpha, beta and gamma) and class III (e.g. Vps34 yeast homologue).

"PI3K $\beta$ " means PI3K $\beta$  protein (also referred to as p110-beta). A human cDNA encoding the PI3K $\beta$  protein was described (Hu et al., 1993. Mol. Cell Biol. 13(12):7677-88). The human PI3K $\beta$  protein is encoded by the PI3KCB gene on chromosome 3q22.3.

"PI3K $\gamma$ " means PI3K $\gamma$  protein, the only member of PI3K class IB (also referred to as p110-gamma). A human cDNA encoding the PI3K $\gamma$  protein of a 1050 amino acid residue long polypeptide was described (Stoyanow et al., 1995, Science 269:690-693). The human PI3K $\gamma$  protein is encoded by the PI3KCG gene which comprises 10 exons and is located on chromosome 7q22 (Kratz et al., 2002, Blood 99:372-374).

"PI3K $\delta$ " means PI3K $\delta$  protein, a member of PI3K class class IA (also referred to as p110-delta). A human cDNA encoding the PI3K $\delta$  protein of 1044 amino acids was reported (Vanhaesebroeck et al., 1997, Proc. Natl. Acad. Sci. 94:4330-4335). The human PI3K $\delta$  protein is encoded by the PI3KCD gene which was mapped to chromosome 1p3.2 (Seki et al., 1997, DNA Research 4:355-358).

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of immunological, inflammatory, autoimmune, or allergic disorders.

More specifically, preferred disorders are autoimmune diseases; organ and bone marrow transplant rejection; graft-versus-host disease; acute or chronic inflammation; pancreatitis; contact dermatitis; psoriasis; rheumatoid arthritis; multiple sclerosis; type I diabetes; inflammatory bowel disease; Crohn's disease; ulcerative colitis; systemic lupus erythematosus; asthma; chronic obstructive pulmonary disease (COPD); acute respiratory distress syndrome (ARDS); bronchitis; conjunctivitis; dermatitis; allergic rhinitis; acute gouty inflammation; cystic fibrosis; familial Mediterranean fever; tissue damage after bacterial infection; Sweet's syndrome; or anaphylaxis.

Quite more preferred are rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), psoriasis, multiple sclerosis (MS), asthma and chronic obstructive pulmonary disease (COPD).

Rheumatoid arthritis (RA) is a chronic progressive, debilitating inflammatory disease that affects approximately 1% of the world's population. RA is a symmetric polyarticular arthritis that primarily affects the small joints of the hands and feet. In addition to inflammation in the synovium, the joint lining, the aggressive front of tissue called pannus invades and destroys local articular structures (Firestein 2003, Nature 423:356-361).

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing intestinal inflammation. IBD is subdivided into Crohn's disease and ulcerative colitis phenotypes. Crohn's disease involves most frequently the terminal ileum and colon, is transmural and discontinuous. In contrast, in ulcerative colitis, the inflammation is continuous and limited to rectal and colonic mucosal layers. In approximately 10% of cases confined to the rectum and colon, definitive classification of Crohn disease or ulcerative colitis cannot be made and are designated 'indeterminate colitis.' Both diseases include extraintestinal inflammation of the skin, eyes, or joints. Neutrophil-induced injuries may be prevented by the use of neutrophils migration inhibitors (Asakura et al., 2007, *World J. Gastroenterol.* 13(15):2145-9).

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease generated by T cell-mediated B-cell activation, which results in glomerulonephritis and renal failure. Human SLE is characterized at early stages by the expansion of long-lasting autoreactive CD4<sup>+</sup> memory cells (D'Cruz et al., 2007, *Lancet* 369(9561):587-596).

Psoriasis is a chronic inflammatory dermatosis that affects approximately 2% of the population. It is characterized by red, scaly skin patches that are usually found on the scalp, elbows, and knees, and may be associated with severe arthritis. The lesions are caused by abnormal keratinocyte proliferation and infiltration of inflammatory cells into the dermis and epidermis (Schön et al., 2005, *New Engl. J. Med.* 352:1899-1912).

Multiple sclerosis (MS) is an inflammatory and demyelating neurological disease. It has been considered as an autoimmune disorder mediated by CD4<sup>+</sup> type 1 T helper cells, but recent studies indicated a role of other immune cells (Hemmer et al., 2002, *Nat. Rev. Neuroscience* 3, 291-301).

Asthma is a complex syndrome with many clinical phenotypes in both adults and children. Its major characteristics include a variable degree of air flow obstruction, bronchial hyperresponsiveness, and airway inflammation (Busse and Lemanske, 2001, *N. Engl. J. Med.* 344:350-362).

Chronic obstructive pulmonary disease (COPD) is characterized by inflammation, airflow limitation that is not fully reversible, and a gradual loss of lung function. In COPD, chronic inhalation of irritants causes an abnormal inflammatory response, remodeling of the airways, and restriction of airflow in the lungs. The inhaled irritant is usually tobacco smoke, but occupational dust and environmental pollution are variably implicated (Shapiro 2005, N. Engl. J. Med. 352, 2016-2019).

Pancreatitis is the inflammation of the pancreas. Acute pancreatitis is a condition that develops when the pancreas is damaged by inflammation that leads to swelling and sometimes to necrosis of part of the pancreas (Carroll et al., 2007. American Family Physician 75(1): 1513-1520). In chronic pancreatitis widespread injury to the pancreas over many years may cause extensive scarring and destruction of the pancreas. It was demonstrated that PI3K $\gamma$  plays a role in a mouse model for pancreatitis. The lethality of of the choline-deficient/ethionine-supplemented diet-induced pancreatitis was significantly reduced in mice lacking PI3K $\gamma$  (Lupia et al., 2004. Am. J. Pathol. 165(6):2003-2011).

Acute gouty inflammation is the consequence of the deposition of monosodium urate crystals in joints. Neutrophils appear to be the major effector of acute gout, accumulating in the joint fluid where they actively ingest urate crystals, aggregate and degranulate. Acute gouty inflammation as well as other diseases associated with crystal deposition like articular chondrocalcinosis, silicosis, soft tissue calcium deposit in patients with chronic renal failure, may be prevented by inhibition of neutrophils chemotaxis (Ryckman et al., 2003, Arthritis & Rheumatism 48 (8): 2310-20).

Cystic fibrosis (CF) is a hereditary disorder caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR), the product of which is a membrane protein thought to function as a chloride channel. The lethal clinical manifestations are clearly related to the thick, infected mucous and chronic neutrophils-dominated airway inflammation. An anti-inflammatory agent with direct effects on neutrophils may represent a good drug candidate for the clinical management of CF (McIntosh et al., 1992, FASEB J 6:2775-82).

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder characterised by recurrent and reversible attacks of fever and serositis. The inflammatory episodes are characterized by massive influx of neutrophils into the serosal and synovial membranes. Secondary amyloidosis, a consequence of long-standing inflammation, is the most severe complication of the disease. Inhibitors of neutrophils activation may result beneficial for the amelioration of the disease (Molad et al., 2004, *J. Investig. Med.* 52(1):58-61).

Tissue damage after acute bacterial infection may partly result from excessive neutrophils infiltration and activation in the infected tissue. During pyelonephritis, bacteria in the kidney parenchyma trigger a burst of neutrophils extravascular migration. Experiments in animal models have shown that renal scarring after acute bacterial pyelonephritis results from parenchymal damage by neutrophils. Tissue damages following infections in pyelonephritis, osteomyelitis, endocarditis, endotoxic shock and acute respiratory distress syndrome, may be prevented by inhibition of neutrophils activation (Bille et al., 1982, *J. Infect. Dis.* 146:220-6).

Sweet's syndrome (named acute febrile neutrophilic dermatosis) is characterized by a constellation of clinical symptoms which include pyrexia, elevated neutrophil count, tender erythematous skin lesions and a diffuse infiltrate consisting predominantly of mature neutrophils typically located in the upper dermis. Inhibition of neutrophils activation may represent a therapy for patient suffering from Sweet's syndrome (Cohen, 2007, *Orphanet J. Rare Dis.* 2:34).

Anaphylaxis is an acute systemic and severe type I hypersensitivity allergic reaction. Anaphylactic shock is the most severe type of anaphylaxis. Anaphylactic shock is a sudden, life-threatening allergic reaction associated with severe hypotension. Platelet-activating factor (PAF) is implicated in the cardiovascular dysfunctions occurring in various shock syndromes, including anaphylaxis. Excessive production of the vasodilator NO causes inflammatory hypotension and shock. Research shows a central role for eNOS, the endothelial isoform of nitric oxide synthase, as a mediator of

anaphylaxis and defines PI3K as new potential targets for treating anaphylaxis (Cauwels et al., 2006, *J. Clin. Invest.* 116(8):2244-51).

Diseases and disorders associated especially with PI3K are cancer, cardiovascular disorders metabolic diseases, neurodegenerative disorders or infectious diseases.

Yet another aspect of the present invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of cancer, metabolic diseases, neurodegenerative disorders, infectious diseases or cardiovascular disorders, more specifically myocardial infarction, stroke, ischemia or atherosclerosis.

Cancer comprises a group of diseases characterized by uncontrolled growth and spread of abnormal cells. All types of cancers generally involve some abnormality in the control of cell growth, division and survival, resulting in the malignant growth of cells. Key factors contributing to said malignant growth of cells are independence from growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genome instability (Hanahan and Weinberg, 2000. *The Hallmarks of Cancer*. *Cell* 100, 57-70).

Typically, cancers are classified as hematological cancers (for example leukemias and lymphomas) and solid cancers such as sarcomas and carcinomas (for example cancers of the brain, breast, lung, colon, stomach, liver, pancreas, prostate, ovary).

Obesity and diabetes mellitus type 2 represent metabolic diseases with a steadily increasing health risk worldwide. Leptin, secreted by adipose tissue and acting in part through its hypothalamic receptor, integrates the energy state of peripheral organs and the action of the central nervous system inhibiting food intake and stimulating energy expenditure. The pancreas-derived peptide hormone insulin enters the central nervous system (CNS) through the blood-brain barrier by receptor-mediated transport to regulate food intake, sympathetic activity and peripheral insulin action through the inhibition of

hepatic gluconeogenesis and reproductive endocrinology. On a molecular level, some of the effects of insulin converge with those of the leptin signaling machinery at the point of activation of phosphatidylinositol 3-kinase (PI3K), resulting in the regulation of ATP-dependent potassium channels. In accordance with this idea, intracerebroventricular (icv) injection of PI3K inhibitors partly abolishes the ability of both insulin and leptin to inhibit food intake (Xu et al., 2005, *J. Clin. Inv.*, 115 (4): 951-8; Niswender et al., 2003, *Diabetes* 52:227-231). Furthermore, insulin inhibits neuronal apoptosis via activation of protein kinase B *in vitro*, and it regulates phosphorylation of tau, metabolism of the amyloid precursor protein and clearance of beta-amyloid from the brain *in vivo*. These findings indicate that neuronal IR signaling has a direct role in the link between energy homeostasis, reproduction and the development of neurodegenerative diseases such as Alzheimer's disease (Plum et al., 2005, *Trends Endocrinol. Metab.* 16(2):59-65). Leptin causes a delayed apoptosis of mature neutrophils through a signaling cascade involving PI3K (Bruno et al., 2005, *J. Immunol.* 174: 8090-96). PI3K inhibitors may be beneficial in the treatment of diseases where the processes mentioned above are involved.

Obesity is associated with a state of chronic inflammation believed to play a role in the development of insulin resistance. This low-grade state of inflammation is characterized by macrophage infiltration into adipose tissue and the chemokine Monocyte Chemoattractant Protein-1 (MCP1) has been identified as a key player in this process. Signaling downstream of the chemokine receptor CCR2, a MCP1 receptor, is partly controlled by PI3K $\gamma$ . In a recent study, Pi3K $\gamma$ <sup>-/-</sup> knockout mice kept on high-fat diet have shown an obesity resistant phenotype, with a decreased efficiency of weight-gain per food intake and improved glucose and insulin tolerance (Solinas et al., 2008. A central role for PI3K gamma in obesity and insulin resistance. *Diabetologia* 51: S295-S296 Suppl. 1 Meeting Abstract: 739), suggesting a potential therapeutic effect of PI3K $\gamma$  inhibitors in metabolic disorders such as obesity.

Recent work has demonstrated that the PI3K (phosphoinositide 3-kinase) signaling pathway is important for efficient influenza A virus replication. Activation of PI3K in virus-infected cells is mediated by the viral NS1 protein, which binds directly to the

p85beta regulatory subunit of PI3K and causes the PI3K-dependent phosphorylation of Akt (protein kinase B). Given that recombinant influenza A viruses unable to activate PI3K signalling are attenuated in tissue culture, the PI3K pathway could be a novel target for the development of future anti-influenza drugs (Ehrhardt et al., 2007, *J. Virol.* 81 (7): 3058-67; Hale et al., 2006, *PNAS* 103, 14194-14199).

Another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more conditions selected from the group consisting of diseases and disorders associated with PI3K, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.

Yet another aspect is a method for treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more conditions selected from the group consisting of immunological; inflammatory; and allergic disorders, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to the present invention or a pharmaceutically acceptable salt thereof.

More specifically the one or more conditions are selected from the group consisting of autoimmune diseases; organ and bone marrow transplant rejection; graft-versus-host disease; acute or chronic inflammation; pancreatitis; contact dermatitis; psoriasis; rheumatoid arthritis; multiple sclerosis; type I diabetes; inflammatory bowel disease; Crohn's disease; ulcerative colitis; systemic lupus erythematosus; asthma; chronic obstructive pulmonary disease (COPD); acute respiratory distress syndrome (ARDS); bronchitis; conjunctivitis; dermatitis; and allergic rhinitis; acute gouty inflammation; cystic fibrosis; familial Mediterranean fever; tissue damage after bacterial infection; Sweet's syndrome; or anaphylaxis.

More preferred are rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), psoriasis, multiple sclerosis (MS), asthma and chronic obstructive pulmonary disease (COPD).

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more conditions selected from the group consisting of cancer; metabolic diseases; neurodegenerative disorders; infectious diseases and cardiovascular disorders, more specifically myocardial infarction, stroke, ischemia or atherosclerosis, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to the present invention or a pharmaceutically acceptable salt thereof.

As used herein, the term "treating" or "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting, or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

Without intending to be limited by theory, the compounds of the invention may also modulate in addition or alternatively immune cell activation via inhibition of PI3K. Especially the important roles of PI3K $\delta$  and PI3K $\gamma$  in signaling and other functions of T cells, B cells, neutrophils, macrophages and mast cells indicate that these kinases are valid therapeutic targets for several inflammation-mediated diseases. These diseases comprise rheumatoid arthritis (in which T cells, B cells and neutrophils are involved), systemic lupus erythematosus (in which neutrophils are involved), psoriasis (in which T cells, neutrophils and macrophages are engaged), multiple sclerosis (in which T cells, B cells and mast cells are implicated), asthma (for which T cell and mast cells are important), and chronic obstructive pulmonary disease (which involves neutrophils, macrophages and T cells) (Rommel et al., 2007, Nat. Rev. Immunology 7:191-201).

In some cases, the link between PI3K $\delta$  and PI3K $\gamma$  as potential drug targets for specific diseases has been experimentally established by testing the respective PI3K-null mice in animal disease models. Additional pharmacological confirmation was obtained by using

small molecule PI3K inhibitors in wild-type mice in which inflammatory diseases were experimentally induced.

Camps and colleagues used structure-based drug design to develop a potent small molecule inhibitor of PIK3 $\gamma$  referred to as AS-605240 (Camps et al., 2005. Nat. Med. 11(9):936-43). It was observed that *Pik3cg*-null mice were protected against arthritis induced by collagen II-specific antibodies, a murine model of lymphocyte-independent rheumatoid arthritis (RA) associated with neutrophil activation. The effect was associated with impaired neutrophil chemotaxis. Treatment of wildtype mice with oral AS-605420 resulted in reduced clinical and histologic signs of collagen II-antibody-induced arthritis, similar to that seen in the *Pik3cg*-null mice. Oral AS-605240 also resulted in decreased joint inflammation and damage in a distinct mouse model of lymphocyte-dependent rheumatoid arthritis induced by direct collagen II injection. The authors concluded that PIK3CG inhibition operates on both the neutrophil and lymphocyte arms of chemokine signaling pathways, and thus may be of therapeutic value in various chronic inflammatory diseases.

In the MRL-*lpr* mouse model of systemic lupus erythematosus (SLE) it was found that intraperitoneal administration of the pharmacologic PI3K $\gamma$  inhibitor AS-605240 reduced CD4<sup>+</sup> T-cell populations, reduced glomerulonephritis, and prolonged life span (Barber et al., 2005, Nat. Med. 11(9):933-935).

The involvement of PI3 kinases in allergic inflammatory diseases such as asthma was demonstrated through pharmacological inhibition by non-selective PI3K inhibitors such as wortmannin and LY294002. However, these compounds were not selective enough to discriminate between distinct PI3K isoforms (Walker et al., 2006, Drug Discovery Today: Disease Mechanisms, 3(1):63-69).

In a recent report, Pi3K $\gamma$ <sup>-/-</sup> knockout mice have been tested in a model of ovalbumin (OVA) specific pulmonary inflammation. After challenge with ovalbumin a drastic reduction of leukocyte influx into the bronchoalveolar lavage (BAL) fluid was observed demonstrating PI3K $\gamma$ 's role in cell infiltration into the airways, in particular of

eosinophils, key effector cells in allergic inflammation. These data suggest PI3K $\gamma$  as an attractive target for pharmacological intervention in asthma (Thomas et al., 2008. Immunology, Epub ahead of print, PMID: 18754810).

Using selective PI3K $\delta$  inhibitors it was demonstrated that PI3K $\delta$  plays a role in neutrophil inflammatory responses. Inhibition of PI3K $\delta$  blocked both fMLP- and TNF1 $\alpha$ -induced neutrophil superoxide generation and elastase exocytosis (Sadhu et al., 2003, Biochem. Biophys. Res. Commun. 2003 Sep 5; 308(4):764-769).

The essential role of PI3K $\delta$  in allergic responses was demonstrated by genetic and pharmacological inactivation of PI3K $\delta$  in mast cells. This inhibition leads to defective SCF-mediated *in vitro* proliferation, adhesion and migration, and to impaired allergen-IgE-induced degranulation and cytokine release. Moreover, inactivation of PI3K $\delta$  protects mice against anaphylactic allergic responses. Taken together, these studies suggest PI3K $\delta$  as a target for therapeutic intervention in allergy and mast-cell-related diseases (Ali et al., 2004, Nature 431:1007-1011).

Recently, the effect of genetic inactivation of the Pi3kcd gene in mice on systemic cytokine and chemokine responses and allergic airway inflammation was reported. Type 2 cytokine responses (IL-4, IL-5, and IL-13) were significantly decreased in PI3K $\delta$  mutants, whereas type 1 cytokine responses (IFN- $\gamma$  CXCL10) were robust. For example, induction of respiratory hyper-responsiveness to inhaled methacholine, a hallmark of asthma, was attenuated in PI3K $\delta$  null mice. In summary, these data suggest PI3K $\delta$  as a new target for TH2-mediated airway diseases (Nashed et al., 2007, Eur. J. Immunol. 37:416-424).

Accordingly, diseases and disorders are preferred which are associated with PI3K delta and/or PI3K gamma. Especially preferred are inflammatory and immunoregulatory disorders rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, multiple sclerosis, asthma and chronic obstructive pulmonary disease.

As mentioned above, PI3K also plays a role with regard to cancer and cardiovascular disorders.

PI3K $\gamma$  has been proposed as a possible target for pharmacological intervention in the primary and secondary prevention of human atherosclerotic cardiovascular disease. Atherosclerosis and its sequelae, including myocardial infarction and stroke, are the leading causes of mortality and morbidity in the developed world. It has been reported that PI3K $\gamma$  is activated in macrophages by oxidized LDL, agonists, chemokines and inflammatory mediators commonly implicated in atherogenesis. Genetic ablation of PI3K $\gamma$  in hypercholesterolemic mice (apoE $^{-/-}$ ) results in reduced atherosclerotic lesions. In addition to retarding plaque progression, it is of clinical relevance the possibility that the inhibition of PI3K might affect plaque stability (Chang et al., 2007, PNAS 104 (19):8077-82).

This may be based on the fact that signaling through PI3K $\gamma$  plays an important role for leucocyte, platelet and cardiovascular stress sensing. The concerted activation of leukocytes and vessels influences many physiological and pathological responses usually leading to the production of intracellular second messenger molecules such as phosphatidylinositol(3,4,5)-trisphosphate (PIP3), which is produced by PI3K $\gamma$ , a crucial signal in both vascular and white blood cells. The study of mice lacking PI3K $\gamma$  revealed that the PIP3 signaling pathway controls immune cell and vascular functions such as respiratory burst, cell recruitment, mast cell reactivity, platelet aggregation, endothelial activation and smooth muscle cell contractility. The specificity of these events suggests that inhibition of PI3K $\gamma$  may be beneficial for major cardiovascular disorders such as hypertension (Hirsch et al., 2006, Thromb. Haemost. 95(1):29-35).

Myocardial infarction (MI) results from a biphasic ischemia/reperfusion (I/R) injury to the heart, initiating with cardiomyocyte apoptosis (Crow et al., 2004, Circ. Res. 95(10):957-970) and then proceeding to a second wave of inflammation-based tissue damage (Frangogiannis et al., 2002, Cardiovasc. Res. 53(1):31-47). Recently, it was reported that a small molecule inhibitor of PI3K gamma and delta provided cardioprotection in an animal model of myocardial infarction. This compound, TG100-115, potently inhibits edema and inflammation in response to multiple mediators known

to play a role in myocardial infarction. Importantly, this was achieved when dosing after myocardial reperfusion (up to 3 hours later), the same time period when patients are most accessible for therapeutic intervention (Doukas et al., 2006, PNAS 103(52):19866-19871; Doukas et al., 2007, Biochem. Soc. Trans. 35(Pt2):204-206; Palanki et al., 2007, J. Med. Chem. 50(18):4279-4294).

The first study to describe point mutations of the PIK3CA gene, which encodes the p110 $\alpha$  catalytic subunit, in colorectal, brain, gastric, breast and lung cancers, was reported in 2004. Subsequently, several additional point mutations were identified in other cancer types (reviewed by Bader et al., 2005, Nat. Rev. Cancer 5(12): 921-929). It was demonstrated that PIK3CA mutants promote cell growth and invasion of human cancer cells and that treatment with the non-selective PI3K inhibitor LY294002 abrogated PIK3A signaling and preferentially inhibited growth of PI3KCA mutant cells (Samuels et al., 2005, Cancer Cell 7(6):561-573), thus suggesting PI3K proteins as promising drug targets for cancer therapy.

Recently, it was reported that the overexpression of the wild-type PI3K isoforms PI3K $\beta$  (p110 $\beta$ ), PI3K $\gamma$  (p110 $\gamma$ ) or PI3K $\delta$  (p110 $\delta$ ) is sufficient to induce an oncogenic phenotype in cultured cells (Kang et al., 2006, PNAS 103(5): 1289-1294). This oncogenic potential required kinase activity suggesting that inhibitors of this activity may block the transforming capacity. The role of the non- $\alpha$  class I PI3K isoforms in human cancer has not been fully explored but there are reports of elevated expression of PI3K $\beta$  and PI3K $\delta$  in various human cancers (Benistant et al., 2000, Oncogene 19(44):5083-5090; Knobbe and Reifenberger, 2003, Brain Pathol. 13(4):507-518). In another study it was demonstrated that a selective inhibitor of PI3K $\delta$  (p110delta) inhibited the proliferation and survival of acute myeloid leukemia (AML) cells and increased the cytotoxic effects of a topoisomerase II inhibitor suggesting PI3K $\delta$  as a potential therapeutic target in AML (Billottet et al., 2006, Oncogene 25(50):6648-6659).

Recent studies with conditional Pi3K $\beta$ <sup>-/-</sup> knockout mice and reconstitution of cells with kinase inactive PI3K $\beta$  mutants have shown that the p110beta protein has an important

physiological function in metabolic regulation and glucose homeostasis, cell proliferation and trafficking, partially via a kinase-independent mechanism. In addition, the kinase activity of p110beta drives oncogenic transformation as shown in a mouse prostate tumour model identifying p110beta as a promising drug target for kinase inhibitors useful for the treatment of cancer (Jia et al., 2008. Nature 454(7205):776-779).

PI3K $\gamma$  inhibitors may be useful for stem cell mobilization. Successful blood and marrow transplant, both autologous and allogeneic, requires the infusion of a sufficient number of hematopoietic progenitor/stem cells (HPCs) capable of homing to the marrow cavity and regenerating a full array of hematopoietic cell lineages. Recruitment of HPCs from the marrow into the blood is termed mobilization, or, more commonly, stem cell mobilization. For example, a peripheral blood stem cell (PBSC) transplant is commonly employed in the treatment of myeloma patients in order to restore the immune system after high-dose chemotherapy treatments. A selective antagonist of stromal cell-derived factor (SDF1) binding to its receptor CXCR4 has been shown to induce rapid mobilization of hematopoietic stem cells (Chavakis et al., 2008. Circulation Research 102(8):942-949). As PI3K $\gamma$  is involved in the signaling downstream CXCR4, small molecule PI3K $\gamma$  inhibitors may be useful for the mobilization of stem cells.

The present invention provides pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made

by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

A pharmaceutical composition of the present invention may comprise one or more additional compounds as active ingredients like one or more compounds of formula (I) not being the first compound in the composition or other PI3K inhibitors.

Other active ingredients for use in combination with other therapies for the treatment of immune, inflammatory, allergic disorders and may include steroids, leukotriene antagonists, anti-histamines, cyclosporine or rapamycin.

Accordingly, a pharmaceutical composition of the present comprises one or more active ingredients. It is also possible that a combination of two or more pharmaceutical compositions is used with at least one pharmaceutical composition of the present invention.

The combination of a compound of formula (I) or pharmaceutically acceptable salt, prodrug or metabolite thereof with another active ingredient may be employed in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both compounds or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

The pharmaceutical compositions of the present invention include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation the compound according to the invention is conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as tetrafluoroethane or heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to

deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally, for example, as liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When

a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula (I) may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

A therapeutically effective amount of a compound of the present invention will normally depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration. However, an effective amount of a compound of formula (I) for the treatment of an inflammatory disease, for example rheumatoid arthritis (RA), will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a pharmaceutically acceptable salt, prodrug or metabolite thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

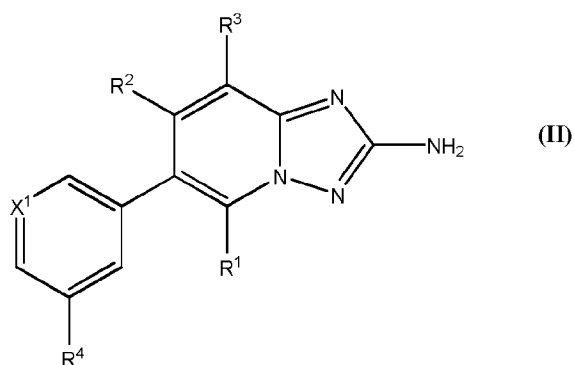
Methods for the synthesis of the compounds of the present invention are described e.g., in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York.

Depending on the circumstances of the individual case, in order to avoid side reactions during the synthesis of a compound of formula (I), it can be necessary or advantageous to temporarily block functional groups by introducing protective groups and to deprotect them in a later stage of the synthesis, or introduce functional groups in the form of precursor groups which in a later stage are converted into the desired functional groups. Such synthesis strategies and protective groups and precursor groups which are suitable in an individual case are known to the person skilled in the art. Suitable protective groups are described, e.g., in Greene, Theodora W., Wuts, Peter G.M., Protective Groups in Organic Synthesis (2006), John Wiley and Sons Ltd.

If desired, the compounds of the formula (I) can be purified by customary purification procedures, for example by distillation, recrystallization or chromatography. The starting compounds for the preparation of the compounds of the formula (I) are commercially available or can be prepared according to or analogously to literature procedures.

In general, compounds of the present invention may be prepared by the following method for the preparation of a compound according to formula (I), comprising the step of

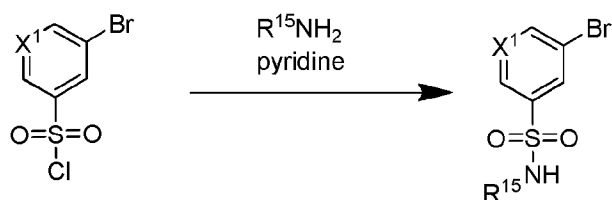
- reacting a compound of formula (II)



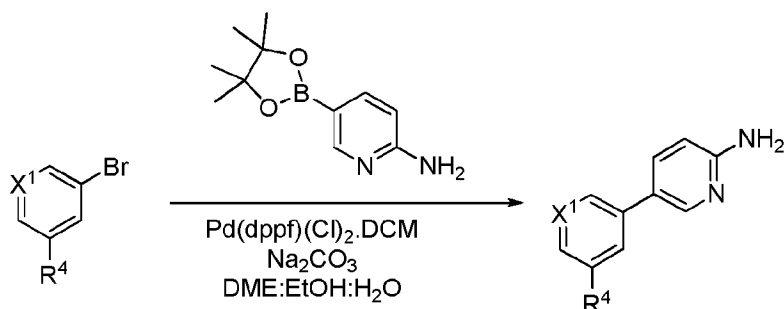
either with triphosgene and subsequently with a compound of formula H-R, wherein the hydrogen of H-R is attached to a heteroatom; or with a compound of formula Cl-C(O)-R to yield a compound of formula (I).

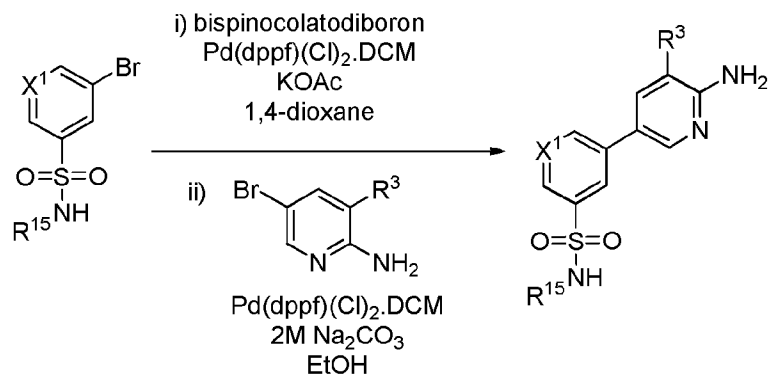
By way of example only, the following Schemes provide exemplary routes for the preparation of compounds of the present invention. Analogous compounds of the present invention may be prepared in an analogous way. Further analogous routes are described in WO-A 2008/025821 and/or are known to a practitioner in the art.

Scheme 1

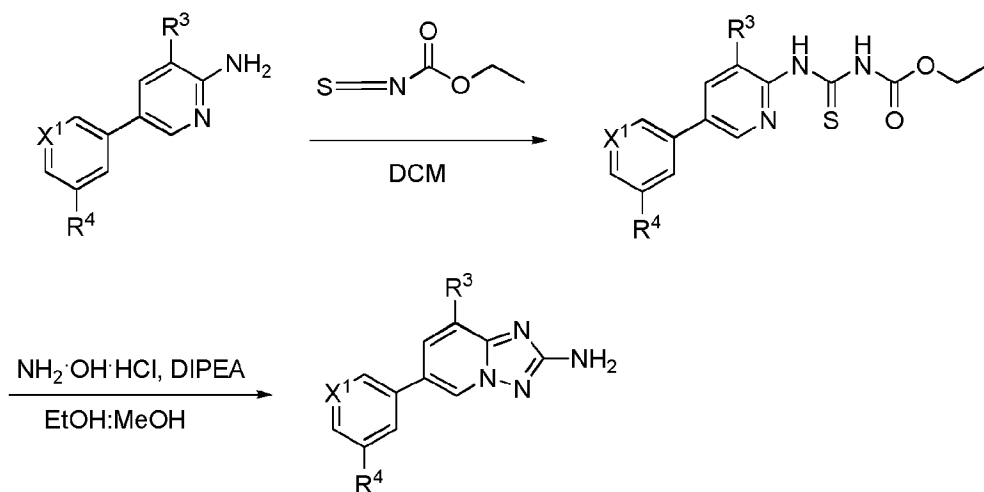


Scheme 2

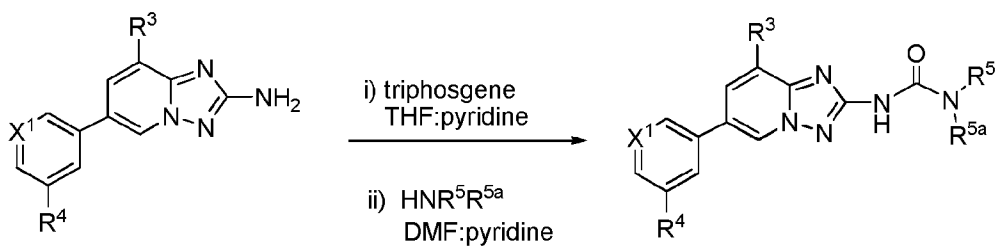


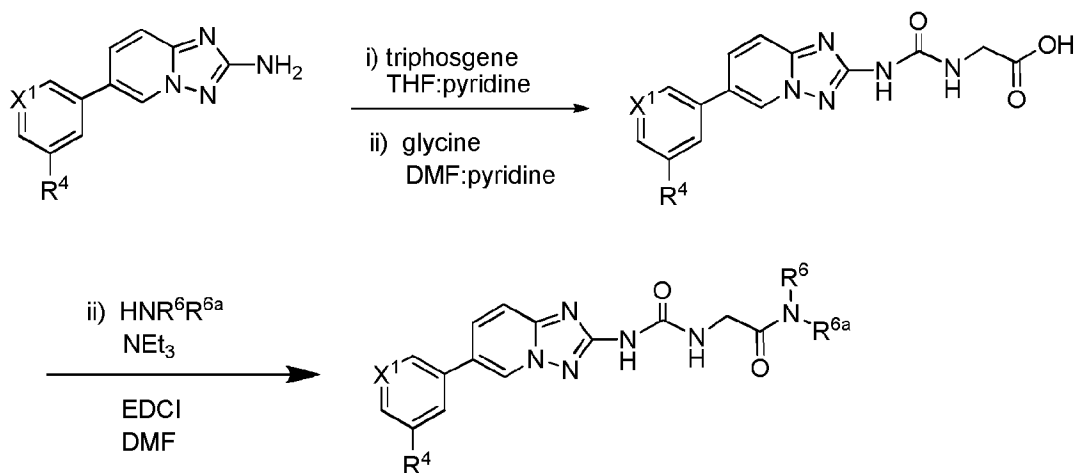


Scheme 3



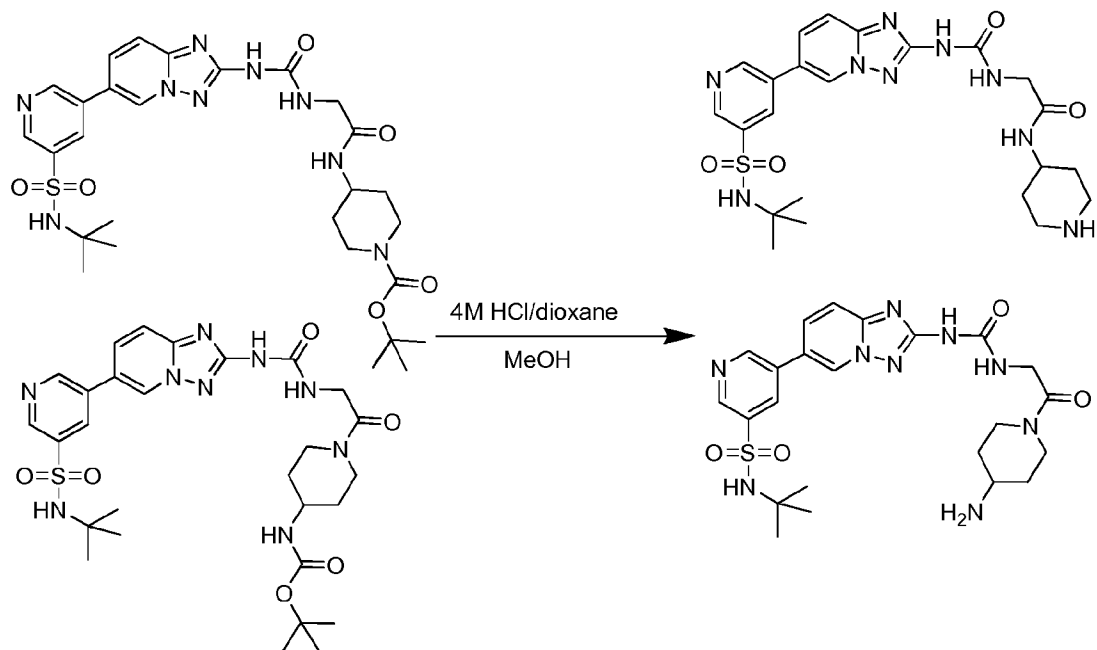
Scheme 4





Examples for the preparation of compounds of the present invention using Boc protection/deprotection are given in Scheme 5.

Scheme 5



Analytical Methods

NMR spectra were obtained on a Bruker dp400. LCMS was carried out on an Agilent 1100 using a Gemini C18, 3 x 30 mm, 3 micron or Gemini C18, 4.6 x 150 mm, 5 microns column. Column flow was 1.0 or 1.2 mL/min. and solvents used were water and acetonitrile (0.1% formic acid) with an injection volume of 3 or 10 $\mu$ l. Wavelengths were 254 and 210nm.

**Method A**

Column: Gemini C18, 3 x 30 mm, 3 microns. Flow rate: 1.2mL/min

Time (min)	Water	Acetonitrile
0	95	5
3	5	95
4.5	5	95
4.6	95	5
5.00	STOP	

**Method B**

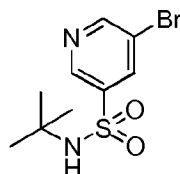
Column: Gemini-C18, 4.6 x 150 mm, 5 microns. Flow rate: 1.0mL/min

Time (min)	%A	%B
0.00	95.0	5.0
11.00	5.0	95.0
13.00	5.0	95.0
13.01	95.0	5.0
14.00	STOP	

**Table 1: Abbreviations**

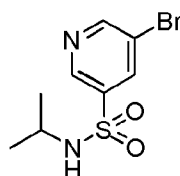
Boc	<i>tert.</i> -Butyloxycarbonyl
CH <sub>3</sub> CN	Acetonitrile
d	Doublet
dd	Doubledoublet
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride)
EtOH	Ethanol
h	hours
H <sub>2</sub> O	Water
L	Litre
m	Multiplet
MeOH	methanol
mL	Millilitres
br	Broad
NEt <sub>3</sub>	Triethyl amine
NH <sub>2</sub> OH·HCl	hydroxylamine hydrochloride
Pd(dppf)(Cl) <sub>2</sub>	[1,1'-bis(diphenylphosphino)ferrocene] dichloro-palladium (II)
q	quartet
quin	quintet
s	singlet
sept	septet
t	triplet
THF	tetrahydrofuran

The following methods were used for the preparation of compounds of formula (I).

**Method 1****5-bromo-*N*-*tert*-butylpyridine-3-sulfonamide**

To a solution of 5-bromopyridine-3-sulfonyl chloride (5g, 17mmol) in pyridine (10mL) at 0°C was added *tert*-butylamine (3.6mL, 2 equiv., 34mmol). The reaction mixture was allowed to warm to room temperature and then heated to 40 °C for 14 h. After this time the crude reaction mixture was again cooled to 0°C and diluted with dilute HCl (0.05M, 40mL). The reaction was stirred at 0°C for 30 min and the resulting precipitate collected by filtration. The solid was washed with water and dried to afford the title compound as a yellow solid (2.12 g, 7.3mmol, 42%). No further purification was required.

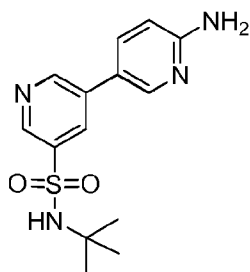
LCMS (method A) (M+H<sup>+</sup>) 292/294, Rt = 2.41 min

**5-bromo-*N*-isopropylpyridine-3-sulfonamide**

Prepared according to Method 1 using *isopropylamine*.

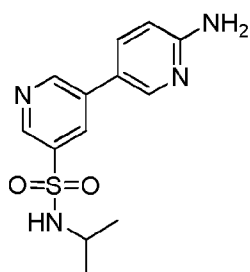
LCMS (method A) (M+H<sup>+</sup>) 281/283, Rt = 2.28 min

**Method 2****6'-amino-*N*-*tert*-butyl-3,3'-bipyridine-5-sulfonamide**



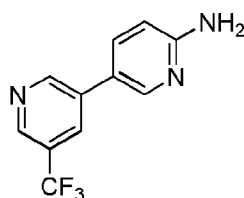
A suspension of 5-bromo-*N-tert*-butylpyridine-3-sulfonamide (2.5 g, 8.55 mmol) 2-Aminopyridine-5-boronic acid pinacol ester (1.97 g, 8.9 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloro-palladium (II) complex with CH<sub>2</sub>Cl<sub>2</sub> (120 mg, 0.17 mmol) and sodium carbonate (2.7 g, 26 mmol) in DME:H<sub>2</sub>O:EtOH, (7:3:2, 10 mL) was heated to 120 °C for 1 hour in the microwave. After this time the reaction solvents were removed *in vacuo* and the brown residue redissolved in 2M HCl (20 mL), the aqueous phase was washed with ethyl acetate (3 x 20 mL) and then neutralized with concentrated sodium hydroxide to pH 7.0. The aqueous phase was then extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and the solvent removed *in vacuo* to afford the desired product as a brown solid (1.86 g, 100 %). No further purification was required. LCMS (method A) (M+H<sup>+</sup>) 307, Rt = 1.41 min

#### 6'-amino-*N*-isopropyl-3,3'-bipyridine-5-sulfonamide



Prepared according to method 2 from 5-bromo-*N*-isopropylpyridine-3-sulfonamide. LCMS (method A) (M+H<sup>+</sup>) 293, Rt = 1.01 min

#### 5-(trifluoromethyl)-3,3'-bipyridin-6-amine

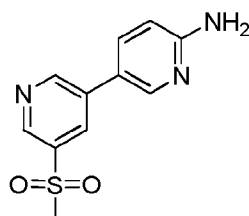


Prepared according to method 2 from 3-bromo-5-(trifluoromethyl)pyridine.

LCMS (method A) (M+H<sup>+</sup>) 240, Rt = 1.01 min

### Method 3

#### 5'-(methylsulfonyl)-3,3'-bipyridin-6-amine

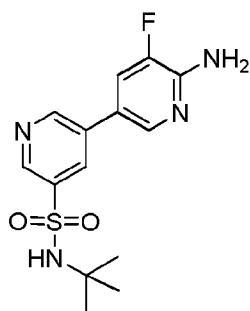


A suspension of 3-bromo-5-(trifluoromethyl)pyridine (2.0 g, 8.40 mmol) 2-Aminopyridine-5-boronic acid pinacol ester (1.94 g, 8.8 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloro-palladium (II) complex with CH<sub>2</sub>Cl<sub>2</sub> (136 mg, 0.17 mmol) and sodium carbonate (2.6 g, 25 mmol) in DME:H<sub>2</sub>O:EtOH, (7:3:2, 2 mL) was heated to 120 °C for 1 hour minutes in the microwave. After this time the reaction solvents were removed *in vacuo* and the brown residue redissolved in 2M HCl (30 mL), the aqueous phase was washed with ethyl acetate (3 x 20 mL) and then neutralized with concentrated sodium hydroxide to pH 7.0. Ethyl acetate (20 mL) was added and the title compound collected by filtration and air-dried (1.95 g, 7.6 mmol, 91 %). No further purification was required.

LCMS (method A) (M+H<sup>+</sup>) 250, Rt = 1.65 min

### Method 4

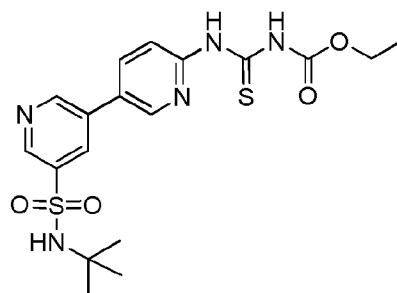
#### 6'-amino-N-tert-butyl-5'-fluoro-3,3'-bipyridine-5-sulfonamide



5-bromo-N-tert-butylpyridine-3-sulfonamide (2 g, 7.04 mmol), bis(pinocolato)diboron (2.0 g, 7.74 mmol), potassium acetate (2.07g, 21 mmol) and 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with CH<sub>2</sub>Cl<sub>2</sub> (290 mg, 0.35 mmol) in dioxane (10 mL) was heated to 120 °C for 60 minutes in the microwave. After this time 2-amino-4-bromopyridine (1g, 5.6 mmol), 2M sodium carbonate (3mL), ethanol (2mL) and further 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with CH<sub>2</sub>Cl<sub>2</sub> (290 mg) were added and the reaction heated for a further 1h at 120°C in the microwave. The reaction solvents were removed *in vacuo* and the brown residue redissolved in 2M HCl (30 mL), the aqueous phase was washed with ethyl acetate (3 x 20 mL) and then neutralized with concentrated sodium hydroxide to pH 7.0. The aqueous phase was then extracted with ethyl acetate (3 x 20 mL), the organic extracts were combined, dried over sodium sulfate, filtered and the solvent removed *in vacuo* to afford the desired product as a brown solid (1.1 g, 3.4 mmol, 48 %).  
LCMS (method A) (M+H<sup>+</sup>) 311, Rt = 1.86 min

#### Method 5

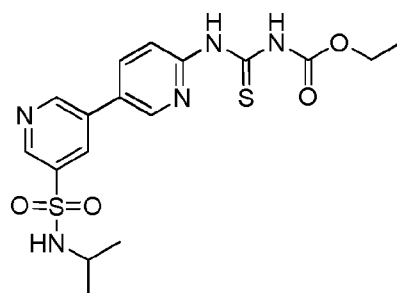
#### N-tert-butyl-6'-(3-(ethoxycarbonyl)thioureido)-3,3'-bipyridine-5-sulfonamide



To a solution of 6'-amino-N-tert-butyl-3,3'-bipyridine-5-sulfonamide (11.4 g, 37 mmol) in DCM (500 mL) cooled to 5 °C was added ethoxycarbonyl isothiocyanate (8.6 mL, 55 mmol) dropwise over 15 min. The reaction mixture was then warmed to 35 °C and stirred for 24 hours. Evaporation *in vacuo* gave a brown solid to which diethyl ether (200 mL) was added. The solid was then collected by filtration, thoroughly washed with petrol (3 × 25 mL) and air-dried to afford the desired product as a brown solid (10.85g, 25 mmol, 74 %).

LCMS (method A) (M+H<sup>+</sup>) 438, Rt = 2.72 min

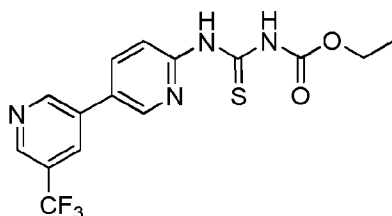
**N-iso-propyl-6'-((3-(ethoxycarbonyl)thioureido)-3,3'-bipyridine-5-sulfonamide**



Prepared according to method 5 from 6'-amino-N-isopropyl-3,3'-bipyridine-5-sulfonamide.

LCMS (method A) (M+H<sup>+</sup>) 408, Rt = 2.42 min

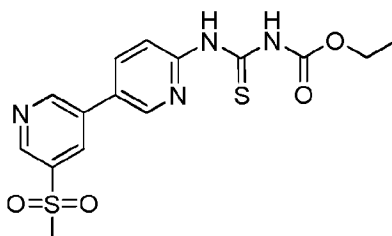
**5-trifluoromethyl-6'-((3-(ethoxycarbonyl)thioureido)-3,3'-bipyridine**



Prepared according to method 5 from 5'-(trifluoromethyl)-3,3'-bipyridin-6-amine.

LCMS (method A) ( $M+H^+$ ) 371,  $R_t$  = 2.89 min

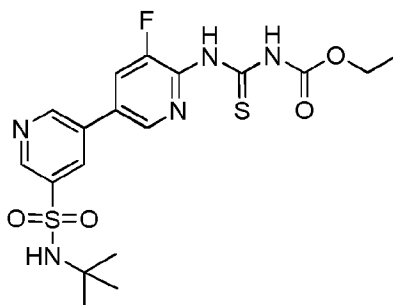
**5-methylsulfonyl-(6'-(3-(ethoxycarbonyl)thioureido)-3,3')-bipyridine**



Prepared according to method 5 from 5'-(methylsulfonyl)-3,3'-bipyridin-6-amine

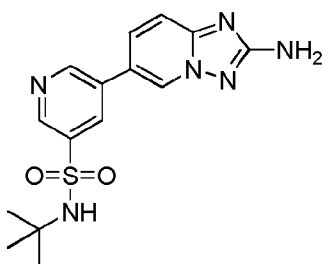
LCMS (method A) ( $M+H^+$ ) 381,  $R_t$  = 2.35 min

**N-tert-butyl-6'-(3-(ethoxycarbonyl)thioureido)-5'-fluoro-3,3'-bipyridine-5-sulfonamide**



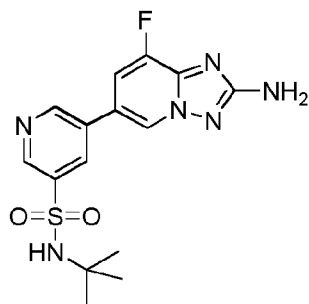
Prepared according to method 5 from 6'-amino-N-tert-butyl-5'-fluoro-3,3'-bipyridine-5-sulfonamide

LCMS (method A) ( $M+H^+$ ) 456,  $R_t$  = 2.59 min

**Method 6****5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide**

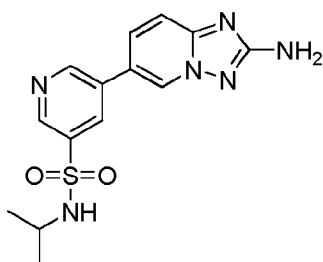
To a suspension of hydroxylamine hydrochloride (8.6 g, 125 mmol) in EtOH/MeOH (1:1, 500 mL) was added *N,N*-diisopropylethylamine (12 mL, 75 mmol), the mixture was stirred at 20 °C for 1 h. *N*-tert-butyl-6'-(3-(ethoxycarbonyl)thioureido)-3,3'-bipyridine-5-sulfonamide (10.80 g, 25 mmol) was then added and the mixture slowly heated to reflux (Note: bleach trap required to quench H<sub>2</sub>S evolved). After 24 h at reflux the mixture was allowed to cool and the solvent removed *in vacuo*. Water (50 mL) was added and the solid filtered. The solid was washed thoroughly with water, cold EtOH/MeOH (1:1) and air-dried to afford the title compound as a white solid (8.65 g, 25 mmol, 100 %). No further purification was required.

LCMS (method A) (M+H<sup>+</sup>) 347, Rt = 1.97 min

**5-(2-amino-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide**

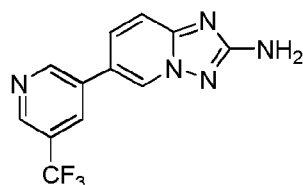
Prepared according to method 6 from *N*-tert-butyl-6'-(3-(ethoxycarbonyl)thioureido)-5'-fluoro-3,3'-bipyridine-5-sulfonamide

LCMS (method A) (M+H<sup>+</sup>) 365, Rt = 2.11 min

**5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-isopropylpyridine-3-sulfonamide**

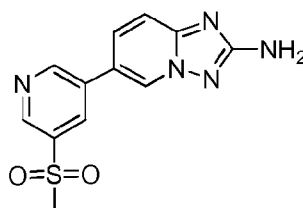
Prepared according to method 6 from N-iso-propyl-6'-(3-(ethoxycarbonyl)thioureido)-3,3'-bipyridine-5-sulfonamide.

LCMS (method A) (M+H<sup>+</sup>) 333, Rt = 1.86 min

**6-(5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine**

Prepared according to method 6 from 5-trifluoromethyl-(6'-(3-(ethoxycarbonyl)thioureido)-3,3')-bipyridine

LCMS (method A) (M+H<sup>+</sup>) 280, Rt = 2.02 min

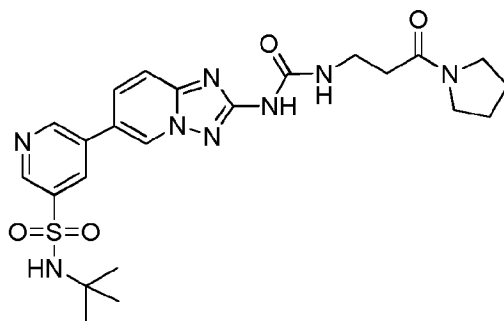
**6-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine**

Prepared according to method 6 from 5-methylsulfonyl-(6'-(3-(ethoxycarbonyl)thioureido)-3,3')-bipyridine  
 LCMS (method A) (M+H<sup>+</sup>) 290, Rt = 1.51 min

### Method 7

#### Example 1

**N-tert-butyl-5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**

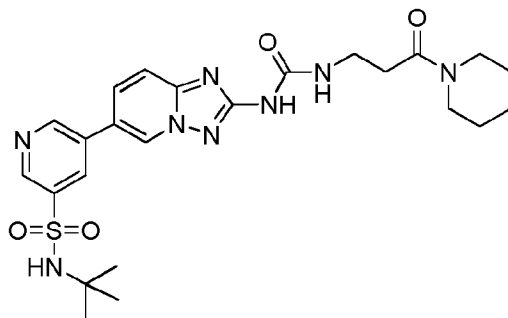


5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide (50 mg, 0.14 mmol) was suspended in tetrahydrofuran:pyridine (5 mL, 5:1) and cooled to 0°C. Triphosgene (41 mg, 0.14 mmol) was added in one portion and the reaction mixture heated at 35 °C for 2 hours. After this time the solvent was decanted and the resultant semi-solid dissolved in DMF:pyridine (1 mL, 10:1). 2-amino-1-(pyrrolidin-1-yl)ethanone (0.32 mmol) was added in one portion and the reaction mixture heated for 18 hours at 65 °C. The title compound was isolated by preparative-LCMS purification of the reaction mixture.

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 10.03 (1H, s), 9.37, (d, 1H), 9.23 (d, 1H), 9.00 (d, 1H), 8.57 (t, 1H), 8.31 (t, 1H), 8.07 (dd, 1H), 7.81-7.79 (m, 2H), 3.45 (quar, 2H), 3.40 (t, 2H), 1.85 (quin, 2H), 1.75, quin, 2H), 1.16 (s, 9H), (2 extra 2H not visible, under solvent peak).  
 LCMS (method A), (M+H<sup>+</sup>) 515.2, Rt = 2.22 min.

#### Example 2

**N-tert-butyl-5-(2-(3-(3-oxo-3-(piperidin-1-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



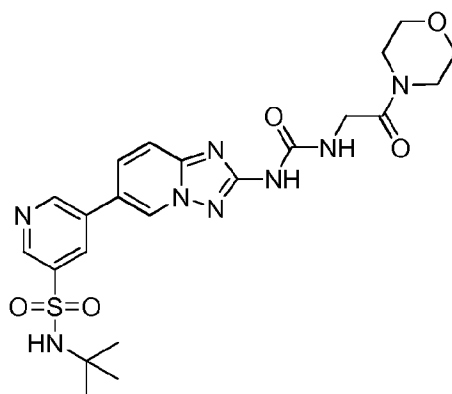
Prepared according to method 7 from 5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide and 2-amino-1-(piperidin-1-yl)ethanone.

$^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  10.02 (s, 1H), 9.37 (s, 1H), 9.23 (s, 1H), 9.00 (s, 1H), 8.57 (s, 1H), 8.29 (t, 1H), 8.07 (d, 1H), 7.81-7.79 (m, 2H), 3.46 (m, 4H), 2.57 (t, 2H), 1.60-1.36 (m, 6H), 1.16 (s, 9H), (1 extra 2H not visible, under solvent peak).

LCMS (method A), ( $\text{M}+\text{H}^+$ ) 529,  $R_t = 2.35$  min.

### Example 3

**N-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



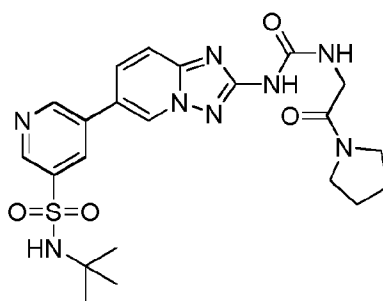
Prepared according to method 7 from 5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide and 2-amino-1-morpholinoethanone.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.18 (s, 1H), 9.38 (d, 1H), 9.23 (d, 1H), 9.00 (d, 1H), 8.61 (t, 1H), 8.58-8.57 (m, 1H), 8.07 (dd, 1H), 7.83-7.81 (m, 2H), 4.17 (d, 1H), 3.63-3.58 (m, 4H), 3.50-3.44 (m, 4H), 1.16 (s, 9H).

LCMS (method A), ( $\text{M}+\text{H}^+$ ) 517,  $R_t$  = 2.14 min.

#### Example 4

**N-tert-butyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



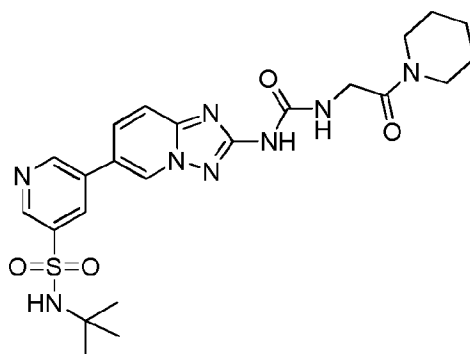
Prepared according to method 7 from 5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide and 2-amino-1-pyrrolidinoethanone.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.16 (2, 1H), 9.38 (d, 1H), 9.24 (d, 1H), 9.00 (d, 1H), 8.61-8.57 (m, 2H), 8.07 (dd, 1H), 7.83-7.80 (m, 2H), 4.06 (d, 2H), 3.44 (t, 2H), 1.92 (quin, 2H), 1.81 (quin, 2H), 1.16 (s, 9H) (1 extra 2H not visible, under solvent peak).

LCMS (method A), ( $\text{M}+\text{H}^+$ ) 501,  $R_t$  = 2.24 min.

#### Example 5

**N-tert-butyl-5-(2-(3-(2-oxo-2-(piperidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



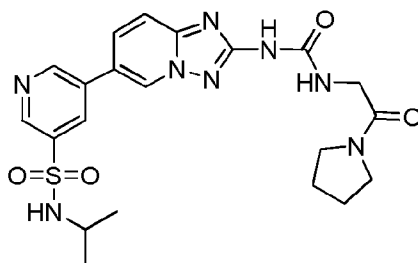
Prepared according to method 7 from 5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide and 2-amino-1-(piperidin-1-yl)ethanone.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.16 (s, 1H), 9.38 (d, 1H), 9.24 (d, 1H), 9.00 (d, 1H), 8.61 (t, 1H), 8.58 (t, 1H), 8.07 (dd, 1H), 7.83-7.80 (m, 2H), 4.14 (d, 1H), 3.46 (t, 1H), 1.64-1.58 (m, 2H), 1.55-1.54 (m, 2H), 1.49, 1.45 (m, 2H), 1.16 (s, 9H) (1 extra 2H not visible, under solvent peak).

LCMS (method A), ( $\text{M}+\text{H}^+$ ) 515,  $R_t = 2.38$  min.

### Example 6

**N-isopropyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



Prepared according to method 7 from 5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-isopropylpyridine-3-sulfonamide and 2-amino-1-pyrrolidinoethanone.

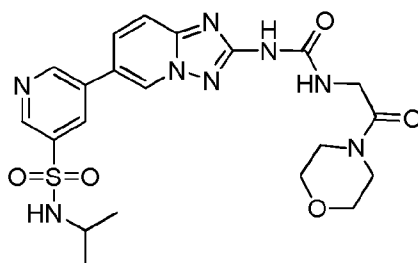
$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.19 (s, 1H), 9.41 (s, 1H), 9.27 (d, 1H), 8.98 (d, 1H), 8.61 (t, 1H), 8.55 (t, 1H), 8.09 (dd, 1H), 7.88 (d, 1H), 7.82 (d, 1H), 4.06 (d, 2H), 3.44 (t, 2H),

1.92 (quin, 2H), 1.80 (quin, 2H), 1.00 (d, 6H), (one extra 2H and 1H not visible as under solvent peak).

LCMS (method B), (M+H<sup>+</sup>) 487, Rt = 7.38 min.

### Example 7

#### N-isopropyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide



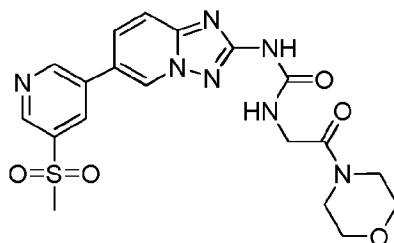
Prepared according to method 7 from 5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-isopropylpyridine-3-sulfonamide and 2-amino-1-morpholinoethanone.

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 10.20 (s, 1H), 9.41 (d, 1H), 9.26 (d, 1H), 8.98 (d, 1H), 8.62 (t, 1H), 8.55 (t, 1H), 8.11-8.08 (dd, 1H), 7.87 (br s, 1H), 7.82 (d, 1H), 4.17 (d, 2H), 3.63-3.57 (m, 4H), 3.49-3.44 (m, 4H), 1.00 (d, 6H), (one extra 2H and 1H not visible as under solvent peak).

LCMS (method B), (M+H<sup>+</sup>) 503, Rt = 6.97 min.

### Example 8

#### 1-(6-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-3-(2-morpholino-2-oxoethyl)urea



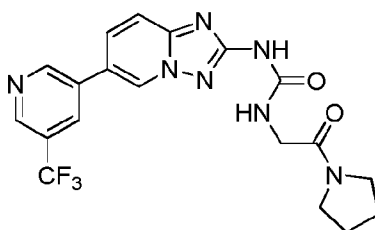
Prepared according to method 7 from 6-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine and 2-amino-1-pyrrolidinoethanone.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.21 (s, 1H), 9.48 (d, 1H), 9.36 (d, 1H), 9.08 (d, 1H), 8.71 (t, 1H), 8.61 (t, 1H), 8.19 (dd, 1H), 7.83 (dd, 1H), 4.17 (d, 2H), 3.63-3.57 (m, 4H), 3.49-3.43 (m, 7H).

LCMS (method B), ( $\text{M}+\text{H}^+$ ) 460,  $R_t$  = 6.08 min.

### Example 9

**1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-3-(6-(5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)urea**



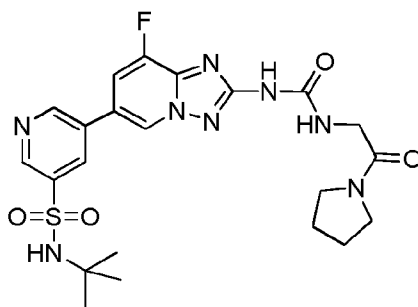
Prepared according to method 7 from 6-(5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine and 2-amino-1-morpholinoethanone.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.19 (s, 1H), 9.47 (d, 1H), 9.34 (d, 1H), 9.03 (d, 1H), 8.68 (br s, 1H), 8.61 (t, 1H), 8.19 (dd, 1H), 7.80 (d, 1H), 4.06 (d, 2H), 3.44 (t, 2H), 1.91 (quin, 2H), 1.79 (quin, 2H) (one extra 2H and 1H not visible as under solvent peak).

LCMS (method B), ( $\text{M}+\text{H}^+$ ) 434,  $R_t$  = 8.01 min.

### Example 10

**N-tert-butyl-5-(8-fluoro-2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



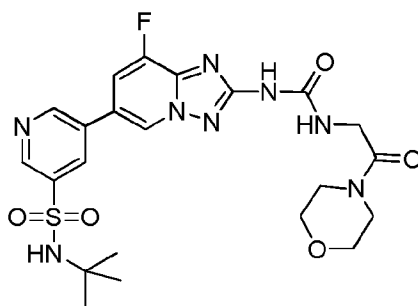
Prepared according to method 7 from 5-(2-amino-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide and 2-amino-1-pyrrolidinoethanone.

$^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  10.30 (s, 1H), 9.33 (d, 1H), 9.24 (d, 1H), 9.02 (d, 1H), 8.60 (t, 1H), 8.42-8.36 (br s, 1H), 8.20 (dd, 1H), 7.79 (s, 1H), 4.05 (d, 2H), 8.44 (t, 2H), 1.92 (quin, 2H), 7.78 (quin, 2H), 1.16 (s, 9H), (one extra 2H not visible as under solvent peak).

LCMS (method A), ( $\text{M}+\text{H}^+$ ) 519,  $R_t$  = 2.28 min.

### Example 11

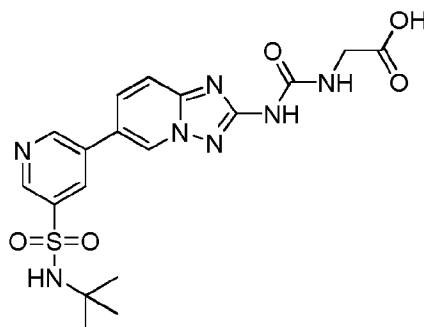
**N-tert-butyl-5-(8-fluoro-2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



Prepared according to method 7 from 5-(2-amino-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide and 2-amino-1-morpholinoethanone.

$^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  10.32 (s, 1H), 9.33 (d, 1H), 9.24 (d, 1H), 9.02 (d, 1H), 8.60 (t, 1H), 8.43-8.38 (m, 1H), 8.20 (dd, 1H), 7.79 (s, 1H), 4.16 (d, 2H), 3.62-2.58 (m, 4H), 3.50-3.44 (m, 4H), 1.16 (s, 9H).

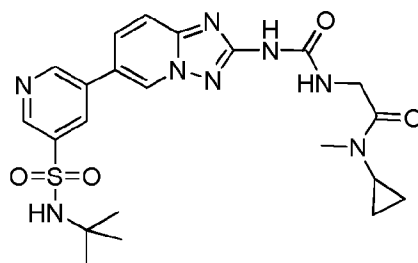
LCMS (method A), ( $\text{M}+\text{H}^+$ ) 535,  $R_t$  = 2.19 min.

**Method 8****2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid**

5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide (250 mg, 0.14 mmol) was suspended in tetrahydrofuran:pyridine (5 mL, 5:1) and cooled to 0°C. Triphosgene (215 mg, 0.72 mmol) was added in one portion and the reaction mixture heated at 35 °C for 2 hours. After this time the solvent was decanted and the resultant semi-solid dissolved in DMF:pyridine (2 mL, 10:1). Glycine hydrochloride (270 mg, 3.6 mmol) was added in one portion and the reaction mixture heated for 18 hours at 65 °C. After this time the solvent was removed in vacuo and hydrochloride acid (1M, aqueous solution) was added to the resultant oil to afford a brown solid. The title compound was collected by filtration (244 mg, 0.55 mmol, 76 %). No further purification was required.

LCMS (method A) (M+H<sup>+</sup>) 448, Rt = 2.07 min

**Method 9****Example 12****2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-cyclopropyl-N-methylacetamide**



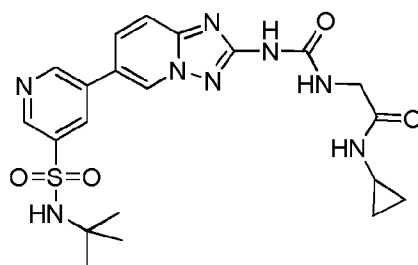
2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid (100 mg, 0.22 mmol), N-methylcyclopropanamine, ethyl-3-(3-dimethylamino-propyl)-carbodiimide (210 mg, 1.1 mmol) and triethylamine (83  $\mu$ L, 0.66 mmol) were heated in the microwave at 80 °C for 1 hour. After this time the reaction mixture was filtered and the title compound isolated by preparative-LCMS purification of the reaction mixture.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.19 (s, 1H), 9.39 (s, 1H), 9.24 (d, 1H), 9.00 (d, 1H), 8.64 (t, 1H), 8.58-8.57 (m, 1H), 8.08 (dd, 1H), 7.83-7.82 (m, 2H), 4.29 (d, 2H), 2.86 (s, 3H), 2.82-2.78 (m, 1H), 1.16 (s, 9H), 0.86-0.82 (m, 4H).

LCMS (method B), ( $\text{M}+\text{H}^+$ ) 501,  $R_t$  = 8.02 min.

### Example 13

#### 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-cyclopropylacetamide



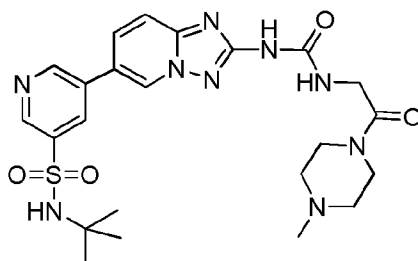
Prepared according to method 9 from 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid and cyclopropylamine.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.17 (s, 1H), 9.40 (d, 1H), 9.24 (d, 1H), 9.00 (d, 1H), 8.58 (t, 1H), 8.50 (t, 1H), 8.11 (d, 1H), 8.08 (dd, 1H), 7.84-7.82 (m, 2H), 3.83 (d, 2H), 2.68-2.61 (m, 1H), 1.16 (s, 9H), 0.65-0.61 (m, 2H), 0.44-0.40 (m, 2H).

LCMS (method A), ( $\text{M}+\text{H}^+$ ) 487,  $R_t$  = 2.10 min.

#### Example 14

**N-tert-butyl-5-(2-(3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



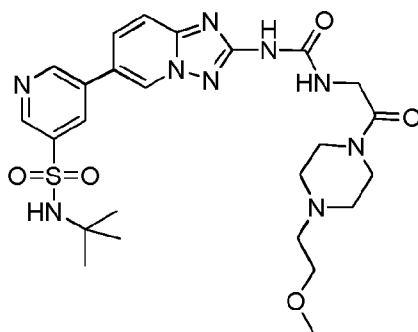
Prepared according to method 9 from 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid and N-methylpiperazine.

$^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  10.19 (s, 1H), 9.39 (d, 1H), 9.24 (d, 1H), 9.00 (d, 1H), 8.61 (t, 1H), 8.57 (t, 1H), 8.14 (s, 1H), 8.08 (dd, 1H), 7.83-7.81 (m, 2H), 4.17 (d, 2H), 2.47-2.38 (m, 4H), 2.24 (s, 3H), 1.15 (s, 9H), (2 extra 2H not visible, under solvent peak).

LCMS (method B), ( $\text{M}+\text{H}^+$ ) 530,  $R_t$  = 5.18 min.

#### Example 15

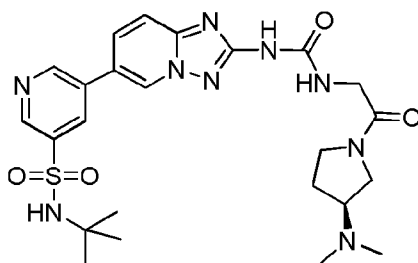
**N-tert-butyl-5-(2-(3-(2-(4-(2-methoxyethyl)piperazin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



Prepared according to method 9 from 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid and 1-(2-methoxyethyl)piperazine.  
 $^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  10.19 (s, 1H), 9.39 (d, 1H), 9.24 (d, 1H), 9.00 (d, 1H), 8.61 (t, 1H), 8.57 (t, 1H), 8.14 (s, 1H), 8.08 (dd, 1H), 7.83-7.81 (m, 2H), 4.17-4.16 (m, 3H), 3.50-3.47 (m, 6H), 3.25 (br s, 4H), 3.17 (br s, 4H), 1.16 (s, 9H).  
 LCMS (B), ( $\text{M}+\text{H}^+$ ) 574,  $R_t$  = 5.28 min.

#### Example 16

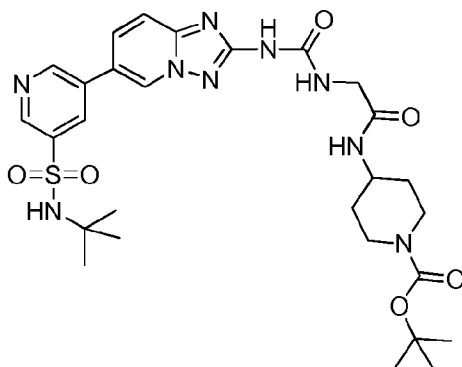
**(S)-N-tert-butyl-5-(2-(3-(2-(3-(dimethylamino)pyrrolidin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide**



Prepared according to method 9 from 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid and (S)-(3-(dimethylamino)pyrrolidin-1-yl).  
 LCMS (method B), ( $\text{M}+\text{H}^+$ ) 544,  $R_t$  = 5.18 min.

#### Example 17

**tert-butyl 4-(2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetamido)piperidine-1-carboxylate**

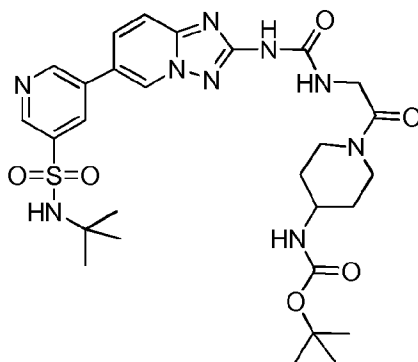


Prepared according to method 9 from 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid and tert-butyl 4-aminopiperidine-1-carboxylate.

LCMS (method A), ( $M+H^+$ ) 630,  $R_t = 2.49$  min.

#### Example 18

**tert-butyl 1-(2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetyl)piperidin-4-ylcarbamate**



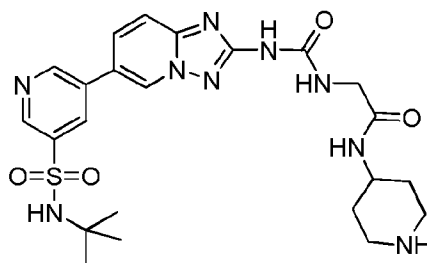
Prepared according to method 9 from 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetic acid and tert-butyl piperidin-4-ylcarbamate.

LCMS (method A), (M+H<sup>+</sup>) 630, Rt = 2.49 min.

## Method 10

### Example 19

#### 2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-(piperidin-4-yl)acetamide



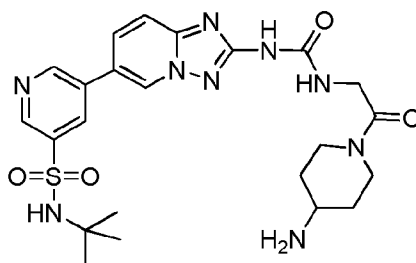
tert-butyl 4-(2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetamido)piperidine-1-carboxylate (50 mg, 0.079 mmol) was suspended in methanol (2 mL) hydrochloric acid (4 M solution in dioxane, 2 mL) was added and the reaction mixture stirred at room temperature for 2 hours. After this time the solvent was removed in vacuo to afford the title compound as a white solid (42 mg, 0.079 mmol, 100 %). No further purification was required.

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 10.20 (s, 1H), 9.41 (s, 1H), 9.24 (d, 1H), 9.01 (d, 1H), 8.59 (d, 1H), 8.49 (t, 1H), 8.23 (d, 1H), 8.10 (dd, 1H), 7.85-7.81 (m, 2H), 3.89 (d, 2H), 2.26 (d, 2H), 2.98 (quar, 2H), 1.95-1.87 (m, 2H), 1.67-1.57 (m, 2H).

LCMS (method B), (M+H<sup>+</sup>) 530, Rt = 5.05 min.

### Example 20

#### 5-(2-(3-(2-(4-aminopiperidin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide



Prepared according to method 10 from tert-butyl 1-(2-(3-(6-(5-(N-tert-tutylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)acetyl)piperidin-4-ylcarbamate

LCMS (method B), (M+H<sup>+</sup>) 530, Rt = 5.13 min.

### Biological Assays

Conventionally, PI3K lipid kinase activity can be measured using purified or recombinant enzyme in a solution-based assay with phospholipid vesicles. The reaction is terminated by the addition of acidified organic solvents and subsequent phase separation by extraction or thin layer chromatography analysis (Carpenter et al., 1990, J. Biol. Chem. 265, 19704-19711).

Another assay described in the art is based on the phosphate transfer from radiolabeled ATP to phosphatidylinositol immobilized on plates. This assay type also uses recombinant PI3K gamma enzyme but can be performed in a high throughput mode (Fuchikami et al., 2002, J. Biomol. Screening 7, 441-450).

### Determination of the effect of the compounds according to the invention on PI3K

The compounds of the present invention as described were tested in the PI3K kinobeads assay as described (EP-A 1 887 359; WO-A 2008/015013). Briefly, test compounds (at various concentrations) and the affinity matrix with the immobilized phenylthiazole ligand 1 were added to cell lysate aliquots and allowed to bind to the proteins in the lysate sample. After the incubation time the beads with captured proteins were separated from the lysate. Bound proteins were then eluted and the presence of PI3K gamma,

PI3K alpha, PI3K beta, PI3K delta and DNA-dependent protein kinase (DNA-PK) was detected and quantified using a specific antibody in a dot blot procedure and the Odyssey infrared detection system.

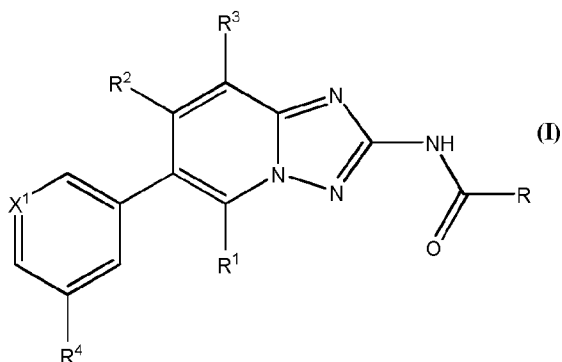
## Results

Table 2: Inhibition values ( $IC_{50}$  in  $\mu M$ ) as determined in the Kinobeads assay (Activity Level: A  $< 0.1 \mu M$ ; B  $> 0.1 \mu M < 1 \mu M$ ; C  $> 1 \mu M < 10 \mu M$ ; D  $> 10 \mu M$ )

Example	PI3K gamma	PI3K alpha	PI3K beta	PI3K delta	DNA-PK
1	A	C	B	A	D
2	A	C	C	A	D
3	A	B	B	A	C
4	A	C	C	A	D
5	A	B	C	A	C
6	A	C	C	A	C
7	A	B	C	A	C
8	A	C	C	B	B
9	A	C	D	C	D
10	A	C	C	B	D
11	A	C	C	A	D
12	A	B	C	A	D
13	A	C	B	B	D
14	A	B	B	A	C
15	A	B	B	A	C
16	A	B	B	A	C
19	A	C	B	B	D
20	A	C	B	A	D

## Patent Claims

1. A compound of formula (I)



or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein

R is N(R<sup>5a</sup>R<sup>5</sup>);

R<sup>5</sup> is (CH<sub>2</sub>)<sub>n</sub>-C(O)N(R<sup>6a</sup>R<sup>6</sup>);

n is 1; 2; or 3;

R<sup>5a</sup>, R<sup>6a</sup> are independently selected from the group consisting of H; and C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more halogen, which are the same or different;

R<sup>6</sup> is T; or CH<sub>2</sub>T;

Optionally, R<sup>6</sup>, R<sup>6a</sup> are joined together with the nitrogen atom to which they are attached to form a ring T<sup>1</sup>.

T is C<sub>3-7</sub> cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T is optionally substituted with one or more R<sup>7</sup>, which are the same or different;

T<sup>1</sup> is an at least the nitrogen atom as ring heteroatom containing at least partially saturated 4 to 7 membered heterocycle; or an at least the nitrogen atom as ring heteroatom containing at least partially saturated 7 to 11 membered heterobicycle, wherein T<sup>1</sup> is optionally substituted with one or more R<sup>7</sup>, which are the same or different;

R<sup>7</sup> is halogen; CN; C(O)OR<sup>8</sup>; OR<sup>8</sup>; oxo (=O), where the ring is at least partially saturated; C(O)R<sup>8</sup>; C(O)N(R<sup>8</sup>R<sup>8a</sup>); S(O)<sub>2</sub>N(R<sup>8</sup>R<sup>8a</sup>); S(O)N(R<sup>8</sup>R<sup>8a</sup>); S(O)<sub>2</sub>R<sup>8</sup>; S(O)R<sup>8</sup>; N(R<sup>8</sup>)S(O)<sub>2</sub>N(R<sup>8a</sup>R<sup>8b</sup>); SR<sup>8</sup>; N(R<sup>8</sup>R<sup>8a</sup>); OC(O)R<sup>8</sup>; N(R<sup>8</sup>)C(O)R<sup>8a</sup>; N(R<sup>8</sup>)S(O)<sub>2</sub>R<sup>8a</sup>; N(R<sup>8</sup>)S(O)R<sup>8a</sup>; N(R<sup>8</sup>)C(O)N(R<sup>8a</sup>R<sup>8b</sup>); N(R<sup>8</sup>)C(O)OR<sup>8a</sup>; OC(O)N(R<sup>8</sup>R<sup>8a</sup>); or C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more R<sup>9</sup>, which are the same or different;

R<sup>8</sup>, R<sup>8a</sup>, R<sup>8b</sup> are independently selected from the group consisting of H; and C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more R<sup>9</sup>, which are the same or different;

R<sup>9</sup> is halogen; CN; C(O)OR<sup>10</sup>; OR<sup>10</sup>; C(O)R<sup>10</sup>; C(O)N(R<sup>10</sup>R<sup>10a</sup>); S(O)<sub>2</sub>N(R<sup>10</sup>R<sup>10a</sup>); S(O)N(R<sup>10</sup>R<sup>10a</sup>); S(O)<sub>2</sub>R<sup>10</sup>; S(O)R<sup>10</sup>; N(R<sup>10</sup>)S(O)<sub>2</sub>N(R<sup>10a</sup>R<sup>10b</sup>); SR<sup>10</sup>; N(R<sup>10</sup>R<sup>10a</sup>); OC(O)R<sup>10</sup>; N(R<sup>10</sup>)C(O)R<sup>10a</sup>; N(R<sup>10</sup>)S(O)<sub>2</sub>R<sup>10a</sup>; N(R<sup>10</sup>)S(O)R<sup>10a</sup>; N(R<sup>10</sup>)C(O)N(R<sup>10a</sup>R<sup>10b</sup>); N(R<sup>10</sup>)C(O)OR<sup>10a</sup>; or OC(O)N(R<sup>10</sup>R<sup>10a</sup>);

R<sup>10</sup>, R<sup>10a</sup>, R<sup>10b</sup> are independently selected from the group consisting of H; and C<sub>1-6</sub> alkyl, wherein C<sub>1-6</sub> alkyl is optionally substituted with one or more halogen, which are the same or different;

$R^1$ ,  $R^2$ ,  $R^3$  are independently selected from the group consisting of H; halogen; CN;  $C(O)OR^{11}$ ;  $OR^{11}$ ;  $C(O)R^{11}$ ;  $C(O)N(R^{11}R^{11a})$ ;  $S(O)_2N(R^{11}R^{11a})$ ;  $S(O)N(R^{11}R^{11a})$ ;  $S(O)_2R^{11}$ ;  $S(O)R^{11}$ ;  $N(R^{11})S(O)_2N(R^{11a}R^{11b})$ ;  $N(R^{11})S(O)N(R^{11a}R^{11b})$ ;  $SR^{11}$ ;  $N(R^{11}R^{11a})$ ;  $OC(O)R^{11}$ ;  $N(R^{11})C(O)R^{11a}$ ;  $N(R^{11})S(O)_2R^{11a}$ ;  $N(R^{11})S(O)R^{11a}$ ;  $N(R^{11})C(O)N(R^{11a}R^{11b})$ ;  $N(R^{11})C(O)OR^{11a}$ ;  $OC(O)N(R^{11}R^{11a})$ ; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more halogen, which are the same or different;

$R^{11}$ ,  $R^{11a}$ ,  $R^{11b}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more halogen, which are the same or different;

$X^1$  is N; or  $C(R^{12})$ ;

$R^4$  is H; or  $R^{13}$ ;

$R^{12}$  is H; or  $R^{14}$ ;

$R^{13}$ ,  $R^{14}$  are independently selected from the group consisting of halogen; CN;  $C(O)OR^{15}$ ;  $OR^{15}$ ;  $C(O)R^{15}$ ;  $C(O)N(R^{15}R^{15a})$ ;  $S(O)_2N(R^{15}R^{15a})$ ;  $S(O)N(R^{15}R^{15a})$ ;  $S(O)_2R^{15}$ ;  $S(O)R^{15}$ ;  $N(R^{15})S(O)_2N(R^{15a}R^{15b})$ ;  $N(R^{15})S(O)N(R^{15a}R^{15b})$ ;  $SR^{15}$ ;  $N(R^{15}R^{15a})$ ;  $OC(O)R^{15}$ ;  $N(R^{15})C(O)R^{15a}$ ;  $N(R^{15})S(O)_2R^{15a}$ ;  $N(R^{15})S(O)R^{15a}$ ;  $N(R^{15})C(O)N(R^{15a}R^{15b})$ ;  $N(R^{15})C(O)OR^{15a}$ ;  $OC(O)N(R^{15}R^{15a})$ ; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more  $R^{16}$ ;

$R^{15}$ ,  $R^{15a}$ ,  $R^{15b}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more  $R^{16}$ ;

$R^{16}$  is halogen; CN;  $C(O)OR^{17}$ ;  $OR^{17}$ ;  $C(O)R^{17}$ ;  $C(O)N(R^{17}R^{17a})$ ;  $S(O)_2N(R^{17}R^{17a})$ ;  $S(O)N(R^{17}R^{17a})$ ;  $S(O)_2R^{17}$ ;  $S(O)R^{17}$ ;  $N(R^{17})S(O)_2N(R^{17a}R^{17b})$ ;  $N(R^{17})S(O)N(R^{17a}R^{17b})$ ;  $SR^{17}$ ;  $N(R^{17}R^{17a})$ ;  $OC(O)R^{17}$ ;  $N(R^{17})C(O)R^{17a}$ ;

$N(R^{17})S(O)_2R^{17a}$ ;  $N(R^{17})S(O)R^{17a}$ ;  $N(R^{17})C(O)N(R^{17a}R^{17b})$ ;  $N(R^{17})C(O)OR^{17a}$ ; or  $OC(O)N(R^{17}R^{17a})$ ;

$R^{17}$ ,  $R^{17a}$ ,  $R^{17b}$  are independently selected from the group consisting of H; and  $C_{1-6}$  alkyl, wherein  $C_{1-6}$  alkyl is optionally substituted with one or more halogen, which are the same or different.

2. A compound of claim 1, wherein  $R^{5a}$  is H.
3. A compound of claim 1 or 2, wherein n is 1; or 2.
4. A compound of any of claims 1 to 3, wherein  $R^{6a}$  is H; or  $CH_3$ .
5. A compound of any of claims 1 to 4, wherein  $R^6$  is T.
6. A compound of any of claims 1 to 5, wherein T is  $C_{3-7}$  cycloalkyl; or saturated 4 to 7 membered heterocyclyl and wherein T is unsubstituted or substituted with one or more  $R^7$ , which are the same or different.
7. A compound of any of claims 1 to 6, wherein T is cyclopropyl; pyrrolidinyl; piperidinyl; or morpholinyl and wherein T is unsubstituted or substituted with one or more  $R^7$ , which are the same or different.
8. A compound of any of claims 1 to 3, wherein  $R^6$ ,  $R^{6a}$  are joined together with the nitrogen atom to which they are attached to form a ring  $T^1$ .
9. A compound of claim 8, wherein  $T^1$  is an at least the nitrogen atom as ring heteroatom containing saturated 4 to 7 membered heterocycle and wherein  $T^1$  is unsubstituted or substituted with one or more  $R^7$ , which are the same or different.

10. A compound of claim 8 or 9, wherein T<sup>1</sup> is pyrrolidine; morpholine; piperidine; or piperazine, and wherein T<sup>1</sup> is unsubstituted or substituted with one or more R<sup>7</sup>, which are the same or different.
11. A compound of any of claims 1 to 10, wherein R<sup>7</sup> is OC<sub>1-6</sub> alkyl; N(C<sub>1-6</sub> alkyl)<sub>2</sub>; or C<sub>1-6</sub> alkyl, which is unsubstituted or substituted with one or more R<sup>9</sup>, which are the same or different and selected from the group consisting of halogen; OC<sub>1-6</sub> alkyl; and N(C<sub>1-6</sub> alkyl)<sub>2</sub>.
12. A compound of any of claims 1 to 11, wherein R<sup>3</sup> is H; CH<sub>3</sub>; or halogen.
13. A compound of any of claims 1 to 12, wherein R<sup>2</sup> is H.
14. A compound of any of claims 1 to 13, wherein R<sup>1</sup> is H.
15. A compound of any of claims 1 to 14, wherein R<sup>4</sup> is R<sup>13</sup>.
16. A compound of any of claims 1 to 15, wherein R<sup>13</sup> is SO<sub>2</sub>N(R<sup>15</sup>R<sup>15a</sup>); SO<sub>2</sub>R<sup>15</sup>; or C<sub>1-6</sub> alkyl, optionally substituted with one or more halogen, which are the same or different.
17. A compound of any of claims 1 to 16, wherein R<sup>15a</sup> is H; or CH<sub>3</sub>.
18. A compound of any of claims 1 to 17, wherein R<sup>15</sup> is C<sub>1-6</sub> alkyl.
19. A compound of any of claims 1 to 18, wherein X<sup>1</sup> is N.
20. A compound of claim 1 selected from the group consisting of  
  
N-tert-butyl-5-(2-(3-(3-oxo-3-(pyrrolidin-1-yl)propyl)ureido)-  
[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(3-oxo-3-(piperidin-1-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-oxo-2-(piperidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide

N-isopropyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-isopropyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

1-(6-(5-(methylsulfonyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-3-(2-morpholino-2-oxoethyl)urea;

1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-3-(6-(5-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)urea;

N-tert-butyl-5-(8-fluoro-2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(8-fluoro-2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-cyclopropyl-N-methylacetamide;

2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-cyclopropylacetamide;

N-tert-butyl-5-(2-(3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

N-tert-butyl-5-(2-(3-(2-(4-(2-methoxyethyl)piperazin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

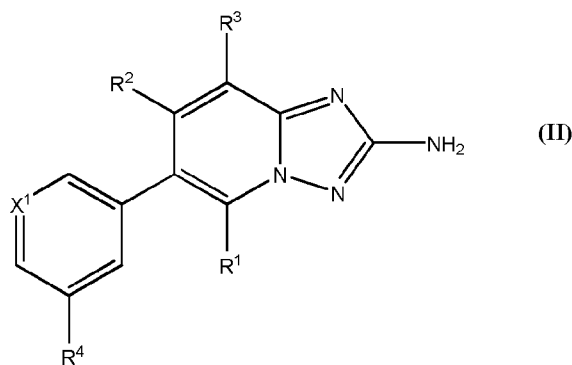
(S)-N-tert-butyl-5-(2-(3-(2-(3-(dimethylamino)pyrrolidin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)pyridine-3-sulfonamide;

2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N-(piperidin-4-yl)acetamide; and

5-(2-(3-(2-(4-aminopiperidin-1-yl)-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide.

21. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 20 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.
22. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 20 for use as a medicament.
23. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 20 for use in a method of treating or preventing diseases and disorders associated with PI3K.

24. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 20 for use in a method of treating or preventing immunological, inflammatory, autoimmune, or allergic disorders.
25. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 20 for use in a method of treating or preventing cancer, cardiovascular disorders, metabolic diseases, neurodegenerative disorders, or infectious diseases.
26. A method for treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more conditions selected from the group consisting of diseases and disorders associated with PI3K, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound according to present invention or a pharmaceutically acceptable salt thereof.
27. A method for the preparation of a compound of any of claims 1 to 20 according to formula (I), comprising the step of
- reacting a compound of formula (II)



either with triphosgene and subsequently with a compound of formula H-R, wherein the hydrogen of H-R is attached to a heteroatom; or with a compound of formula Cl-C(O)-R to yield a compound of formula (I).

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/051462

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 A61K31/437 A61P29/00 A61P9/00 A61P35/00  
 A61P31/00 A61P25/00

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EAST, STEPHEN P. ET AL: "DNA gyrase (GyrB)/topoisomerase IV (ParE) inhibitors: Synthesis and antibacterial activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, 19(3), 894-899 CODEN: BMCLE8; ISSN: 0960-894X, 2009, XP002540073 page 895; figure 2; compound 2	1-27
X	WO 2009/010530 A1 (NOVARTIS AG, SWITZ.; LEGRAND, DARREN MARK) 22 January 2009 (2009-01-22) page 65; example 3; table 4	1-27

 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 document 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.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

5 March 2010

Date of mailing of the international search report

12/03/2010

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

Bourghida, E

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/051462

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009010530 A1	22-01-2009	AR 067562 A1	14-10-2009
		AU 2008277628 A1	22-01-2009
		PE 04922009 A1	27-05-2009
-----			