**Title:** 7-PYRIDINYL- OR PHENYL- SUBSTITUTED TRIAZOLO [1, 5-A] PYRIDINES AS PI3K INHIBITORS

**Abstract:** The invention relates to compounds of formula (I), wherein \( X, X^1, R \) and \( R^4 \) to \( R^4 \) 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.

**Claims:**

1. A compound having the formula:

   ![Chemical Structure](image)

   where \( X, X^1, R \) and \( R^4 \) to \( R^4 \) have the meaning as described.

2. A method of treating disorders associated with PI3K inhibition using the compound(s) of claim 1.

3. A pharmaceutical composition comprising the compound(s) of claim 1 and a pharmaceutically acceptable carrier.

**Abstract:** The invention relates to compounds of formula (I), wherein \( X, X^1, R \) and \( R^4 \) to \( R^4 \) 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.
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 PBK 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, PBKs) 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 PBK family also display protein kinase activity (Vanhaesebroeck et al., 2001, Annu. Rev. Biochem. 70:535-602).
PBKs belongs to a superfamily of signaling lipid kinases that catalyse the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) or phosphatidylinositol (PtdIns) at the 3'-OH group, giving rise to the second messengers phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3) or phosphatidylinositol-1,3-phosphate (PtdIns(3)P). PtdIns(3,4,5)P3 can be converted into PtdIns(3,4)P2 by SH2-containing inositol phosphatase (SHIP), or can be dephosphorylated by phosphatase and tensin homologue (PTEN) phosphatase to regenerate PtdIns(4,5)P2. The 3'-phosphorylated phosphoinositides, PtdIns(3,4,5)P3, PtdIns(3,4)P2 PtdIns(4,5)P2, 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)P3) 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 (γ) and delta (δ) isoforms appear to be involved in a number of aspects of leukocyte activation (Rommel et al., 2007, Nat. Rev. Immunol. 7(3):191-201; Ruckle et al., 2006, Nat. Rev. Drug Discov. 5(1):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 PBK, 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 PBKs 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 - PBK α, β and δ (PIK3CA, PIK3CB and PIK3CD) - consists 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, p110α, p110β or p110δ (Bader et al., 2005, Nat. Rev. Cancer 5(12):921-9).

Genetic polymorphisms within the PBK pathway are also associated with an increased risk of type 2 diabetes. Downstream of the insulin-like growth factor 1 (IGFl) receptor, signaling through class I PBK controls growth and development. Amplification and point mutations of the gene encoding PBKα 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). PBK activation and PIP3 production are fundamental for most biological responses exerted by insulin. Activated insulin receptor (IR) triggers PBK activity by binding and phosphorylating adaptor proteins of the insulin receptor substrate (IRS) family. Upon phosphophorylation IRS serves as a docking site for p85 regulatory subunits that consequently recruit p110 enzymes (mainly α and β 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).

PBKβ has been implicated in regulating the formation and stability of integrin α(IIb)β(3), which is necessary for the activation and aggregation of platelets. Isoform-selective PBK p110β inhibitors have been developed which in vivo eliminate occlusive thrombus formation but do not prolong bleeding time. These studies define PBK p110β as an important new target for antithrombotic therapy (Jackson et al., 2005, Nat. Med. 11 (5):507-14).
PBKδ is predominantly expressed in the haematopoietic system and PBKδ-deficient mice are viable, fertile, apparently healthy and have a normal life span (Vanhaesebroeck et al., 2005. Trends in Biochemical Sciences 30, 194-204). PBKδ has important roles in T- and B-cell signaling, mast-cell-mediated allergic responses, the neutrophils oxidative burst and, possibly, extravasation. PBK inhibitors selective for PBKδ were reported to block neutrophil activation in an animal model for neutrophil activation, thus pointing to PI3kδ as a target for the development of anti-inflammatory drugs (Sadhu et al., 2003, Biochem. Biophys. Res. Communications 308, 764-769).

PBKy, the only member of class IB (PIK3CG), associates with either of two regulatory subunits, p101 and p84, that control its activation and subcellular location. PBKy activation is driven by the direct association of its catalytic domain with the βγ subunits of G proteins following activation of pertussis-toxin-sensitive Goi-coupled G-protein-coupled receptors (GPCRs). In addition, PBKy can be activated by Ras by a direct interaction with the catalytic subunit. Beside its lipid kinase activity, PBKy 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 PBKy, indicating a protein-scaffold function in addition to its enzymatic activity. PBKy 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 PBKγ protein is encoded by the Pik3cg locus. Mice lacking functional PBKγ (PBKγ-/− 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) P3 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 PBKγ is the sole PBK 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) P3-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-/- mice showed impaired thymocyte development and increases in
neutrophil, monocyte, and eosinophil populations. Furthermore, neutrophils and macrophages isolated from Pi3kcg-/-mice exhibited severe defects in migration and respiratory burst in response to GPCR agonists and chemotactic agents. Work with knockout mice also established that PBK γ is required for the homing of dendritic cells to lymph nodes and in the development and activation of T lymphocytes (together with PBK δ). In concert with IgE-dependent activation of PBK δ, PBK γ 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. PBK γ also contributes to the activation of platelet aggregation by ADP in concert with PBK β (Ferguson et al., 2007, Nat. Cell Biol. 9(1):86-91).

Collectively, the class IB phosphoinositide 3-kinase PBK γ seems to be pivotal in the control of leukocyte trafficking and accordingly the development of isotype-selective inhibitors of PBK γ should be an attractive anti-inflammatory therapeutic strategy (Rommel et al., 2007, Nat. Rev. Immunol. 7(3):191-201; Ruckle et al., 2006, Nat. Rev. Drug Discov. 5(1):903-18).

PBK γ 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 PBK γ 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 PBK γ 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 PBK γ (Lupia et al., 2004. Am. J. Pathol. 165(6):2003-2011).

Recently, the development of potent and selective PBK γ 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.

Triazolopyridine derivatives are described in WO-A 01/17999 as modulators of adenosine A₂A receptor and in WO-A 2006/0381 16 as antibacterial agents.
Thus, an object of the present invention is to provide a new class of compounds as kinase inhibitors, especially as PBK inhibitors, which may be effective in the treatment or prophylaxis of immunological, inflammatory, autoimmune, allergic disorders or other diseases or disorders associated with PBK. 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 PBK.

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

![Chemical Structure](image)

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

15 $X$ is O; or S;

$R$ is $R^5$; OR$^5$; orN(R$^5$R$^5$);

$R^5$ is H; or Ci$_6$ alkyl, wherein Ci$_6$ alkyl is optionally substituted with one or more halogen, which are the same or different;

$R^5$ is H; T; or Ci$_6$ alkyl, wherein Ci$_6$ alkyl is optionally substituted with one or more R$^6$, which are the same or different;

25 R$^6$ is halogen; CN; C(O)OR$^7$; OR$^7$; C(O)R$^7$; C(O)N(R$^7$R$^7$a); S(O)$_2$N(R$^7$R$^7$a); S(O)N(R$^7$R$^7$a); S(O)$_2$S(O)$_2$R$^7$; S(O)R$^7$; N(R$^7$)S(O)$_2$N(R$^7$R$^7$b); SR$^7$; N(R$^7$R$^7$a); OC(O)R$^7$; N(R$^7$)C(O)R$^7$; N(R$^7$)S(O)R$^7$a; N(R$^7$)S(O)N(R$^7$R$^7$b); N(R$^7$)C(O)N(R$^7$R$^7$b); N(R$^7$)C(O)OR$^7$a; OC(O)N(R$^7$R$^7$a); or T;
R\textsuperscript{7}, R\textsubscript{7}\textsuperscript{a}, R\textsubscript{7}b are independently selected from the group consisting of H; T; and Ci\textsubscript{6} alkyl, wherein Ci\textsubscript{6} alkyl is optionally substituted with one or more R\textsuperscript{8}, which are the same or different;

T is C\textsubscript{3}\textsubscript{-7} cycloalkyl; 4 to 7 membered heterocycl; 7 to 11 membered heterobicyc; phenyl; naphthyl; indenyl; or indanyl; wherein T is optionally substituted with one or more R\textsuperscript{9}, which are the same or different;

R\textsuperscript{9} is T\textsuperscript{1}; halogen; CN; C(O)OR\textsuperscript{10}; OR\textsuperscript{10}; oxo (=0), where the ring is at least partially saturated; C(O)R\textsuperscript{10}; C(O)N(R\textsuperscript{10}R\textsubscript{10}\textsuperscript{a}); S(O)\textsubscript{2}N(R\textsuperscript{10}R\textsubscript{10}\textsuperscript{a}); S(O)N(R\textsuperscript{10}R\textsubscript{10}\textsuperscript{a}); S(O)\textsubscript{2}R\textsuperscript{10}; S(O)R\textsuperscript{10}; N(R\textsuperscript{10})S(O)\textsubscript{2}N(R\textsuperscript{10}R\textsubscript{10}\textsuperscript{b}); SR\textsuperscript{10}; N(R\textsuperscript{10}R\textsubscript{10}\textsuperscript{a}); OC(O)R\textsuperscript{10}; N(R\textsuperscript{10})C(O)R\textsuperscript{10a}; N(R\textsuperscript{10})S(O)\textsubscript{2}R\textsuperscript{10a}; N(R\textsuperscript{10})S(O)R\textsuperscript{10a}; N(R\textsuperscript{10})C(O)N(R\textsuperscript{10}R\textsubscript{10}\textsuperscript{b}); N(R\textsuperscript{10})C(O)OR\textsuperscript{10a}; OC(O)N(R\textsuperscript{10}R\textsuperscript{10}\textsuperscript{a}); Ci\textsubscript{6} alkyl, wherein Ci\textsubscript{6} alkyl is optionally substituted with one or more R\textsuperscript{11}, which are the same or different;

R\textsuperscript{10}, R\textsuperscript{10a}, R\textsuperscript{10b} are independently selected from the group consisting of H; T\textsuperscript{1}; and Ci\textsubscript{6} alkyl, wherein Ci\textsubscript{6} alkyl is optionally substituted with one or more R\textsuperscript{12}, which are the same or different;

R\textsuperscript{8}, R\textsuperscript{11} are independently selected from the group consisting of halogen; CN; C(O)OR\textsuperscript{13}; OR\textsuperscript{13}; C(O)R\textsuperscript{13}; C(O)N(R\textsuperscript{13}R\textsubscript{13}\textsuperscript{a}); S(O)\textsubscript{2}N(R\textsuperscript{13}R\textsubscript{13}\textsuperscript{a}); S(O)N(R\textsuperscript{13}R\textsubscript{13}\textsuperscript{a}); S(O)\textsubscript{2}R\textsuperscript{13}; S(O)R\textsuperscript{13}; N(R\textsuperscript{13})S(O)\textsubscript{2}N(R\textsuperscript{13}R\textsubscript{13}\textsuperscript{b}); SR\textsuperscript{13}; N(R\textsuperscript{13}R\textsubscript{13}\textsuperscript{a}); OC(O)R\textsuperscript{13}; N(R\textsuperscript{13})C(O)R\textsuperscript{13a}; N(R\textsuperscript{13})S(O)\textsubscript{2}R\textsuperscript{13a}; N(R\textsuperscript{13})S(O)R\textsuperscript{13a}; N(R\textsuperscript{13})C(O)N(R\textsuperscript{13}R\textsubscript{13}\textsuperscript{b}); N(R\textsuperscript{13})C(O)OR\textsuperscript{13a}; OC(O)N(R\textsuperscript{13}R\textsuperscript{13}\textsuperscript{a}); and T\textsuperscript{1};

R\textsuperscript{13}, R\textsubscript{13}a, R\textsubscript{13b} are independently selected from the group consisting of H; T\textsuperscript{1}; and Ci\textsubscript{6} alkyl, wherein Ci\textsubscript{6} alkyl is optionally substituted with one or more R\textsuperscript{14}, which are the same or different;

R\textsuperscript{12}, R\textsuperscript{14} are independently selected from the group consisting of halogen; CN; C(O)OR\textsuperscript{15}; OR\textsuperscript{15}; C(O)R\textsuperscript{15}; C(O)N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{a}); S(O)\textsubscript{2}N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{a}); S(O)N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{a}); S(O)\textsubscript{2}R\textsuperscript{15}; S(O)R\textsuperscript{15}; N(R\textsuperscript{15})S(O)\textsubscript{2}N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{b}); SR\textsuperscript{15}; N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{a}); OC(O)R\textsuperscript{15}; N(R\textsuperscript{15})C(O)R\textsuperscript{15a}; N(R\textsuperscript{15})S(O)\textsubscript{2}R\textsuperscript{15a}; N(R\textsuperscript{15})S(O)R\textsuperscript{15a}; N(R\textsuperscript{15})C(O)N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{b}); N(R\textsuperscript{15})C(O)OR\textsuperscript{15a}; and OC(O)N(R\textsuperscript{15}R\textsubscript{15}\textsuperscript{a});
T₁ is C₃-7 cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl; wherein T₁ is optionally substituted with one or more R₁₆, which are the same or different;

R₁₆ is halogen; CN; C(O)OR; OR; oxo (=0), where the ring is at least partially saturated; C(O)R; C(O)N(R₁₇R₁₇a); S(O)₂N(R₁₇R₁₇a); S(O)N(R₁₇R₁₇a); S(O)₂R; S(O)R; N(R₁₇)N(S(O)₂R₁₇b); S(R₁₇); N(R₁₇)C(O)R; N(R₁₇)S(O)₂R₁₇a; N(R₁₇)S(O)R₁₇a; N(R₁₇)C(O)N(R₁₇R₁₇b); N(R₁₇)C(O)OR; OC(O)N(R₁₇R₁₇a); d₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

R₁₅; R₁₅a; R₁₅b; R₁₇; R₁₇a; R₁₇b are independently selected from the group consisting of H; C₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

R₁, R₂, R₃ are independently selected from the group consisting of H; halogen; CN; C(O)OR; OR; C(O)R; C(O)N(R₁₈R₁₈a); S(O)₂N(R₁₈R₁₈a); S(O)N(R₁₈R₁₈a); S(O)₂R; S(O)R; N(R₁₈)S(O)₂N(R₁₈R₁₈b); N(R₁₈)S(O)N(R₁₈R₁₈b); S(R₁₈); N(R₁₈)C(O)R; N(R₁₈)S(O)₂R₁₈a; N(R₁₈)S(O)R₁₈a; N(R₁₈)C(O)N(R₁₈R₁₈b); N(R₁₈)C(O)OR; OC(O)N(R₁₈R₁₈a); and C₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

R₁₈, R₁₈a, R₁₈b are independently selected from the group consisting of H; and C₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

X₁ is N; or C(R₄₉);

R₄ is H; R₁⁹; or R₂₀;

R₄a is H; or R₁₉a;

R₁₉, R₁₉a are independently selected from the group consisting of halogen; CN; C(O)OR; OR; oxo (=0), where the ring is at least partially saturated; C(O)R; C(O)N(R₁ᵡ₁R₁ᵡ₂);
S(O)₂N(R ²¹R ²²); S(O)N(R ²¹R ²²); S(O)₂R ²¹; S(O)R ²¹; N(R ²¹)S(O)₂N(R ²²R ²³);
N(R ²¹)S(O)N(R ²²R ²³); SR ²¹; N(R ²¹R ²²); OC(O)R ²¹; N(R ²¹)C(O)R ²²; N(R ²¹)S(O)₂R ²²;
N(R ²¹)S(O)R ²²; N(R ²¹)C(O)N(R ²²R ²³); N(R ²¹)C(O)OR ²²; OC(O)N(R ²¹R ²²); and Ci₆ alkyl,
wherein Ci₆ alkyl is optionally substituted with one or more R ²⁴;

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R ²⁰ is T ²; C(O)OR ²⁵; OR ²⁵; C(O)R ²⁵; C(O)N(R ²⁵R ²⁵a); S(O)₂N(R ²⁵R ²⁵a); S(O)N(R ²⁵R ²⁵a);
S(O)₂R ²⁵; S(O)R ²⁵; N(R ²⁵)S(O)₂N(R ²⁵aR ²⁵b); N(R ²⁵)S(O)N(R ²⁵aR ²⁵b); SR ²⁵; N(R ²⁵R ²⁵a);
OC(O)R ²⁵; N(R ²⁵)C(O)R ²⁵a; N(R ²⁵)S(O)₂R ²⁵a; N(R ²⁵)S(O)R ²⁵a; N(R ²⁵)C(O)N(R ²⁵aR ²⁵b);
N(R ²⁵)C(O)OR ²⁵a; OC(O)N(R ²⁵R ²⁵a); or Ci₆ alkyl substituted with one or more T ² and
optionally substituted with one or more R ²⁴;

10

R ²⁵, R ²⁵a, R ²⁵b are independently selected from the group consisting of R ²⁵c; and R ²⁵d,
provided that at least one of R ²⁵, R ²⁵a, R ²⁵b is R ²⁵c;

15

R ²⁵c is T ²; or Ci₆ alkyl, wherein Ci₆ alkyl is substituted with one or more T ² and optionally
substituted with one or more R ²⁴;

R ²¹, R ²², R ²³, R ²⁵d are independently selected from the group consisting of H; and Ci₆ alkyl,
wherein Ci₆ alkyl is optionally substituted with one or more R ²⁶;

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R ²⁴ is halogen; CN; C(O)OR ²⁶; OR ²⁶; C(O)R ²⁶; C(O)N(R ²⁶R ²⁶a); S(O)₂N(R ²⁶R ²⁶a);
S(O)N(R ²⁶R ²⁶a); S(O)₂R ²⁶; S(O)R ²⁶; N(R ²⁶)S(O)₂N(R ²⁶aR ²⁶b); N(R ²⁶)S(O)N(R ²⁶aR ²⁶b); SR ²⁶;
N(R ²⁶R ²⁶a); OC(O)R ²⁶; N(R ²⁶)C(O)R ²⁶a; N(R ²⁶)S(O)₂R ²⁶a; N(R ²⁶)S(O)R ²⁶a;
N(R ²⁶)C(O)N(R ²⁶aR ²⁶b); N(R ²⁶)C(O)OR ²⁶a; or OC(O)N(R ²⁶R ²⁶a);

25

R ²⁶, R ²⁶a, R ²⁶b are independently selected from the group consisting of H; and Ci₆ alkyl,
wherein Ci₆ alkyl is optionally substituted with one or more halogen, which are the same or
different;

30

T ² is C₃₋₇ cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclcyl;
phenyl; naphthyl; indenyl; or indanyl, wherein T ² is optionally substituted with one or more
R ²⁷;
R\textsuperscript{27} is halogen; CN; C(O)OR\textsuperscript{28}; OR\textsuperscript{28}; oxo (=0), where the ring is at least partially saturated; C(O)R\textsuperscript{28}; C(O)N(R\textsuperscript{28}R\textsuperscript{28a}); S(O)\textsubscript{2}N(R\textsuperscript{28}R\textsuperscript{28a}); S(O)N(R\textsuperscript{28}R\textsuperscript{28a}); S(O)\textsubscript{2}R\textsuperscript{28}; S(O)R\textsuperscript{28}; N(R\textsuperscript{28})S(O)\textsubscript{2}N(R\textsuperscript{28}R\textsuperscript{28a}); N(R\textsuperscript{28})S(O)N(R\textsuperscript{28}R\textsuperscript{28a}); SR\textsuperscript{28}; N(R\textsuperscript{28}R\textsuperscript{28a}); OC(O)R\textsuperscript{28}; N(R\textsuperscript{28})C(O)R\textsuperscript{28a}; N(R\textsuperscript{28})S(O)\textsubscript{2}R\textsuperscript{28a}; N(R\textsuperscript{28})S(O)R\textsuperscript{28a}; N(R\textsuperscript{28})C(O)N(R\textsuperscript{28}R\textsuperscript{28a}); or Ci\textsubscript{6} alkyl, wherein Ci\textsubscript{6} alkyl is optionally substituted with one or more halogen which are the same or different;

R\textsuperscript{28}, R\textsuperscript{28a}, R\textsuperscript{28b} are independently selected from the group consisting of H; and Ci\textsubscript{6} alkyl, wherein Ci\textsubscript{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.

"Ci\textsubscript{4} 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\textsubscript{2}-, -CH\textsubscript{2}-CH\textsubscript{2}-, -CH(CH\textsubscript{3})-, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-, -CH(CH\textsubscript{3})\textsubscript{2}-, -C(CH\textsubscript{3})\textsubscript{2}-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a Ci\textsubscript{4} alkyl carbon may be replaced by a substituent.

"Ci\textsubscript{6} alkyl" means an alkyl chain having 1 to 6 carbon atoms, e.g. if present at the end of a molecule: Ci\textsubscript{4} alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl; tert-butyl, n-pentyl, n-hexyl, or e.g. -CH\textsubscript{2}-, -CH\textsubscript{2}-CH\textsubscript{2}-, -CH(CH\textsubscript{3})-, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-, -CH(CH\textsubscript{3})\textsubscript{2}-, -CH(C\textsubscript{2}H\textsubscript{5})-, -C(CH\textsubscript{3})\textsubscript{2}-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a Ci\textsubscript{6} alkyl carbon may be replaced by a substituent.
"C3-7 cycloalkyl" or "C3-7 cycloalkyl ring" means a cyclic alkyl chain having 3 to 7 carbon atoms, e.g. 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)₂-), 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, pyrrole, 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.

"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)₂-), 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, benzo furan, benzo thiophene, benzoazole, 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-dioxa-8-azaspiro[4.5]decane or bridged 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.

A preferred compound of formula (I) is a carbamate of formula (Ia)

or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein X₁, R₁, R₂, R₃, R₄, R⁵ are defined as indicated above.

Also a preferred compound of formula (I) is an urea of formula (Ib)

or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein
X₁, R₁, R₂, R₃, R₄ are defined as indicated above;

R⁵b is R⁵a and R⁵c is R⁵; or

optionally R⁵b, R⁵c are joined together with the nitrogen atom to which they are attached to form a 4 to 7 membered heterocycle; or a 7 to 11 membered heterobicycle, wherein the 4 to 7 membered heterocycle and the 7 to 11 membered heterobicycle are optionally substituted with one or more R⁹, which are the same or different and defined as indicated above.

Even more preferred are compounds of formula (Ia).

Preferably, R⁵b, R⁵c are joined together with the nitrogen atom to which they are attached to form a 4 to 7 membered heterocycle, which is optionally substituted with one or more R⁹, which are the same or different and defined as indicated above. Preferably, the 4 to 7 membered heterocycle is pyrrolidine; oxazolidine; piperidine; morpholine; or piperazine.

Preferably, R⁵a is H; or methyl.

Preferably, R⁵ is H; or unsubstituted Ci₆ alkyl; more preferably, R⁵ is unsubstituted Ci₆ alkyl; even more preferably, R⁵ is unsubstituted Ci₄ alkyl; even more preferably, R⁵ is methyl.

Preferably, R⁵ is Ci₆ alkyl, wherein Ci₆ alkyl is substituted with one or more R⁶, which are the same or different; wherein

R⁶ is halogen; CN; C(O)OR ⁷; OR⁷; C(O)R ⁷; C(O)N(R ⁷R⁷a); S(O)₂N(R ⁷R⁷a); S(O)N(R ⁷R⁷a); S(O)₂R⁷; S(O)R ⁷; N(R ⁷)S(O)₂N(R ⁷aR⁷b); SR⁷; N(R ⁷R⁷a); OC(O)R ⁷; N(R ⁷)C(O)R ⁷a; N(R ⁷)S(O)₂R⁷a; N(R ⁷)S(O)R ⁷a; N(R ⁷)C(O)N(R ⁷aR⁷b); N(R ⁷)C(O)OR ⁷a; or OC(O)N(R ⁷R⁷a); R⁷, R⁷a, R⁷b are independently selected from the group consisting of H; and Ci₆ alkyl, wherein Ci₆ alkyl is optionally substituted with one or more R⁸, which are the same or different;

R⁸ is halogen; CN; C(O)OR ¹³; OR¹³; C(O)R ¹³; C(O)N(R ¹³R¹³a); S(O)₂N(R ¹³R¹³a); S(O)N(R ¹³R¹³a); S(O)₂R¹³; S(O)R ¹³; N(R ¹³)S(O)₂N(R ¹³aR¹³b); SR¹³; N(R ¹³R¹³a); OC(O)R ¹³; N(R ¹³)C(O)R ¹³a; N(R ¹³)S(O)₂R¹³a; N(R ¹³)S(O)R ¹³a; N(R ¹³)C(O)N(R ¹³aR¹³b); N(R ¹³)C(O)OR ¹³a; or OC(O)N(R ¹³R¹³a);
R_{1}, \text{R}_{13}, \text{R}_{13a}, \text{R}_{13b} \text{ are independently selected from the group consisting of } H; \text{ and } \text{Ci}_6 \text{ alkyl, wherein } \text{Ci}_6 \text{ alkyl is optionally substituted with one or more } R_{14}, \text{ which are the same or different;}

R_{14} \text{ is halogen; } \text{CN; } \text{C(O)OR}_{15}; \text{ OR}_{15}; \text{ C(O)R}_{15}; \text{ C(O)N(R}_{15})_{15a}; \text{ S(O)}_{2}N(R_{15})_{15a}; \text{ S(O)}_{2}N(R_{15})_{15a}; 5
\text{ S(O)}_{2}N(R_{15})_{15a}; \text{ S(O)}_{2}R_{15}; \text{ S(O)}_{2}R_{15}; \text{ N(R}_{15})S(O)_{2}N(R_{15})_{15a}; 10 \text{ SR}_{15}; \text{ N(R}_{15})R_{15a}; \text{ OC(O)R}_{15}; \text{ N(R}_{15})C(O)R_{15a}; \text{ N(R}_{15})S(O)_{2}R_{15a}; \text{ N(R}_{15})S(O)_{2}R_{15a}; \text{ N(R}_{15})C(O)N(R_{15})_{15a}; 15 \text{ or OC(O)N(R}_{15})_{15a}; \text{ R}_{15}; \text{ R}_{15a}; \text{ R}_{15b} \text{ are independently selected from the group consisting of } H; \text{ Ci}_6 \text{ alkyl, wherein } \text{Ci}_6 \text{ alkyl is optionally substituted with one or more halogen, which are the same or different.}

Preferably, } R_{6} \text{ is halogen; } \text{CN; } \text{C(O)OR}_{7}; \text{ OR}_{7}; \text{ C(O)R}_{7}; \text{ C(O)N(R}_{7})_{7a}; \text{ S(O)}_{2}N(R_{7})_{7a}; 20 \text{ S(O)}_{2}N(R_{7})_{7a}; \text{ S(O)}_{2}R_{7}; \text{ S(O)}_{2}R_{7}; \text{ N(R}_{7})S(O)_{2}N(R_{7})_{7a}; \text{ SR}_{7}; \text{ N(R}_{7})R_{7a}; \text{ OC(O)R}_{7}; \text{ N(R}_{7})C(O)R_{7a}; \text{ N(R}_{7})S(O)_{2}R_{7a}; \text{ N(R}_{7})S(O)_{2}R_{7a}; \text{ N(R}_{7})C(O)N(R_{7})_{7a}; \text{ or OC(O)N(R}_{7})_{7a}, \text{ wherein}

\text{R}_{7}, \text{R}_{7a}, \text{R}_{7b} \text{ are independently selected from the group consisting of } H; \text{ and } \text{Ci}_6 \text{ alkyl, wherein } \text{Ci}_6 \text{ alkyl is optionally substituted with one or more halogen, which are the same or different.}

Preferably, } R_{6} \text{ is } N(R_{7})_{7a}; \text{ or C(O)N(R}_{7})_{7a}, \text{ wherein } \text{R}_{7}, \text{R}_{7a} \text{ are independently selected from the group consisting of } H; \text{ and } \text{Ci}_6 \text{ alkyl, wherein } \text{Ci}_6 \text{ alkyl is optionally substituted with one or more halogen, which are the same or different.}

Preferably, } R_{5} \text{ is } T, \text{ wherein } T \text{ is optionally substituted with one or more } R_{9} \text{ and wherein } R_{9} \text{ is defined as indicated above.}

Preferably, } R_{3} \text{ is } \text{Ci}_6 \text{ alkyl, wherein } \text{Ci}_6 \text{ alkyl is substituted with one or more } R_{6}, \text{ which are the same or different, wherein}

\text{R}_{6} \text{ is halogen; } \text{CN; } \text{C(O)OR}_{7}; \text{ OR}_{7}; \text{ C(O)R}_{7}; \text{ C(O)N(R}_{7})_{7a}; \text{ S(O)}_{2}N(R_{7})_{7a}; 30 \text{ S(O)}_{2}N(R_{7})_{7a}; \text{ S(O)}_{2}R_{7}; \text{ S(O)}_{2}R_{7}; \text{ N(R}_{7})S(O)_{2}N(R_{7a})_{7b}; \text{ SR}_{7}; \text{ N(R}_{7})R_{7a}; \text{ OC(O)R}_{7}; \text{ N(R}_{7})C(O)R_{7a}; \text{ N(R}_{7})S(O)_{2}R_{7a}; \text{ N(R}_{7})S(O)_{2}R_{7a}; \text{ N(R}_{7})C(O)N(R_{7})_{7a}; \text{ or OC(O)N(R}_{7})_{7a}; \text{ or } T; \text{ R}_{7}, \text{R}_{7a}, \text{R}_{7b} \text{ are independently selected from the group consisting of } H; \text{ T; and } \text{Ci}_6 \text{ alkyl, wherein } \text{Ci}_6 \text{ alkyl is optionally substituted with one or more } R_{8}, \text{ which are the same or different;
T is C3-7 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^9, which are the same or different;

R^9 is T^1; halogen; CN; C(O)OR \(^{10}\); OR \(^{10}\); oxo (=0), where the ring is at least partially saturated; C(O)R \(^{10}\); C(O)N(R \(^{10}\)R \(^{10a}\)); S(O)\(_2\)N(R \(^{10}\)R \(^{10a}\)); S(O)N(R \(^{10}\)R \(^{10a}\)); S(O)\(_2\)R \(^{10}\); S(O)R \(^{10}\); N(R \(^{10}\))S(O)\(_2\)N(R \(^{10}\)R \(^{10b}\)); SR \(^{10}\); N(R \(^{10}\)R \(^{10a}\)); OC(O)R \(^{10}\); N(R \(^{10}\))C(O)R \(^{10a}\); N(R \(^{10}\))S(O)\(_2\)R \(^{10a}\); N(R \(^{10}\))S(O)R \(^{10a}\); N(R \(^{10}\))C(O)N(R \(^{10a}\)R \(^{10b}\)); N(R \(^{10}\))C(O)OR \(^{10a}\); OC(O)N(R \(^{10}\)R \(^{10a}\)); Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more R \(^{11}\), which are the same or different;

R \(^{10}\), R \(^{10a}\), R \(^{10b}\) are independently selected from the group consisting of H; T^1; and Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more R \(^{12}\), which are the same or different;

R \(^{8}\), R \(^{11}\) are independently selected from the group consisting of halogen; CN; C(O)OR \(^{13}\); OR \(^{13}\); C(O)R \(^{13}\); C(O)N(R \(^{13R}\)R \(^{13a}\)); S(O)\(_2\)N(R \(^{13}\)R \(^{13a}\)); S(O)N(R \(^{13}\)R \(^{13a}\)); S(O)\(_2\)R \(^{13}\); S(O)R \(^{13}\); N(R \(^{13}\))S(O)\(_2\)N(R \(^{13}\)R \(^{13b}\)); SR \(^{13}\); N(R \(^{13}\)R \(^{13a}\)); OC(O)R \(^{13}\); N(R \(^{13}\))C(O)R \(^{13a}\); N(R \(^{13}\))S(O)\(_2\)R \(^{13a}\); N(R \(^{13}\))S(O)R \(^{13a}\); N(R \(^{13}\))C(O)N(R \(^{13}\)R \(^{13b}\)); N(R \(^{11}\))C(O)OR \(^{13a}\); OC(O)N(R \(^{13}\)R \(^{13a}\)); and T^1;

R \(^{13}\), R \(^{13a}\), R \(^{13b}\) are independently selected from the group consisting of H; T^1; and Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more R \(^{14}\), which are the same or different;

R \(^{12}\), 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)\(_2\)N(R \(^{15}\)R \(^{15a}\)); S(O)N(R \(^{15}\)R \(^{15a}\)); S(O)\(_2\)R \(^{15}\); S(O)R \(^{15}\); N(R \(^{15}\))S(O)\(_2\)N(R \(^{15}\)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)\(_2\)R \(^{15a}\); N(R \(^{15}\))S(O)R \(^{15a}\); N(R \(^{15}\))C(O)N(R \(^{15}\)R \(^{15b}\)); N(R \(^{15}\))C(O)OR \(^{15a}\); and OC(O)N(R \(^{15}\)R \(^{15a}\));

T^1 is C3-7 cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl; wherein T^1 is optionally substituted with one or more R \(^{16}\), which are the same or different;

R \(^{16}\) is halogen; CN; C(O)OR \(^{17}\); OR \(^{17}\); oxo (=0), where the ring is at least partially saturated; C(O)R \(^{17}\); C(O)N(R \(^{17}\)R \(^{17a}\)); S(O)\(_2\)N(R \(^{17}\)R \(^{17a}\)); S(O)N(R \(^{17}\)R \(^{17a}\)); S(O)\(_2\)R \(^{17}\); S(O)R \(^{17}\); N(R \(^{17}\))S(O)\(_2\)N(R \(^{17}\)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)\(_2\)R \(^{17a}\); N(R \(^{17}\))S(O)R \(^{17a}\); N(R \(^{17}\))C(O)N(R \(^{17}\)R \(^{17b}\)); N(R \(^{17}\))C(O)OR \(^{17a}\); OC(O)N(R \(^{17}\)R \(^{17a}\)); Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more halogen, which are the same or different;
R^{15}; R^{15a}; R^{15b}; R^{17}; R^{17a}; R^{17b} are independently selected from the group consisting of H; Ci_{6} alkyl, wherein Ci_{6} alkyl is optionally substituted with one or more halogen, which are the same or different;

provided that at least one of the following prerequisites is fulfilled:

5  \( R^6 \) is T;

at least one of \( R^7, R^{7a}, R^{7b} \) is T;

\( R^8 \) is \( T^1 \);

at least one of \( R^{13}, R^{13a}, R^{13b} \) is \( T^1 \).

10 Preferably, \( R^5 \) is of formula \((CH_2)_n-X^0-T\), wherein

n is 1, 2, 3, or 4, more preferably n is 2 or 3;

\( X^0 \) is a covalent chemical single bond; C(O); C(O)N(R^{7a}); N(R^{7a}); or N(R^{7a})C(O);

\( R^{7a}, T \) are defined as indicated above.

15 Preferably, \( X^0 \) is a covalent chemical single bond; or C(O).

Preferably, T is 4 to 7 membered heterocyclyl; or phenyl, wherein T is optionally substituted with one or more \( R^9 \), which are the same or different.

20 Preferably, T is pyrrolyl; furyl; thiophenyl; pyrazolyl; imidazolyl; oxazolyl; thiazolyl; triazolyl; oxadiazolyl; thiadiazolyl; tetrazolyl; phenyl; pyridyl; pyrimidyl; pyrazinyl; pyridazinyl; pyrrolidinyl; tetrahydrofuryl; piperidyl; piperazinyl; or morpholinyl.

Preferably, \( R^9 \) is \( T^1; Ci_{6} \) alkyl; or oxo, where the ring is at least partially saturated.

25 Preferably, \( T^1 \) is cyclopropyl.

Preferably, \( R^1, R^2, R^3 \) are H.

30 Preferably, \( R^4 \) is \( R^{19} \).

Preferably, \( R^{19} \) is \( S(O)_{2}N(R^{22}R^{21}) \).

Preferably, \( R^{22} \) is H; or \( CH_3 \).
Preferably, $R^2_1$ is $C_i_6$ alkyl.

Preferably, $R^4$ is $R^{20}$.

Preferably, $X^1$ is $N$.

Preferably, $X^1$ is $C(R^{4a})$.

Preferably, $R^{4a}$ is $H$.

Preferably, $X$ is $O$.

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

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

- $2-(3-(6-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)ureido)-N,N$-dimethylacetamide;
- $N$-tert-butyl-5-(2-(3-(2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-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-7-yl)pyridine-3-sulfonamide;
- $N$-tert-butyl-5-(2-(3-(3-(5-cyclopropyl-2H-tetrazol-2-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide;
- $N$-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide;
- $N$-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide;
- $N$-tert-butyl-5-(2-(3-(5-cyclopropyl-2H-tetrazol-2-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-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, palmitoxyloxy, pivaloxyloxy, succinylloxy, fumaroyloxy, 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 PBK 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 object of the present invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use as a medicament.
Another object 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 PBK.

Yet another object 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 PBK, preferably PBKγ.

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

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

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

"PBKδ" means PBK δ protein, a member of PBK class class IA (also referred to as p110-delta). A human cDNA encoding the PBKδ protein of 1044 amino acids was reported (Vanhaesebroeck et al., 1997, Proc. Natl. Acad Sci. 94:4330-4335). The human PBKδ protein is encoded by the PBKCD gene which was mapped to chromosome Ip3.2 (Seki et al., 1997, DNA Research 4:355-358).

Yet another object 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+ 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 (Schón 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+ 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 PI3Kγ 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 PI3Kγ (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 PBK as new potential targets for treating anaphylaxis (Cauwels et al, 2006, J. Clin. Invest. 116(8):2244-51).

Diseases and disorders associated especially with PBK 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 (PBK), resulting in the regulation of ATP-dependent potassium channels. In
accordance with this idea, intracerebroventricular (icv) injection of PBK 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
PBK 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 (MCPl) has been identified as a key player in this process. Signaling downstream
of the chemokine receptor CCR2, a MCPl receptor, is partly controlled by PBKγ. In a recent
study, Pi3Kγ-/- 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 (Solina et al., 2008. A central role for PBK gamma in obesity and
insulin resistance. Diabetologia 51: S295-S296 Suppl. 1 Meeting Abstract: 739), suggesting
a potential therapeutic effect of PBKγ inhibitors in metabolic disorders such as obesity.

Recent work has demonstrated that the PBK (phosphoinositide 3-kinase) signaling pathway is
important for efficient influenza A virus replication. Activation of PBK in virus-infected cells
is mediated by the viral NS1 protein, which binds directly to the p85beta regulatory subunit of
PBK and causes the PBK-dependent phosphorylation of Akt (protein kinase B). Given that
recombinant influenza A viruses unable to activate PBK signalling are attenuated in tissue culture, the PBK 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 object 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 PBK, 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 object 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 object 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.

5 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 PBK. Especially the
important roles of PBKδ and PBKγ 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,

10 In some cases, the link between PBKδ and PBKγ as potential drug targets for specific
diseases has been experimentally established by testing the respective PBK-null mice in
animal disease models. Additional pharmacological confirmation was obtained by using small
molecule PBK 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 PIK3γ 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 PBKγ inhibitor AS-605240 reduced CD4+ T-cell populations, reduced glomerulonephritis, and prolonged life span (Barber et al, 2005, Nat. Med. 11(9):933-935).

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

In a recent report, Pi3Kγ-/− 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 PBKγ’s role in cell infiltration into the airways, in particular of eosinophils, key effector cells in allergic inflammation. These data suggest PBKγ as an attractive target for pharmacological intervention in asthma (Thomas et al., 2008, Immunology, Epub ahead of print, PMID: 18754810).

Using selective PBKδ inhibitors it was demonstrated that PBKδ plays a role in neutrophil inflammatory responses. Inhibition of PBKδ blocked both fMLP- and TNFα-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 PBKδ in allergic responses was demonstrated by genetic and pharmacological inactivation of PBKδ in mast cells. This inhibition leads to to defective SCF-mediated in vitro proliferation, adhesion and migration, and to impaired allergen-IgE-induced degranulation and cytokine release. Moreover, inactivation of PBKδ protects mice against anaphylactic allergic responses. Taken together, these studies suggest PBKδ as a...

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 PI3Kδ mutants, whereas type 1 cytokine responses (IFN-γ CXCL10) were robust. For example, induction of respiratory hyper-responsiveness to inhaled methacholine, a hallmark of asthma, was attenuated in PI3Kδ null mice. In summary, these data suggest PI3Kδ 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. PI3Kγ 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 PI3Kγ is activated in macrophages by oxidized LDL, agonists, chemokines and inflammatory mediators commonly implicated in atherogenesis. Genetic ablation of PBKγ 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 PBK might affect plaque stability (Chang et al., 2007, PNAS 104 (19):8077-82).

This may be based on the fact that signaling through PBKγ plays an important role for leucocyte, platelet and cardiovascular stress sensing. The concerted activation of leukocytes and vessels influences may 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 PBKγ, a crucial signal in both vascular and white blood cells. The study of mice lacking PBKγ 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 PBKγ 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, TGlOO-1 15, 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 after), 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 p110α 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 PI3Kβ (p110β), PBKγ (p110γ) or PBKδ (p110δ) 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-α class I PBK isoforms in human cancer has not been fully explored but there are reports of elevated expression of PBKβ and PBKδ in various human cancers (Benistant et al., 2000, Oncogene 19(44):5083-5090; Rnobbe and Reifenberger, 2003,
Brain Pathol. 13(4):507-518). In another study it was demonstrated that a selective inhibitor of PI3Kδ (pl1Odelta) inhibited the proliferation and survival of acute myeloid leukemia (AML) cells and increased the cytotoxic effects of a topoisomerase II inhibitor suggesting PI3Kδ as a potential therapeutic target in AML (Billottet et al, 2006. Oncogene 25(50):6648-6659).

Recent studies with conditional PI3Kβ/- knockout mice and reconstitution of cells with kinase inactive PI3Kβ 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).

PI3Kγ 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 PI3Kγ is involved in the signaling downstream CXCR4, small molecule PI3Kγ 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 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.

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.

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), wherein X is O, 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), wherein X is O.

Compounds of formula (I), wherein X is S, can be prepared by analogous methods known in the art.

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.

Schemes

Scheme 1:
Scheme 2:

Scheme 3:
Scheme 4:

\[
\text{R}^5\text{C(O)Cl, DMAP}
\]
Analytical Methods

NMR spectra were obtained on a Brucker dpx400. LCMS (method A) 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 10μL. Wavelengths were 254 and 210nm.

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

<table>
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<tr>
<th>Time (min)</th>
<th>Water</th>
<th>Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
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<td>95</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
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<tr>
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<td>95</td>
<td>5</td>
</tr>
<tr>
<td>5.00</td>
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</tbody>
</table>

Method B

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>%A</th>
<th>%B</th>
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<tbody>
<tr>
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</tr>
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<td>14.00</td>
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</table>

20 Table 1: Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>NH$_2$OH·HCl</td>
<td>Hydroxylamine hydrochloride</td>
</tr>
<tr>
<td>Pd(dpdpf)(Cl)$_2$</td>
<td>[1,1’bis(diphenylphosphino)ferrocene] dichloro-palladium (II)</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>Water</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doubledoublet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
</tbody>
</table>
The following methods were used for the preparation of compounds of formula I.

1.1 5-bromo-7-tert-butylpyridine-3-sulfonamide

![Chemical structure of 5-bromo-7-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 collection 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.

2'-amino-N-tert-butyl-3,4'-bipyridine-5-sulfonamide

![Chemical structure of 2'-amino-N-tert-butyl-3,4'-bipyridine-5-sulfonamide]

5-bromo-N-tert-butylpyridine-3-sulfonamide (1.86 g, 6.36 mmol), bis(pinolato)diboron (1.78 g, 7.99 mmol), potassium acetate (1.62 g, 17 mmol) and 1,1'-bis(diphenylphosphino)ferrocene|dichloropalladium(II), complex with CH₂Cl₂ (52 mg) in dioxane (20 mL) was heated to 120°C for 60 minutes in the microwave. After this time 2'-amino-4-bromopyridine (1g, 5.78 mmol), 2M sodium carbonate (10mL), ethanol (10mL) and
further l,r-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with CH₂Cl₂ (52 mg) were added and the reaction heated for a further 1h at 140°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 NaOH 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 (1.88 g, 97%).

N-tert-butyl-2'-l-(3-(ethoxycarbonyl)thiourea)-3,4'-bipyridine-5-sulfonamide

To a solution of 6'-amino-N-tert-butyl-3,3'-bipyridine-5-sulfonamide (1) (1.89 g, 6.15 mmol) in DCM (50 mL) cooled to 0°C was added ethoxycarbonyl isothiocyanate (699 µL, 6.15 mmol) dropwise over 15 min. The reaction mixture was then warmed to 35 °C and stirred for 24 h after which time a further portion of ethoxycarbonyl isothiocyanate was added and the reaction mixture stirred for a further 24 hours. Evaporation in vacuo gave a brown solid to which petrol (20 mL) was added. The solid was then collected by filtration, thoroughly washed with petrol (3 x 25 mL) and air-dried to afford the desired product as a brown solid (2.30 g, 85%).

5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-2'-N-tert-butyldipyridine-3-sulfonamide

To a suspension of hydroxylamine hydrochloride (1.83 g, 26.28 mmol) in EtOH/MeOH (1:1, 70 mL) was added N,N-diisopropylethylamine (2.75 mL, 15.77 mmol), the mixture was stirred at room temperature (20 °C) for 1 h.
3,4'-bipyridine-5-sulfonamide (2.30 g, 5.26 mmol) was then added and the mixture slowly heated to reflux (Note: bleach trap required to quench H₂S 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 pale brown solid (1.47 g).

Example 1

N-(7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)[1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide

5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-N-tert-butylpyridine-3-sulfonamide (150 mg, 0.43 mmol) was suspended in acetonitrile (10 mL). Acetyl chloride (204 µL, 2.89 mmol) and 4-(Dimethylamino)pyridine (52 mg, 0.43 mmol) were added in one portion and the suspension heated at 50 °C for 18 hours. After this time the white solid was filtered and washed with diethyl ether (10 mL) to afford the title compounds as a white solid (20 mg, 0.05 mmol).

\[
\text{Example 1}
\]

\[
\text{N-(7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)[1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide}
\]

\[
\text{5-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-N-tert-butylpyridine-3-sulfonamide}
\]

\[
\text{(150 mg, 0.43 mmol) was suspended in acetonitrile (10 mL). Acetyl chloride (204 µL, 2.89 mmol) and 4-(Dimethylamino)pyridine (52 mg, 0.43 mmol) were added in one portion and the suspension heated at 50 °C for 18 hours. After this time the white solid was filtered and washed with diethyl ether (10 mL) to afford the title compounds as a white solid (20 mg, 0.05 mmol).}
\]

\[
\text{1H NMR (d-DMSO) δ 11.00 (s, IH), 9.32 (d, IH), 9.05-9.04 (m, 2H), 8.66 (s, IH), 8.21 (d, IH), 7.89 (s, IH), 7.60 (dd, IH), 2.16 (s, 3H), 1.15 (s, 9H).}
\]

\[
\text{LCMS (method A) (M+H) + 389, Rt = 1.98 min.}
\]

General Procedure for the synthesis of ureas/carbamates

5-(2-Amino-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-pyridine-3-sulfonic acid tert-butylamide (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), the amine or alcohol (0.32 mmol) was added in
one portion and the reaction mixture heated for 18 hours at 65 °C. The desired products were either isolated by filtration or by prep-LCMS purification of the reaction mixture.

Example 2

5 N-tert-butyl-5-(2-(3-(2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide

\[
\text{\text{N-tert-butyl-5-(2-(3-(2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide}}
\]

\[
\begin{align*}
\text{H NMR (de-DMSO) } & \delta 10.10 \text{ (s, IH), 9.29 (d, IH), 9.03 (d, IH), 8.93 (d, IH), 8.62 (d, IH), 8.40 (t, IH), 8.12 (d, IH), 7.82 (br s, IH), 7.53 (dd, IH), 3.70 (q, 2H), 3.02 (t, 2H), 2.20-2.14 (m, IH), 1.14 (s, 9H), 1.07-1.02 (m, 2H), 0.95-0.91 (m, 2H).} \\
\text{LCMS (method A) (MH+) 526, } & \text{RT = 2.25 min.}
\end{align*}
\]

Example 3

N-tert-butyl-5-(2-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide

\[
\begin{align*}
\text{H NMR (de-DMSO) } & \delta 10.14 \text{ (s, IH), 9.31 (d, IH), 9.02 (d, IH), 8.95 (dd, IH), 8.64 (t, IH), 8.62 (t, IH), 8.14 (d, IH), 7.82 (s, IH), 7.57 (dd, IH), 4.04 (d, 2H), 3.42 (t, 2H), 1.90 (pent, 2H), 1.78 (pent, 2H), 1.14 (s, 9H), one extra peak not visible as under solvent peak.} \\
\text{LCMS (method A) (MH+) 501, } & \text{RT = 2.21 min.}
\end{align*}
\]

Example 4
N-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide

¹H NMR (de-DMSO) δ 10.16 (s, 1H), 9.30 (d, 1H), 9.03 (d, 1H), 8.95 (d, 1H), 8.64-8.62 (m, 2H), 8.14 (d, 1H), 7.81 (s, 1H), 7.57 (dd, 1H), 4.16 (d, 2H), 3.61-3.58 (m, 4H), 3.48-3.43 (m, 4H), 1.14 (s, 9H).

LCMS (method A) (MH+) 517, RT = 2.12 min.

Example 5

N-tert-butyl-5-(2-(3-(3-(5-cyclopropyl-2H-tetrazol-2-yl)propyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide

¹H NMR (de-DMSO) δ 10.06 (s, 1H), 9.29 (d, 1H), 9.03 (d, 1H), 8.95 (dd, 1H), 8.62 (t, 1H), 8.27 (t, 1H), 8.15 (d, 1H), 7.81 (s, 1H), 7.57 (dd, 1H), 4.65 (t, 2H), 3.32-3.26 (m, 2H), 2.18-2.10 (m, 3H), 1.14 (s, 9H), 1.03-0.98 (m, 2H), 0.87-0.83 (m, 2H).

LCMS (method A) (MH+) 540, RT = 2.41 min.

Example 6

5-(2-(3-(3-(1H-1,2,4-triazol-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-N-tert-butylpyridine-3-sulfonamide
Example 7

N-tert-butyl-5-(2-(3-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide

1H NMR (de-DMSO) δ 10.13 (s, IH), 9.30 (d, IH), 9.05 (d, IH), 8.93 (dd, IH), 8.62 (t, IH), 8.54 (s, IH), 8.29 (t, IH), 8.11 (d, IH), 8.04 (s, IH), 7.84 (s, IH), 7.57 (dd, IH), 4.37 (t, 2H), 3.67 (q, 2H), 1.16 (s, 9H).  

LCMS (method A) (MH+) 485, RT = 2.05 min.

Example 8

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

1H NMR (de-DMSO) δ 10.35 (s, IH), 9.29 (d, IH), 9.03 (d, IH), 8.97 (dd, IH), 8.78 (t, IH), 8.63 (t, IH), 8.18 (d, IH), 7.81 (br s, IH), 7.58 (dd, IH), 4.68 (d, 2H), 2.47 (s, 3H), 1.14 (s, 9H).  

LCMS (method A) (MH+) 486, RT = 2.10 min.
Example 9

3-(dimethylamino)-3-oxopropyl 7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-ylcarbamate

\[
\begin{align*}
\text{NMR (de-DMSO)} & \quad \delta 10.16 \text{ (s, IH)}, 9.32 \text{ (d, IH)}, 9.04 \text{ (d, IH)}, 8.96 \text{ (d, IH)}, 8.66-8.62 \text{ (m, 2H)}, 8.15 \text{ (s, IH)}, 7.84 \text{ (s, IH)}, 7.58 \text{ (dd, IH)}, 4.12 \text{ (d, 2H)}, 2.98 \text{ (s, 3H)}, 2.88 \text{ (s, 3H)}, 1.15 \text{ (s, 9H).}
\end{align*}
\]

LCMS (method A) (M+H\(^+\)) 475, \(R_t = 2.08 \text{ min}\)

Example 10

2-(lH-tetrazol-5-yl)ethyl 7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-ylcarbamate

\[
\begin{align*}
\text{NMR (de-DMSO)} & \quad \delta 10.64 \text{ (s, IH)}, 9.30 \text{ (d, IH)}, 9.04 \text{ (d, IH)}, 9.00 \text{ (dd, IH)}, 8.62 \text{ (t, IH)}, 8.18 \text{ (d, IH)}, 7.85 \text{ (s, IH)}, 7.55 \text{ (dd, IH)}, 4.31 \text{ (t, 2H)}, 2.98 \text{ (s, 3H)}, 2.83 \text{ (s, 3H)}, 2.72 \text{ (t, 2H)}, 1.15 \text{ (s, 9H).}
\end{align*}
\]

LCMS (method B), (M+H\(^+\)) 490, \(R_t = 7.22 \text{ min}\).

Example 11
2-(4-methylpiperazin-1-yl)ethyl 7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-ylcarbamate

\[
\begin{align*}
\text{HNMR (de-DMSO)} & \delta 10.69 (s, 1H), 9.30 (d, 1H), 9.04 (dd, 1H), 9.00 (dd, 1H), 8.61 (t, 1H), 8.17-8.16 (m, 2H), 7.84 (s, 1H), 7.54 (dd, 1H), 4.20 (t, 2H), 2.58 (t, 3H), 2.39-2.32 (m, 4H), 2.16 (s, 3H), 1.14 (s, 9H).
\end{align*}
\]

LCMS (method B), \((M+H^+)^{517}, \text{Rt} = 4.95 \text{ min.}\)

Example 12: Determination of the effect of the compounds according to the invention on PI3K

The compounds of the present invention as described in example 1 can be tested in the PI3K kinobeads assay as described (EP-A 1 887 359; WO2008/015013). Briefly, test compounds (at various concentrations) and the affinity matrix with the immobilized phenylthiazole ligand are 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 are separated from the lysate. Bound proteins are then eluted and the presence of PI3K gamma is detected and quantified using a specific antibody in a dot blot procedure and the Odyssey infrared detection system.

Conventionally, PI3K lipid kinase activity can be measured using purified or recombinant enzyme in a solution-based assay with phosopholipid 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).

In general, compounds of the invention are effective for the inhibition of PBK gamma, with an IC$_{50}$ of $<10\mu$M.
Patent Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein X is O; or S;

R is R^5; OR^5; orN(R^5)R^5;

R^5a is H; or Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H; T; or Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more R^6, which are the same or different;

R^6 is halogen; CN; C(O)OR^7; OR^7; C(O)R^7; C(O)N(R^7R^7a); S(O)N(R^7R^7a); S(O)N(R^7R^7a); S(O)N(R^7R^7a); S(O)R^7; S(O)R^7; N(R^7)S(O)R^7b; SR^7; N(R^7R^7a); OC(O)R^7; N(R^7)C(O)R^7a; N(R^7)S(O)R^7b; N(R^7)C(O)N(R^7R^7b); N(R^7)C(O)OR^7a; OC(O)N(R^7R^7a); or T;

R^7, R^7a, R^7b are independently selected from the group consisting of H; T; and Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more R^8, which are the same or different;
T is C3-7 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 R9, which are the same or different;

R9 is T1; halogen; CN; C(O)OR 10; OR 10; oxo (=O), where the ring is at least partially saturated; C(O)R 10; C(O)N(R 10R 10a); S(O) 2N(R 10R 10a); S(O)N(R 10R 10a); S(O)R 10; S(O)R 10; N(R 10)S(O) 2N(R 10aR 10b); SR 10; N(R 10R 10a); OC(O)R 10; N(R 10)C(O)R 10a; N(R 10)S(O) 2R 10a; N(R 10)S(O)R 10a; N(R 10)C(O)N(R 108R 10b); N(R 10)C(O)OR 10a; OC(O)N(R 10R 10a); C6 6 alkyl, wherein C6 6 alkyl is optionally substituted with one or more R 11, which are the same or different;

R10, R10a, R10b are independently selected from the group consisting of H; T1; and C6 6 alkyl, wherein C6 6 alkyl is optionally substituted with one or more R 12, which are the same or different;

R8, R11 are independently selected from the group consisting of halogen; CN; C(O)OR 13; OR 13; C(O)R 13; C(O)N(R 13R 13a); S(O) 2N(R 13R 13a); S(O)N(R 13R 13a); S(O)R 13; S(O)R 13; N(R 13)S(O) 2N(R 13aR 13b); SR 13; N(R 13R 13a); OC(O)R 13; N(R 13)C(O)R 13a; N(R 13)S(O) 2R 13a; N(R 13)S(O)R 13a; N(R 13)C(O)N(R 13aR 13b); N(R 13)C(O)OR 13a; OC(O)N(R 13R 13a); and T1;

R13, R13a, R13b are independently selected from the group consisting of H; T1; and C6 6 alkyl, wherein C6 6 alkyl is optionally substituted with one or more R 14, which are the same or different;

R12, R14 are independently selected from the group consisting of halogen; CN; C(O)OR 15; OR 15; C(O)R 15; C(O)N(R 15R 15a); S(O) 2N(R 15R 15a); S(O)N(R 15R 15a); S(O)R 15; S(O)R 15; N(R 15)S(O) 2N(R 15aR 15b); SR 15; N(R 15R 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 15aR 15b); N(R 15)C(O)OR 15a; and OC(O)N(R 15R 15a);

T1 is C3-7 cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl; wherein T1 is optionally substituted with one or more R16, which are the same or different;
R\textsuperscript{16} is halogen; CN; C(O)OR \textsuperscript{17}; OR\textsuperscript{17}; oxo (=0), where the ring is at least partially saturated; C(O)R \textsuperscript{17}; C(O)N(R \textsuperscript{17}R \textsuperscript{17a}); S(O)\textsubscript{2}N(R \textsuperscript{17}R \textsuperscript{17a}); S(O)N(R \textsuperscript{17}R \textsuperscript{17a}); S(O)\textsubscript{2}R \textsuperscript{17}; S(O)R \textsuperscript{17}; N(R \textsuperscript{17})S(O)\textsubscript{2}N(R \textsuperscript{17}R \textsuperscript{17b}); SR \textsuperscript{17}; N(R \textsuperscript{17}R \textsuperscript{17a}); OC(O)R \textsuperscript{17}; N(R \textsuperscript{17})C(O)R \textsuperscript{17a}; N(R \textsuperscript{17})S(O)\textsubscript{2}R \textsuperscript{17a}; N(R \textsuperscript{17})S(O)\textsubscript{2}R \textsuperscript{17b}; N(R \textsuperscript{17})C(O)OR \textsuperscript{17a}; OC(O)N(R \textsuperscript{17}R \textsuperscript{17a}); C\textsubscript{1}6 alkyl, wherein C\textsubscript{1}6 alkyl is optionally substituted with one or more halogen, which are the same or different;

R\textsuperscript{15}; R\textsuperscript{15a}; R\textsuperscript{15b}; R \textsuperscript{17}; R \textsuperscript{17a}; R \textsuperscript{17b} are independently selected from the group consisting of H; C\textsubscript{1}6 alkyl, wherein C\textsubscript{1}6 alkyl is optionally substituted with one or more halogen, which are the same or different;

R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3} are independently selected from the group consisting of H; halogen; CN; C(O)OR \textsuperscript{18}; OR \textsuperscript{18}; C(O)R \textsuperscript{18}; C(O)N(R \textsuperscript{18}R \textsuperscript{18a}); S(O)\textsubscript{2}N(R \textsuperscript{18}R \textsuperscript{18a}); S(O)N(R \textsuperscript{18}R \textsuperscript{18a}); S(O)\textsubscript{2}R \textsuperscript{18}; S(O)R \textsuperscript{18}; N(R \textsuperscript{18})S(O)\textsubscript{2}N(R \textsuperscript{18}aR \textsuperscript{18b}); N(R \textsuperscript{18})S(O)N(R \textsuperscript{18}aR \textsuperscript{18b}); SR \textsuperscript{18}; N(R \textsuperscript{18}R \textsuperscript{18a}); OC(O)R \textsuperscript{18}; N(R \textsuperscript{18}C(O)R \textsuperscript{18a}; N(R \textsuperscript{18})S(O)\textsubscript{2}R \textsuperscript{18a}; N(R \textsuperscript{18})S(O)R \textsuperscript{18a}; N(R \textsuperscript{18})C(O)N(R \textsuperscript{18}aR \textsuperscript{18b}); N(R \textsuperscript{18})C(O)OR \textsuperscript{18a}; OC(O)N(R \textsuperscript{18}R \textsuperscript{18a}); and C\textsubscript{1}6 alkyl, wherein C\textsubscript{1}6 alkyl is optionally substituted with one or more halogen, which are the same or different;

R\textsuperscript{18}, R\textsuperscript{18a}, R\textsuperscript{18b} are independently selected from the group consisting of H; and C\textsubscript{1}6 alkyl, wherein C\textsubscript{1}6 alkyl is optionally substituted with one or more halogen, which are the same or different;

X\textsuperscript{1} is N; or C(R\textsuperscript{4a});

R\textsuperscript{4} is H; R\textsuperscript{19}; or R\textsuperscript{20};

R\textsuperscript{4a} is H; or R\textsuperscript{19a};

R\textsuperscript{19}, R\textsuperscript{19a} are independently selected from the group consisting of halogen; CN; C(O)OR \textsuperscript{21}; OR\textsuperscript{21}; oxo (=0), where the ring is at least partially saturated; C(O)R \textsuperscript{21}; C(O)N(R \textsuperscript{21}R \textsuperscript{22}); S(O)\textsubscript{2}N(R \textsuperscript{21}R \textsuperscript{22}); S(O)N(R \textsuperscript{21}R \textsuperscript{22}); S(O)\textsubscript{2}R \textsuperscript{21}; S(O)R \textsuperscript{21}; N(R \textsuperscript{21})S(O)\textsubscript{2}N(R \textsuperscript{22}R \textsuperscript{23}); N(R \textsuperscript{21})S(O)N(R \textsuperscript{22}R \textsuperscript{23}); SR \textsuperscript{21}; N(R \textsuperscript{21}R \textsuperscript{22}); OC(O)R \textsuperscript{21};
N(R\(^{21}\))C(O)R\(^{22}\); N(R\(^{21}\))S(O)\(_2\)R\(^{22}\); N(R\(^{21}\))S(O)N(R\(^{22}\)R\(^{23}\)); N(R\(^{21}\))C(O)N(R\(^{22}\)R\(^{23}\)); N(R\(^{21}\))C(O)OR\(^{22}\); OC(O)N(R\(^{21}\)R\(^{22}\)); and Ci\(_6\) alkyl, wherein Ci\(_6\) alkyl is optionally substituted with one or more R\(^{24}\);

R\(^{20}\) is T\(^2\); C(O)OR \(^{25}\); OR \(^{25}\); C(O)R \(^{25}\); C(O)N(R \(^{25}\)R \(^{25a}\)); S(O)\(_2\)N(R \(^{25}\)R \(^{25a}\)); S(O)N(R \(^{25}\)R \(^{25a}\)); S(O)\(_2\)R \(^{25}\); S(O)R \(^{25}\); N(R \(^{25}\)S(O)\(_2\)N(R \(^{25a}\)R \(^{25b}\)); N(R \(^{25}\)S(O)N(R \(^{25a}\)R \(^{25b}\)); SR \(^{25}\); N(R \(^{25}\)R \(^{25a}\)); OC(O)R \(^{25}\); N(R \(^{25}\)C(O)R \(^{25a}\); N(R \(^{25}\)S(O)R \(^{25}\)); N(R \(^{25}\)S(O)R \(^{25}\)); N(R \(^{25}\)C(O)N(R \(^{25}\)R \(^{25b}\)); N(R \(^{25}\)C(O)OR \(^{25a}\); OC(O)N(R \(^{25}\)R \(^{25a}\)); or Ci\(_6\) alkyl substituted with one or more T\(^2\) and optionally substituted with one or more R\(^{24}\);

R\(^{25}\), R\(^{25a}\), R\(^{25b}\) are independently selected from the group consisting of R\(^{25c}\); and R\(^{25d}\), provided that at least one of R\(^{25}\), R\(^{25a}\), R\(^{25b}\) is R\(^{25c}\);

R\(^{25c}\) is T\(^2\); or Ci\(_6\) alkyl, wherein Ci\(_6\) alkyl is substituted with one or more T\(^2\) and optionally substituted with one or more R\(^{24}\);

R\(^{21}\), R\(^{22}\), R\(^{23}\), R\(^{25d}\) are independently selected from the group consisting of H; and Ci\(_6\) alkyl, wherein Ci\(_6\) alkyl is optionally substituted with one or more R\(^{26}\);

R\(^{24}\) is halogen; CN; C(O)OR \(^{26}\); OR \(^{26}\); C(O)R \(^{26}\); C(O)N(R \(^{26}\)R \(^{26a}\)); S(O)\(_2\)N(R \(^{26}\)R \(^{26a}\)); S(O)N(R \(^{26}\)R \(^{26a}\)); S(O)\(_2\)R \(^{26}\); S(O)R \(^{26}\); N(R \(^{26}\)S(O)\(_2\)N(R \(^{26a}\)R \(^{26b}\)); N(R \(^{26}\)S(O)N(R \(^{26a}\)R \(^{26b}\)); SR \(^{26}\); N(R \(^{26}\)R \(^{26a}\)); OC(O)R \(^{26}\); N(R \(^{26}\)C(O)R \(^{26a}\); N(R \(^{26}\)S(O)R \(^{26}\)); N(R \(^{26}\)S(O)R \(^{26}\)); N(R \(^{26}\)C(O)N(R \(^{26a}\)R \(^{26b}\)); N(R \(^{26}\)C(O)OR \(^{26a}\); or OC(O)N(R \(^{26}\)R \(^{26a}\));

R\(^{26}\), R\(^{26a}\), R\(^{26b}\) are independently selected from the group consisting of H; and Ci\(_6\) alkyl, wherein Ci\(_6\) alkyl is optionally substituted with one or more halogen, which are the same or different;

T\(^2\) is C\(_{3-7}\) cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl, wherein T\(^2\) is optionally substituted with one or more R\(^{27}\);

R\(^{27}\) is halogen; CN; C(O)OR \(^{28}\); OR \(^{28}\); oxo (=O), where the ring is at least partially saturated; C(O)R \(^{28}\); C(O)N(R \(^{28}\)R \(^{28a}\)); S(O)\(_2\)N(R \(^{28}\)R \(^{28a}\)); S(O)N(R \(^{28}\)R \(^{28a}\)); S(O)\(_2\)R \(^{28}\);
2. A compound of claim 1 of formula (Ia)

\[
\text{S(O)R}^{28}; \quad \text{N(R}^{28})\text{S(O)}_2\text{N(R}^{28a}\text{R}^{28b}); \quad \text{N(R}^{28})\text{S(O)N(R}^{28a}\text{R}^{28b}); \quad \text{SR}^{28}; \quad \text{N(R}^{28})\text{R}^{28a}; \\
\text{OC(O)R}^{28}; \quad \text{N(R}^{28})\text{C(O)R}^{28a}; \quad \text{N(R}^{28})\text{S(O)}_2\text{R}^{28a}; \quad \text{N(R}^{28})\text{S(O)R}^{28a}; \\
\text{N(R}^{28})\text{C(O)N(R}^{28a}\text{R}^{28b}); \quad \text{N(R}^{28})\text{C(O)OR}^{28a}; \quad \text{OC(O)NR}^{28a}; \quad \text{or C}^{6}_\text{alkyl, wherein} \\
\text{C}^{6}_\text{alkyl is optionally substituted with one or more halogen which are the same or} \\
different; \text{R}^{28}, \text{R}^{28a}, \text{R}^{28b} \text{are independently selected from the group consisting of H; and C}^{6}_\text{alkyl, wherein C}^{6}_\text{alkyl is optionally substituted with one or more halogen, which are} \\
\text{the same or different.}
\]

3. A compound of claim 1 of formula (Ib)

or a pharmaceutically acceptable salt, prodrug or metabolite thereof, wherein X^1, R^1, 
R^2, R^3, R^4, R^5 are defined as indicated in claim 1.
X_1, R_1, R_2, R_3, R_4 are defined as indicated in claim 1;

R^{5b} is R^{5a} and R^{5c} is R^5; or
optionally R^{5b}, R^{5c} are joined together with the nitrogen atom to which they are attached to form a 4 to 7 membered heterocycle; or a 7 to 11 membered heterobicycle, wherein the 4 to 7 membered heterocycle and the 7 to 11 membered heterobicycle are optionally substituted with one or more R^9, which are the same or different and defined as indicated in claim 1.

A compound of claim 3, wherein R^{5b}, R^{5c} are joined together with the nitrogen atom to which they are attached to form a 4 to 7 membered heterocycle, which is optionally substituted with one or more R^9, which are the same or different and defined as indicated in claim 1.

A compound of claim 4, wherein the 4 to 7 membered heterocycle is pyrrolidine; oxazolidine; piperidine; morpholine; or piperazine.

A compound according to any of claims 1 to 3, wherein R^{5a} is H; or methyl.

A compound of any of claims 1 to 6, wherein R^5 is H; or unsubstituted Ci_6 alkyl.

A compound of any of claims 1 to 7, wherein R^5 is Ci_6 alkyl, wherein Ci_6 alkyl is substituted with one or more R^6, which are the same or different;

R^6 is halogen; CN; C(O)OR; OR; C(O)R; C(O)N(R^7R^7a); S(O)_2N(R^7R^7a); S(O)N(R^7R^7a); S(O)_2R^7; S(O)R^7; N(R^7)S(O)_2N(R^7R^7b); SR^7; N(R^7R^7a); OC(O)R^7; N(R^7)C(O)R^7a; N(R^7)S(O)_2R^7a; N(R^7)S(O)R^7a; N(R^7)C(O)N(R^7aR^7b); N(R^7)C(O)OR^7a; or OC(O)N(R^7R^7a);

R^7, R^7a, R^7b are independently selected from the group consisting of H; and Ci_6 alkyl, wherein Ci_6 alkyl is optionally substituted with one or more R^8, which are the same or different;
R^8 is halogen; CN; C(O)OR; OR; C(O)R; C(O)N(R^13R^13a); S(O)₂N(R^13R^13a); S(O)N(R^13R^13a); S(O)₂R^13; S(O)R^13; N(R^13)S(O)₂N(R^13aR^13b); SR; N(R^13)S(O)R^13a; OC(O)R; N(R^13)C(O)R; N(R^13)S(O)₂R; N(R^13)S(O)R; N(R^13)C(O)N(R^13aR^13b); N(R^13)C(O)OR; or OC(O)N(R^13R^13a);  

R^13, R^13a, R^13b are independently selected from the group consisting of H; and C₆₅ alkyl, wherein C₆ alkyl is optionally substituted with one or more R^14, which are the same or different;  

R^14 is halogen; CN; C(O)OR; OR; C(O)R; C(O)N(R^15R^15a); S(O)₂N(R^15R^15a); S(O)N(R^15R^15a); S(O)₂R^15; S(O)R^15; N(R^15)S(O)₂N(R^15aR^15b); SR; N(R^15)S(O)R^15a; OC(O)R; N(R^15)C(O)R; N(R^15)S(O)₂R; N(R^15)S(O)R^15a; N(R^15)C(O)N(R^15aR^15b); N(R^15aC(O)OR; or OC(O)N(R^15R^15a);  

R^15; R^15a; R^15b are independently selected from the group consisting of H; C₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different.  

A compound of claim 8, wherein R^6 is halogen; CN; C(O)OR; OR; C(O)R; C(O)N(R^7R^7a); S(O)₂N(R^7R^7a); S(O)N(R^7R^7a); S(O)₂R; S(O)R; N(R^7)S(O)₂N(R^7aR^7b); SR; N(R^7)S(O)R; OC(O)R; N(R^7)C(O)R; N(R^7)S(O)₂R; N(R^7)S(O)R^7a; N(R^7)S(O)R^7b; N(R^7)C(O)N(R^7aR^7b); N(R^7)C(O)OR; or OC(O)N(R^7R^7a);  

R^7, R^7a, R^7b are independently selected from the group consisting of H; and C₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different.  

A compound of claim 8, wherein R^6 is N(R^7R^7a); or C(O)N(R^7R^7a), and wherein R^7, R^7a are independently selected from the group consisting of H; and C₆ alkyl, wherein C₆ alkyl is optionally substituted with one or more halogen, which are the same or different.  

A compound of any of claims 1 to 3 or 6, wherein R^5 is T, wherein T is optionally substituted with one or more R^9 and wherein R^9 is defined as indicated in claim 1.
12. A compound of any of claims 1 to 3 or 6, wherein \( R^5 \) is \( C_i_6 \) alkyl, wherein \( C_i_6 \) alkyl is substituted with one or more \( R^6 \), which are the same or different;

\[
\begin{align*}
R^6 \text{ is halogen; } & \text{CN; } C(O)OR \; 7; \; OR^7; \; C(O)R \; 7; \; C(O)N(R \; 7R^{7a}); \; S(O)_2N(R \; 7R^{7a}); \\
& S(O)N(R \; 7R^{7a}); \; S(O)_2R^7; \; S(O)R^7; \; N(R \; 7)S(O) \; 2N(R \; 7aR^{7b}); \; SR^7; \; N(R \; 7R^{7a}); \; OC(O)R \; 7; \\
& N(R \; 7)C(O)R \; 7a; \; N(R \; 7)S(O) \; 2R^{7a}; \; N(R \; 7)S(O)R \; 7a; \; N(R \; 7)C(O)N(R \; 7aR^{7b}); \; N(R \; 7)C(O)OR \; 7a; \\
& OC(O)N(R \; 7R^{7a}); \; \text{or } T; \\
\end{align*}
\]

10. \( R^7, R^{7a}, R^{7b} \) are independently selected from the group consisting of \( H; T; \) and \( C_i_6 \) alkyl, wherein \( C_i_6 \) alkyl is optionally substituted with one or more \( R^8 \), which are the same or different;

\[
\begin{align*}
T \text{ is } C3-7 \text{ cycloalkyl; } & \text{4 to 7 membered heterocyclyl; } \text{7 to 11 membered heterobicyclyl; } \\
& \text{phenyl; naphthyl; indenyl; or indanyl, wherein } T \text{ is optionally substituted with one or more } R^9, \text{which are the same or different;} \\
\end{align*}
\]

\[
\begin{align*}
R^9 \text{ is } T^1; \text{halogen; } C(N)OR \; 10; \; OR^10; \; \text{oxo } (=0), \text{ where the ring is at least partially saturated;} \\
& C(O)R \; 10; \; C(O)N(R \; 10R^{10a}); \; S(O)_2N(R \; 10R^{10a}); \; S(O)N(R \; 10R^{10a}); \; S(O)_2R^10; \\
& S(O)R \; 10; \; N(R \; 10)S(O) \; 2N(R \; 10aR^{10b}); \; SR \; 10; \; N(R \; 10R^{10a}); \; OC(O)OR \; 10; \; N(R \; 10)C(O)R \; 10a; \\
& N(R \; 10)S(O) \; 2R^{10a}; \; N(R \; 10)S(O)R \; 10a; \; N(R \; 10)C(O)N(R \; 10aR^{10b}); \; N(R \; 10)C(O)OR \; 10a; \\
& OC(O)N(R \; 10R^{10a}); \; C_i_6 \text{ alkyl, wherein } C_i_6 \text{ alkyl is optionally substituted with one or more } R^{11}, \text{which are the same or different;} \\
\end{align*}
\]

25. \( R \; 10, R^{10a}, R^{10b} \) are independently selected from the group consisting of \( H; T \; 1; \) and \( C_i_6 \) alkyl, wherein \( C_i_6 \) alkyl is optionally substituted with one or more \( R^{12} \), which are the same or different;

\[
\begin{align*}
R^8, R^{11} \text{ are independently selected from the group consisting of halogen; } CN; \\
& C(O)OR \; 13; \; OR^13; \; C(O)R \; 13; \; C(O)N(R \; 13R^{13a}); \; S(O)_2N(R \; 13R^{13a}); \; S(O)N(R \; 13R^{13a}); \\
& S(O)_2R^13; \; S(O)R^13; \; N(R \; 13)S(O) \; 2N(R \; 13aR^{13b}); \; SR \; 13; \; N(R \; 13R^{13a}); \; OC(O)R \; 13; \\
& N(R \; 13)C(O)R \; 13a; \; N(R \; 13)S(O) \; 2R^{13a}; \; N(R \; 13)S(O)R \; 13a; \; N(R \; 13)C(O)N(R \; 13aR^{13b}); \\
& N(R \; 13)C(O)OR \; 13a; \; OC(O)N(R \; 13R^{13a}); \; \text{and } T; \\
\end{align*}
\]
R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H; T^{1}; and C_{i6} alkyl, wherein C_{i6} alkyl is optionally substituted with one or more R^{14}, which are the same or different;

R^{12}, 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)_{2}N(R^{15}R^{15a}); S(O)N(R^{15}R^{15a}); S(O)_{2}R^{15}; S(O)R^{15}; N(R^{15})S(O)_{2}N(R^{15}R^{15b}); S(R^{15}); N(R^{15}R^{15a}); OC(O)R^{15}; N(R^{15})C(O)R^{15a}; N(R^{15})S(O)_{2}R^{15a}; N(R^{15})S(O)R^{15a}; N(R^{15})C(O)N(R^{15}R^{15a}); N(R^{15})C(O)OR^{15a}; and OC(O)N(R^{15}R^{15a});

T^{1} is C_{3-7} cycloalkyl; 4 to 7 membered heterocyclyl; 7 to 11 membered heterobicyclyl; phenyl; naphthyl; indenyl; or indanyl; wherein T^{1} is optionally substituted with one or more R^{16}, which are the same or different;

R^{16} is halogen; CN; C(O)OR^{17}; OR^{17}; oxo (=O), where the ring is at least partially saturated; C(O)R^{17}; C(O)N(R^{17}R^{17a}); S(O)_{2}N(R^{17}R^{17a}); S(O)N(R^{17}R^{17a}); S(O)_{2}R^{17}; S(O)R^{17}; N(R^{17})S(O)_{2}N(R^{17}R^{17b}); S(R^{17}); N(R^{17}R^{17a}); OC(O)R^{17}; N(R^{17})C(O)R^{17a}; N(R^{17})S(O)_{2}R^{17a}; N(R^{17})S(O)R^{17a}; N(R^{17})C(O)N(R^{17}R^{17b}); N(R^{17})C(O)OR^{17a}; OC(O)N(R^{17}R^{17a}); C_{i6} alkyl, wherein C_{i6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{15}; R^{15a}; R^{15b}; R^{17}; R^{17a}; R^{17b} are independently selected from the group consisting of H; C_{i6} alkyl, wherein C_{i6} alkyl is optionally substituted with one or more halogen, which are the same or different;

provided that at least one of the following prerequisites is fulfilled:

R^{6} is T;
at least one of R^{7}, R^{7a}, R^{7b} is T;
R^{8} is T^{1};
at least one of R^{13}, R^{13a}, R^{13b} is T^{1}.

A compound of claim 12, wherein R^{5} is of formula (CH_{2})_{n}X^{n}-T, wherein n is 1, 2, 3, or 4;
X₀ is a covalent chemical single bond; C(O); C(O)N(R⁷a); N(R⁷a); or N(R⁷a)C(O); R⁷a, T are defined as indicated in claim 1.

14. A compound of claim 13, wherein X₀ is a covalent chemical single bond; or C(O).

15. A compound of any of claims 1 to 3 and 6 to 14, wherein T is 4 to 7 membered heterocyclyl; or phenyl, wherein T is optionally substituted with one or more R⁹, which are the same or different.

16. A compound of claim 15, wherein T is pyrrolyl; furyl; thiophenyl; pyrazolyl; imidazolyl; oxazolyl; thiazolyl; triazolyl; oxadiazolyl; thiadiazolyl; tetrazolyl; phenyl; pyridyl; pyrimidyl; pyrazinyl; pyridazinyl; pyrrolidinyl; tetrahydro furyl; piperidyl; piperazinyl; or morpholinyl.

17. A compound of any of claims 1 to 16, wherein R⁹ is T¹; Ci₆ alkyl; or oxo, where the ring is at least partially saturated.

18. A compound of any of claims 1 to 17, wherein T¹ is cyclopropyl.

19. A compound of any of claims 1 to 18, wherein R¹, R², R³ are H.

20. A compound of any of claims 1 to 19, wherein R⁴ is R¹⁹.

21. A compound of any of claims 1 to 20, wherein R¹⁹ is S(O)₂N(R²²R²¹).

22. A compound of any of claims 1 to 21, wherein R²² is H; or CH₃.

23. A compound of any of claims 1 to 22, wherein R²¹ is Ci₆ alkyl.

24. A compound of any of claims 1 to 23, wherein R⁴ is R²⁰.

25. A compound of any of claims 1 to 24, wherein X¹ is N.

26. A compound of any of claims 1 to 25, wherein X¹ is C(R⁴α).
27. A compound of claim 26, wherein $R^4_a$ is H.

28. A compound according to claim 1 selected from the group consisting of

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

- N-tert-butyl-5-(2-(3-(2-(3-(2-(5-cyclopropyl-l,3,4-oxadiazol-2-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-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-7-yl)pyridine-3-sulfonamide;

- N-tert-butyl-5-(2-(3-(2-morpholino-2-oxoethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide;

- N-tert-butyl-5-(2-(3-(2-(lH-1,2,4-triazol-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide;

- 5-(2-(3-(2-(lH-1,2,4-triazol-1-yl)ethyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-N-tert-butylpyridine-3-sulfonamide;

- N-tert-butyl-5-(2-(3-((5-methyl-l,3,4-oxadiazol-2-yl)methyl)ureido)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridine-3-sulfonamide;

- N-(7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)acetamide;

- 3-(dimethylamino)-3-oxopropyl 7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-ylcarbamate;

- 2-(lH-tetrazol-5-yl)ethyl 7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-ylcarbamate; and
2-(4-methylpiperazin-1-yl)ethyl 7-(5-(N-tert-butylsulfamoyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-ylcarbamate.

29. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 28 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

30. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 28 for use as a medicament.

31. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 28 for use in a method of treating or preventing diseases and disorders associated with PI3K.

32. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 28 for use in a method of treating or preventing immunological, inflammatory, autoimmune, or allergic disorders.

33. A compound or a pharmaceutically acceptable salt thereof of any of claims 1 to 28 for use in a method of treating or preventing cancer, cardiovascular disorders, metabolic diseases, neurodegenerative disorders, or infectious diseases.

34. A method for the preparation of a compound according to formula (I), wherein X is O, 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), wherein X is O.
### INTERNATIONAL SEARCH REPORT

**International application No:** PCT/EP2009/065292

**A. CLASSIFICATION OF SUBJECT MATTER**

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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)

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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

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>WO 2006/038116 A (WARNER LAMBERT CO [US]; BUTLER DAVID CHARLES DONNELL [US]; CHEN HUIFEN) 13 April 2006 (2006-04-13) page 43 - page 54; claims 1,11,12; table 1 page 4, line 7 - line 12</td>
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<td><strong>A</strong></td>
<td>WO 2008/025821 A (CELLZOME UK LTD [GB]; WILSON FRANCIS [GB]; RAMSDEN NIGEL [GB]; BELL KA) 6 March 2008 (2008-03-06) compounds disclosed on pages 42-81; abstract</td>
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<td>UO 2007/095588 A (NOVARTIS AG [CH]; NI ZHI-JIE [US]; PECCHI SABINA [US]; BURGER MATTHEW) 23 August 2007 (2007-08-23) claims 1,56-61; examples 3-10; table 3</td>
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### D

Further documents are listed in the continuation of Box C. See patent family annex.

- **X** 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)
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- **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 of the invention
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- **B** document member of the same patent family

**Date of the actual completion of the international search:** 10 February 2010

**Date of mailing of the international search report:** 17/02/2010

**Name and mailing address of the ISA/**

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**Authorized officer:**

Lange, Tim
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