The invention is directed to certain novel compounds. Specifically, the invention is directed to compounds of formula (I) and salts thereof. The compounds of the invention are inhibitors of PI3-kinase activity.

Declarations under Rule 4.17:
— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(i))
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INDAZOLE DERIVATIVES AS PI3 - KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention is directed to certain novel compounds which are inhibitors of the activity or function of the phosphoinositide 3O II kinase family (hereinafter PI3-kinases), processes for their preparation, pharmaceutical compositions comprising the compounds, and the use of the compounds or the compositions in the treatment of various disorders. More specifically, the compounds of the invention are inhibitors of the activity or function of, for example, PI3Kα, PI3Kα, PI3Kβ and/or PI3Kγ. Compounds which are inhibitors of the activity or function of PI3-kinases may be useful in the treatment of disorders such as respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD); allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; cystic fibrosis; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trama), trigeminal neuralgia and central pain.

BACKGROUND OF THE INVENTION

Cellular membranes represent a large store of second messengers that can be enlisted in a variety of signal transduction pathways. In relation to function and regulation of effector enzymes in phospholipids signaling pathways, class I PI3- kinases (e.g. PI3Kdelta) generate second messengers from the membrane phospholipid pools. Class I PI3Ks convert the membrane phospholipid PI(4,5)P2 into PI(3,4,5)P3, which functions as a second messenger. PI and PI(4)P are also substrates of PI3K and can be phosphorylated and converted into PI3P and PI(3,4)P2, respectively. In addition, these phosphoinositides can be converted into other phosphoinositides by 5'-specific and 3'-specific phosphatases. Thus, PI3K enzymatic activity results either directly or indirectly in the generation of two 3'-phosphoinositide subtypes which function as second messengers in intracellular signal transduction pathways (Trends Biochem. Sci. 22(7) p. 267-72 (1997) by Vanhaesebroeck et al.; Chem. Rev. 101 (8) p. 2365-80 (2001) by Leslie et al.; Annu. Rev. Cell Dev. Biol. 17 p. 615-75 (2001) by Katso et al.; and Cell. Mol. Life Sci. 59(5) p. 761-79 (2002) by Toker). To date, eight mammalian PI3Ks have been identified, divided into three main classes (I, II, and III) on the basis of sequence homology, structure,
binding partners, mode of activation, and substrate preference. In vitro, class I PI3Ks can phosphorylate phosphatidylinositol (PI), phosphatidylinositol-4-phosphate (PI4P), and phosphatidylinositol-4,5-bisphosphate (PI(4,5)P₂) to produce phosphatidylinositol-3-phosphate (PI3P), phosphatidylinositol-3,4-bisphosphate (PI(3,4)P₂), and phosphatidylinositol-3,4,5-trisphosphate (PI(3,4,5)P₃), respectively. Class II PI3Ks can phosphorylate PI and PI4P. Class III PI3Ks can only phosphorylate PI (Vanhaesebroeck et al. (1997), above; Vanhaesebroeck et al., Exp. Cell Res. 253(1) p. 239-54 (1999); and Leslie et al. (2001), above).

Class I PI3K is a heterodimer consisting of a ρ₁₁₀ catalytic subunit and a regulatory subunit, and the family is further divided into class Ia and class Ib enzymes on the basis of regulatory partners and mechanism of regulation. Class Ia enzymes consist of three distinct catalytic subunits (ρ₁₁₀α, ρ₁₁₀β, and ρ₁₁₀δ) that dimerise with five distinct regulatory subunits (p85a, p55a, p50a, ρ₈₅β, and ρ₅₅γ), with all catalytic subunits being able to interact with all regulatory subunits to form a variety of heterodimers. Class Ia PI3K are generally activated in response to growth factor-stimulation of receptor tyrosine kinases, via interaction of the regulatory subunit SH2 domains with specific phosphotyrosine residues of the activated receptor or adaptor proteins such as IRS-1. Small GTPases (ras as an example) are also involved in the activation of PI3K in conjunction with receptor tyrosine kinase activation. Both ρ₁₁₀α and ρ₁₁₀β are constitutively expressed in all cell types, whereas ρ₁₁₀δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a ρ₁₁₀γ catalytic subunit that interacts with a ρ₁₀₁ regulatory subunit. Furthermore, the Class Ib enzyme is activated in response to G-protein coupled receptor (GPCR) systems and its expression appears to be limited to leukocytes.

Scheme A: Conversion of PI(4,5)P₂ to PI(3,4,5)P₃
As illustrated in Scheme A above, phosphoinositide 3-kinases (PI3Ks) phosphorylate the hydroxyl of the third carbon of the inositol ring. The phosphorylation of phosphoinositides to generate PtdIns(3,4,5)P_3, PtdIns(3,4)P_2 and PtdIns(3)P, produces second messengers for a variety of signal transduction pathways, including those essential to cell proliferation, cell differentiation, cell growth, cell size, cell survival, apoptosis, adhesion, cell motility, cell migration, chemotaxis, invasion, cytoskeletal rearrangement, cell shape changes, vesicle trafficking and metabolic pathway (Katso et al. (2001), above; and Mol. Med. Today 6(9) p. 347-57 (2000) by Stein et al.).

The activity of PI3-kinases responsible for generating these phosphorylated signalling products was originally identified as being associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylate phosphatidylinositol (PI) and its phosphorylated derivatives at the 3'-hydroxyl of the inositol ring (Panayotou et al. Trends Cell Biol. 2 p. 358-60 (1992)). However, more recent biochemical studies have revealed that class I PI3-kinases (e.g. class IA isoform PI3K5) are dual-specific kinase enzymes,
meaning they display both lipid kinase (phosphorylation of phosphoinositides) as well as protein kinase activity, and are capable of phosphorylation of other protein as substrates, including auto-phosphorylation as an intramolecular regulatory mechanism (EMBO J. 18(5) p. 1292-302 (1999) by Vanhaesebroeck et al.). Cellular processes in which PI3Ks play an essential role include suppression of apoptosis, reorganization of the actin skeleton, cardiac myocyte growth, glycogen synthase stimulation by insulin, TNFα-mediated neutrophil priming and superoxide generation, and leukocyte migration and adhesion to endothelial cells.

PI3-kinase activation is believed to be involved in a wide range of cellular responses including cell growth, differentiation, and apoptosis (Parker, Current Biology, 5(6) p. 577-79 (1995); and Yao et al. Science 267(5206) p. 2003-06 (1995)). PI3-kinase appears to be involved in a number of aspects of leukocyte activation. A p85-associated PI3-kinase has been shown to physically associate with the cytoplasmic domain of CD28, which is an important costimulatory molecule for the activation of T-cells in response to antigen (Pages et al. Nature 369 p. 327-29 (1994); and Rudd, Immunity 4 p. 527-34 (1996)). Activation of T cells through CD28 lowers the threshold for activation by antigen and increases the magnitude and duration of the proliferative response. These effects are linked to increases in the transcription of a number of genes including interleukin-2 (IL2), an important T cell growth factor (Fraser et al. Science 251 (4991) p. 313-16 (1991)).

P13Kγ has been identified as a mediator of G beta-gamma-dependent regulation of JNK activity, and G beta-gamma are subunits of heterotrimeric G proteins (Lopez-llasaca et al. J. Biol. Chem. 273(5) p. 2505-8 (1998)). Recently, (Laffargue et al. Immunity 16(3) p. 441-51 (2002)) it has been described that P13Kγ relays inflammatory signals through various G(i)-coupled receptors and is central to mast cell function, stimuli in the context of leukocytes, and immunology including cytokines, chemokines, adenosines, antibodies, integrins, aggregation factors, growth factors, viruses or hormones for example (J. Cell Sci. 114 (Pt 16) p. 2903-10 (2001) by Lawlor et al.; Laffargue et al. (2002), above; and Curr. Opinion Cell Biol. 14(2) p. 203-13 (2002) by Stephens et al.).

Specific inhibitors against individual members of a family of enzymes provide invaluable tools for deciphering functions of each enzyme. Two compounds, LY294002 and wortmannin (hereinafter), have been widely used as PI3-kinase inhibitors. These compounds are non-specific PI3K inhibitors, as they do not distinguish among the four members of Class I PI3-kinases. For example, the IC50 values of wortmannin against each of the various Class I PI3-kinases are in the range of 1-10 nM. Similarly, the IC50
values for LY294002 against each of these PI3-kinases is about 15-20 µM (Fruman *et al.* Ann. Rev. Biochem. 67 p. 481-507 (1998)), also 5-10 microM on CK2 protein kinase and some inhibitory activity on phospholipases. Wortmannin is a fungal metabolite which irreversibly inhibits PI3K activity by binding covalently to the catalytic domain of this enzyme. Inhibition of PI3K activity by wortmannin eliminates subsequent cellular response to the extracellular factor. For example, neutrophils respond to the chemokine fMet-Leu-Phe (fMLP) by stimulating PI3K and synthesizing PtdIns (3, 4, 5)P$_3$. This synthesis correlates with activation of the respiratory burst involved in neutrophil destruction of invading microorganisms. Treatment of neutrophils with wortmannin prevents the fMLP-induced respiratory burst response (Thelen *et al.* Proc. Natl. Acad. Sci. USA 91 p. 4960-64 (1994)). Indeed, these experiments with wortmannin, as well as other experimental evidence, show that PI3K activity in cells of hematopoietic lineage, particularly neutrophils, monocytes, and other types of leukocytes, is involved in many of the non-memory immune response associated with acute and chronic inflammation.

Based on studies using wortmannin, there is evidence that PI3-kinase function is also required for some aspects of leukocyte signaling through G-protein coupled receptors (Thelen *et al.* (1994), above). Moreover, it has been shown that wortmannin and LY294002 block neutrophil migration and superoxide release.

It is now well understood that deregulation of oncogenes and tumour suppressor genes contributes to the formation of malignant tumours, for example by way of increased cell growth and proliferation or increased cell survival. It is also now known that signaling pathways mediated by the PI3K family have a central role in a number of cell processes including proliferation and survival, and deregulation of these pathways is a causative

In B and T cells PI3Ks have an important role through activation of the Tec family of protein tyrosine kinases which include Bruton's tyrosine kinase (BTK) in B cells and Interleukin-2-inducible T-cell kinase (ITK) in T cells. Upon PI3K activation, BTK or ITK translocate to the plasma membrane where they are subsequently phosphorylated by Src kinases. One of the major targets of activated ITK is phospholipase C-gamma (PLCγ1), which hydrolyses PtdIns(4,5)P2 into Ins(3,4,5)P3 and initiates an intracellular increase in calcium levels and diacylglycerol (DAG) which can activate Protein Kinases C in activated T cells.

Unlike the Class IA 110α and 110β, 110δ is expressed in a tissue restricted fashion. Its high expression level in lymphocytes and lymphoid tissues suggests a role in PI3K-mediated signalling in the immune system. The 1105 kinase dead knock-in mice are also viable and their phenotype is restricted to defects in immune signalling (Okkenhaug et al. Science (2002) 297 p. 1031-4). These transgenic mice have offered insight into the function of PI3Kδ in B-cell and T-cell signalling. In particular, 110δ is required for PtdIns(3,4,5)P3 formation downstream of CD28 and/or T cell Receptor (TCR) signalling. A key effect of PI3K signalling downstream of TCR is the activation of Akt, which phosphorylates anti-apoptotic factors as well as various transcription factors for cytokine production. As a consequence, T cells with inactive 110δ have defects in proliferation and Th1 and Th2 cytokine secretion. Activation of T cells through CD28 lowers the threshold for TCR activation by antigen and increases the magnitude and duration of the proliferative response. These effects are mediated by the PI3Kδ-dependent increase in the transcription of a number of genes including IL2, an important T cell growth factor.

Therefore, PI3K inhibitors are anticipated to provide therapeutic benefit via its role in modulating T-cell mediated inflammatory responses associated to respiratory diseases such as asthma, COPD and cystic fibrosis. In addition, there is indication that T-cell
directed therapies may provide corticosteroid sparing properties (Alexander et al. Lancet (1992) 339 p. 324-8) suggesting that it may provide a useful therapy either as a standalone or in combination with inhaled or oral glucocorticosteroids in respiratory diseases. A PI3K inhibitor might also be used alongside other conventional therapies such as a long acting beta-agonist (LABA) in asthma.


The role of PI3K5 in B cell proliferation, antibody secretion, B-cell antigen and IL-4 receptor signalling, B-cell antigen presenting function is also well established Okkenhaug et al. (2002), above; Al-Alwan et al. J. Immunol. (2007) 178(4) p. 2328-35; and Bilancio et al. Blood (2006) 107(2) p. 642-50 and indicates a role in autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus. Therefore PI3K inhibitors may also be of benefit for these indications.

In addition, there is also good evidence that class Ia PI3K enzymes also contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, Nature Reviews Cancer (2002) 2(7) p. 489-501). For example, inhibition of PI3K5 may have a therapeutic role for the treatment of malignant haematological disorders such as acute myeloid leukaemia (Billottet et al. Oncogene (2006) 25(50) p. 6648-59). Moreover, activating mutations within p110a (PIK3CA gene) have been associated with various other tumors such as those of the colon and of the breast and lung (Samuels et al. Science (2004) 304(5670) p. 554).

It has also been shown that PI3K is involved in the establishment of central sensitization in painful inflammatory conditions (Pezet et al. The J. of Neuroscience (2008) 28 (16) p. 4261-4270).

Attempts have been made to prepare compounds which inhibit PI3-kinase activity and a number of such compounds have been disclosed in the art. However, in view of the number of pathological responses which are mediated by PI3-kinases, there remains a continuing need for inhibitors of PI3-kinase which can be used in the treatment of a variety of conditions.

The present inventors have discovered novel compounds which are inhibitors of PI3-kinase activity. Compounds which are PI3-kinase inhibitors may be useful in the treatment of disorders associated with inappropriate PI3-kinase activity, for example in the treatment and prevention of disorders mediated by PI3-kinase mechanisms. Such disorders include respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD); allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; cystic fibrosis; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trama), trigeminal neuralgia and central pain.

In one embodiment, compounds of the invention may show selectivity for PI3-kinases over other kinases.
In one embodiment, compounds of the invention may show selectivity for PI3K5 over other PI3-kinases.

**SUMMARY OF THE INVENTION**

The invention is directed to certain novel compounds. Specifically, the invention is directed to compounds of formula (I)

![Chemical Structure](image)

wherein $R^1$ and $R^2$ are as defined below, and salts thereof.

The compounds are inhibitors of PI3-kinase activity. Compounds which are PI3-kinase inhibitors may be useful in the treatment of disorders associated with inappropriate PI3-kinase activity, such as asthma and chronic obstructive pulmonary disease (COPD). Accordingly, the invention is further directed to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof. The invention is still further directed to methods of inhibiting PI3-kinase activity and treatment of disorders associated therewith using a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof. The invention is yet further directed towards processes for the preparation for the compounds of the invention.

**DETAILED DESCRIPTION OF THE INVENTION**

In one embodiment, the invention is directed to compounds of formula (I)

![Chemical Structure](image)

wherein
R\(^1\) is phenyl optionally substituted by -OR\(^3\), -CH\(_2\)OR\(^4\) or -CH\(_2\)CN; 5-membered heteroaryl wherein the 5-membered heteroaryl contains one or two heteroatoms independently selected from oxygen, nitrogen and sulphur and is optionally substituted by -CH\(_2\)phenyl; pyridinyl wherein the pyridinyl is substituted by one substituent selected from -NH\(_2\), -CH\(_2\)OR\(^5\), -CO\(_2\)R\(^6\), -CONR\(^7\)R\(^8\), -NHCO\(_2\)R\(^9\), -XS\(_2\)R\(^{10}\), -S\(_{\text{O2}}\)R\(^{11}\)R\(^{12}\) and -NHS\(_{\text{O2}}\)R\(^{13}\), and is optionally substituted by a second substituent selected from halo and -OR\(^{14}\); 9- or 10-membered bicyclic heteroaryl wherein the 9- or 10-membered bicyclic heteroaryl contains from one to three heteroatoms independently selected from oxygen and nitrogen and is substituted by -S\(_{\text{O2}}\)R\(^{15}\); or phenyl fused to pyrrolidinyl wherein the pyrrolidinyl is substituted by -COR\(^{16}\);

R\(^2\) is 5-membered heteroaryl wherein the 5-membered heteroaryl contains one or two heteroatoms independently selected from oxygen, nitrogen and sulphur and is optionally substituted by C\(_{1-6}\)alkyl;

R\(^3\) is C\(_{1-6}\)alkyl substituted by -CO\(_2\)R\(^{17}\);

R\(^4\), R\(^5\), R\(^6\), R\(^{14}\) and R\(^{17}\) are each independently hydrogen or C\(_{1-6}\)alkyl;

R\(^7\) and R\(^8\) are each hydrogen, or R\(^7\) and R\(^8\), together with the nitrogen atom to which they are attached, are linked to form a 6-membered heterocyclyl optionally containing an oxygen atom;

R\(^9\) is C\(_{1-6}\)alkyl optionally substituted by phenyl;

R\(^{10}\) and R\(^{16}\) are each independently C\(_{1-6}\)alkyl or phenyl;

R\(^{11}\) and R\(^{12}\), together with the nitrogen atom to which they are attached, are linked to form a 6-membered heterocyclyl optionally containing an oxygen atom;

R\(^{13}\) is phenyl substituted by -CF\(_3\) and halo;

R\(^{16}\) is C\(_{1-6}\)alkyl; and

X is -CH\(_2\), -CHF- or -N(CH\(_3\))_2_;
and salts thereof (hereinafter "compounds of the invention").

In one embodiment, R¹ is phenyl substituted by -OR³ or -CH₂OR⁴; pyridinyl wherein the pyridinyl is substituted by one substituent selected from -NH₂, -CH₂OR⁵ and -NHSO₂R¹³, and is optionally substituted by a second substituent selected from halo and -OR¹⁴; or 9- or 10-membered bicyclic heteroaryl wherein the 9- or 10-membered bicyclic heteroaryl contains from one to three heteroatoms independently selected from oxygen and nitrogen and is substituted by -SO₂R¹⁵. In a further embodiment, R¹ is pyridinyl wherein the pyridinyl is substituted by one substituent selected from -NH₂ and -NHSO₂R¹³, and is optionally substituted by a second substituent which is -OR¹⁴; or 9-membered bicyclic heteroaryl wherein the 9-membered bicyclic heteroaryl contains three nitrogen atoms and is substituted by -SO₂R¹⁵.

In one embodiment, R² is 5-membered heteroaryl wherein the 5-membered heteroaryl contains one or two heteroatoms independently selected from nitrogen and sulphur and is optionally substituted by C₄₋₆alkyl. In a further embodiment, R² is thiazolyl optionally substituted by C₄₋₆alkyl.

In one embodiment, R³ is methyl substituted by -C₀₂R¹⁷;

In one embodiment, R⁴ is hydrogen.

In one embodiment, R⁵ is hydrogen.

In one embodiment, R⁶ is hydrogen.

In one embodiment, R⁷ and R⁸ are each hydrogen. In a further embodiment, R⁷ and R⁸, together with the nitrogen atom to which they are attached, are linked to form morpholinyl.

In one embodiment, R⁹ is methyl substituted by phenyl.

In one embodiment, R¹⁰ is phenyl.

In one embodiment, R¹¹ and R¹², together with the nitrogen atom to which they are attached, are linked to form morpholinyl.

In one embodiment, R¹³ is 4-chloro-3-(trifluoromethyl)phenyl.

In one embodiment, R¹⁴ is 4-chloro-3-(trifluoromethyl)phenyl.
In one embodiment, R\textsuperscript{14} is methyl.

In one embodiment, R\textsuperscript{15} is methyl.

5

In one embodiment, R\textsuperscript{16} is methyl.

In one embodiment, R\textsuperscript{17} is hydrogen.

10

In one embodiment, X is -N(CH\textsubscript{3})\textsuperscript{-}.

It is to be understood that the present invention covers all combinations of substituent groups described hereinabove.

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Compounds of the invention include the compounds of Examples 1 to 24 and salts thereof.

In one embodiment, the compound of the invention is:

/\V{-[6-[5-amino-6-(methyloxy)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1 ,3-thiazole-4-carboxamide; 20

5-(4-\{[2-methyl-1 ,3-thiazol-4-yl]carbonyl[amino]-1 H-indazol-6-yl]-3-pyridinecarboxylic acid; 2-methyl-N-(6-phenyl-1 H-indazol-4-yl)-1 ,3-thiazole-4-carboxamide; 25

N-[6-[3-(cyanomethyl)phenyl]-1 H-indazol-4-yl]-2-methyl-1 ,3-thiazole-4-carboxamide; \V{-[6-[3-(hydroxymethyl)phenyl]-1 H-indazol-4-yl]-2-methyl-1 ,3-thiazole-4-carboxamide;}

N-[6-[5-(hydroxymethyl)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1 ,3-thiazole-4-carboxamide; 30

\{[3-(4-\{[2-methyl-1 ,3-thiazol-4-yl]carbonyl[amino]-1 H-indazol-6-yl]phenyl\}oxy]acetic acid;}

N-[6-[5-amino-6-chloro-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1 ,3-thiazole-4-carboxamide; 35

N-[6-[5-chloro-5-(hydroxymethyl)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1 ,3-thiazole-4-carboxamide; N-(6-[6-chloro-5-[methyl(phenylsulfonyl)-amino]-3-pyridinyl]-1 H-indazol-4-yl)-2-methyl-1 ,3-thiazole-4-carboxamide;
2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)carbonyl]amino)-1 H-indazol-6-yl)-3-pyridinecarboxylic acid; 
5-[(2-methyl-1,3-thiazol-4-yl)carbonyl]amino)-1 H-indazol-6-yl)-3-pyridinecarboxamide; 
phenylmethyl [2-chloro-5-[(2-methyl-1,3-thiazol-4-yl)carbonyl]amino)-1 H-indazol-6-yl)-3-pyridinecarboxamide; 
/V-(6-[6-chloro-5-[fluoro(phenylsulfonyl)methyl]-3-pyridinyl]-1H-indazol-4-yl)-2-methyl-1,3-thiazole-4-carboxamide; 
2-methyl-N-[6-[3-(methylsulfonyl)phenyl]-1 H-pyrazolo[3,4-b]pyridin-5-yl]-1 H-indazol-4-yl)-1,3-thiazole-4-carboxamide; 
2-methyl-1/V-[6-[5-(4-morpholinylsulfonyl)-3-pyridinyl]-1 H-indazol-4-yl]-1,3-thiazole-4-carboxamide; 
2-methyl-N-[6-[5-(4-morpholinylcarbonyl)-3-pyridinyl]-1 H-indazol-4-yl]-1,3-thiazole-4-carboxamide; 
2-methyl-N-{6-[1-(phenylmethyl)-1 H-pyrazol-4-yl]-1 H-indazol-4-yl]-1,3-thiazole-4-carboxamide; 
\N-[6-(1-acetyl-2,3-dihydro-1 H-indol-4-yl)-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; 
/V-[6-[5-[[4-chloro-3-(trifluoromethyl)phenyl]sulfonyl]amino)-6-(methyloxy)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; or a salt thereof.

In a further embodiment, the compound of the invention is: 
/V-[6-[5-amino-6-(methyloxy)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; 
/V-[6-(5-amino-3-pyridinyl)-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; 
N-[6-[3-(hydroxymethyl)phenyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; 
N-[6-[5-(hydroxymethyl)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; 
{[3-(4-[[2-methyl-1,3-thiazol-4-yl]carbonyl]amino)-1 H-indazol-6-yl]phenyl}oxy)acetic acid; 
N-[6-(5-amino-6-chloro-3-pyridinyl)-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; 
2-methyl-N-[6-[3-(methylsulfonyl)phenyl]-1 H-pyrazolo[3,4-b]pyridin-5-yl]-1 H-indazol-4-yl)-1,3-thiazole-4-carboxamide; 
/V-[6-[5-[[4-chloro-3-(trifluoromethyl)phenyl]sulfonyl]amino)-6-(methyloxy)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide; or a salt thereof.
Terms and Definitions
"Alkyl" refers to a saturated hydrocarbon chain having the specified number of member atoms. For example, \( C_{1-6} \) alkyl refers to an alkyl group having from 1 to 6 member atoms. Alkyl groups may be optionally substituted with one or more substituents if so defined herein. Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl includes methyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, isobutyl, and t-butyl), pentyl (n-pentyl, isopentyl, and neopentyl), and hexyl.

"Enantiomerically enriched" refers to products whose enantiomeric excess is greater than zero. For example, enantiomerically enriched refers to products whose enantiomeric excess is greater than 50% ee, greater than 75% ee, and greater than 90% ee.

"Enantiomeric excess" or "ee" is the excess of one enantiomer over the other expressed as a percentage. As a result, since both enantiomers are present in equal amounts in a racemic mixture, the enantiomeric excess is zero (0% ee). However, if one enantiomer was enriched such that it constitutes 95% of the product, then the enantiomeric excess would be 90% ee (the amount of the enriched enantiomer, 95%, minus the amount of the other enantiomer, 5%).

"Enantiomerically pure" refers to products whose enantiomeric excess is 99% ee or greater.

"Half-life" (or "half-lives") refers to the time required for half of a quantity of a substance to be converted to another chemically distinct species in vitro or in vivo.

"Halo" refers to the halogen radical fluoro, chloro, bromo, or iodo.

"Heteroaryl", unless otherwise defined, refers to an aromatic ring or rings containing from 1 to 3 heteroatoms, for example 1 or 2 heteroatoms, as member atoms in the ring or rings. Heteroaryl groups containing more than one heteroatom may contain different heteroatoms. Heteroaryl groups may be optionally substituted with one or more substituents if so defined herein. The heteroaryl groups herein are monocyclic ring systems or are fused bicyclic ring systems. Monocyclic heteroaryl rings have 5 member atoms. Bicyclic heteroaryl rings have 9 or 10 member atoms. Monocyclic heteroaryl includes pyrrolyl, furanyl, thieryl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl and isothiazolyl. In one embodiment, monocyclic heteroaryl is pyrazolyl. Bicyclic heteroaryl
includes indolyl, isoindolyl, indoliziny, benzofuranyl, isobenzofuranyl, indazolyl, purinyl, benzimidazolyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrrolopyrimidinyl, quinolyl, isoquinoliny, quinoxaliny, quinazoliny, cinnoliny, benzopyranyl, benzoazolyl, furopyridinyl and naphthridinyl. In one embodiment, bicyclic heteroaryl is pyrazolopyridinyl.

"Heteroatom" refers to a nitrogen, sulphur, or oxygen atom.

"Heterocycl" unless otherwise defined, refers to a saturated or unsaturated ring containing 1 or 2 heteroatoms as member atoms in the ring. However, heterocycl rings are not aromatic. In certain embodiments, heterocycl is saturated. In other embodiments, heterocycl is unsaturated but not aromatic. Heterocycl groups containing more than one heteroatom may contain different heteroatoms. The heterocycl groups herein are monocyclic ring systems having 6 member atoms. Heterocycl includes piperidinyl and morpholiny.

"Member atoms" refers to the atom or atoms that form a chain or ring. Where more than one member atom is present in a chain and within a ring, each member atom is covalently bound to an adjacent member atom in the chain or ring. Atoms that make up a substituent group on a chain or ring are not member atoms in the chain or ring.

"Optionally substituted" indicates that a group, such as heteroaryl, may be unsubstituted or substituted with one or more substituents if so defined herein.

"Substituted" in reference to a group indicates that a hydrogen atom attached to a member atom within a group is replaced. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as by rearrangement, cyclization, or elimination). In certain embodiments, a single atom may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

"Pharmaceutically acceptable" refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity,
irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

aq       Aqueous
DCM      Dichloromethane
DIPEA    Diisopropylethylamine
DMF      N,N,N,N',N'-Dimethylformamide
DMSO     Dimethylsulfoxide
Et₃N     Triethylamine
g        Grams
HATU     0-(7-Azabenzotriazol-1 -yl)-/V,/,V',/,V'-tetramethyluronium hexafluorophosphate
HCl      Hydrogen Chloride
HPLC     High performance liquid chromatography
IPA      Isopropanol
LCMS     Liquid chromatography/mass spectroscopy
M        Molar
MDAP     Mass Directed Automated Preparative HPLC
MeOH     Methanol
MeCN     Acetonitrile
mg       Milligrams
min      Minutes
ml       Millilitres
mmol     Millimoles
mp       Melting point
Pd(dppf)Cl₂ [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)
Pd(dppf)Cl₂·CH₂Cl₂ [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) dichloromethane adduct
Pd(PPh₃)₄ Tetrakis(triphenylphosphine)palladium(0)
Rₜ Retention time
5 RT room temperature
s Seconds
SCX Strong cation exchange
10 SPE Solid Phase Extraction
THF Tetrahydrofuran
TFA Trifluoroacetic acid

All references to brine are to a saturated aqueous solution of NaCl.

Included within the scope of the "compounds of the invention" are all solvates (including hydrates), complexes, polymorphs, prodrugs, radiolabeled derivatives, stereoisomers and optical isomers of the compounds of formula (I) and salts thereof.

The compounds of the invention may exist in solid or liquid form. In the solid state, the compounds of the invention may exist in crystalline or noncrystalline form, or as a mixture thereof. For compounds of the invention that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and EtOAc, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of the invention that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs". The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs,
therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making or recrystallising the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

The invention also includes isotopically-labelled compounds, which are identical to the compounds of formula (I) and salts thereof, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into the compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen and fluorine, such as 3H, 11C, 14C and 18F.

The compounds according to formula (I) may contain one or more asymmetric center (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral centers, such as chiral carbon atoms, may also be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in formula (I), or in any chemical structure illustrated herein, is not specified the structure is intended to encompass any stereoisomer and all mixtures thereof. Thus, compounds according to formula (I) containing one or more chiral center may be used as racemic mixtures, enantiomerically enriched mixtures, or as enantiomerically pure individual stereoisomers.

Individual stereoisomers of a compound according to formula (I) which contain one or more asymmetric center may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzymatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. The skilled artisan will appreciate that where the desired stereoisomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired form. Alternatively, specific stereoisomers may be synthesized by
asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

The compounds according to formula (I) may also contain centers of geometric asymmetry. Where the stereochemistry of a center of geometric asymmetry present in formula (I), or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass the trans geometric isomer, the cis geometric isomer, and all mixtures thereof. Likewise, all tautomeric forms are also included in formula (I) whether such tautomers exist in equilibrium or predominately in one form.

It is to be understood that the references herein to compounds of formula (I) and salts thereof covers the compounds of formula (I) as free acids or free bases, or as salts thereof, for example as pharmaceutically acceptable salts thereof. Thus, in one embodiment, the invention is directed to compounds of formula (I) as the free acid or free base. In another embodiment, the invention is directed to compounds of formula (I) and salts thereof. In a further embodiment, the invention is directed to compounds of formula (I) and pharmaceutically acceptable salts thereof.

The skilled artisan will appreciate that pharmaceutically acceptable salts of the compounds according to formula (I) may be prepared. Indeed, in certain embodiments of the invention, pharmaceutically acceptable salts of the compounds according to formula (I) may be preferred over the respective free base or free acid because such salts impart greater stability or solubility to the molecule thereby facilitating formulation into a dosage form. Accordingly, the invention is further directed to compounds of formula (I) and pharmaceutically acceptable salts thereof.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared in situ during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

Salts and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their
pharmaceutically acceptable salts. Thus one embodiment of the invention embraces compounds of formula (I) and salts thereof.

In certain embodiments, compounds according to formula (I) may contain an acidic functional group. Suitable pharmaceutically-acceptable salts include salts of such acidic functional groups. Representative salts include pharmaceutically acceptable metal salts such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc salts; carbonates and bicarbonates of a pharmaceutically acceptable metal cation such as sodium, potassium, lithium, calcium, magnesium, aluminum, and zinc; pharmaceutically acceptable organic primary, secondary, and tertiary amines including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines such as methylamine, ethylamine, 2-hydroxyethylamine, diethylamine, TEA, ethylenediamine, ethanolamine, diethanolamine, and cyclohexylamine.

In certain embodiments, compounds according to formula (I) may contain a basic functional group and are therefore capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and pharmaceutically acceptable organic acids. Representative pharmaceutically acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methyl nitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenyl acetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, p-aminosalicylate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, o-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, naphthoate, hydroxynaphthoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), p-aminobenzenesulfonate, p-toluenesulfonate (tosylate), and naphthalene-2-sulfonate.

**Compound Preparation**

The compounds of the invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the Examples section.
Process a

Compounds of formula (I) wherein R¹ and R² are as defined above, and salts thereof, may be prepared from compounds of formula (II)

\[
\begin{align*}
\text{Compounds of formula (II) wherein } R^2 \text{ is as defined above, by a process comprising treatment with a suitable halide such as a 5-bromo-2-(methyloxy)-3-pyridinamine, under microwave irradiation, in the presence of a suitable palladium catalyst such as Solvias catalyst or Pd(dppf)Cl₂, in a suitable solvent such as 1,4-dioxane, in the presence of a suitable base such as aqueous potassium triphosphate or sodium carbonate, and at a suitable temperature such as from 60 to 180°C, for example about 110°C, followed by deprotection.}
\end{align*}
\]

Compounds of formula (II) wherein R² is as defined above, may be prepared from compounds of formula (III)

\[
\begin{align*}
\text{Compounds of formula (III) wherein } R^2 \text{ is as defined above, by treatment with a suitable boronate such as 4,4',4',6,6,6',6'-octamethyl-2,2'-bi-1,3,2-dioxaborinane, under microwave irradiation, in the presence of a suitable palladium catalyst such as Pd(dppf)Cl₂, in a suitable solvent such as 1,4-dioxane, in the presence of a suitable base such as potassium acetate, and at a suitable temperature such as from 60 to 150°C, for example about 80°C.}
\end{align*}
\]

Compounds of formula (III) wherein R² is as defined above, may be prepared from the compound of formula (IV)
by treatment either with (i) a suitable acid of formula \( R^2 \text{COOH} \), wherein \( R^2 \) is as defined above, or (ii) by treatment with an acid chloride of formula \( R^2 \text{COCl} \), wherein \( R^2 \) is as defined above. Suitable conditions for (i) include stirring an acid such as, for example, 2-methyl-1,3-thiazole-4-carboxylic acid (commercially available), in a suitable solvent such as \( \text{CH}_3\text{CN} \)/\( \text{H}_2\text{O} \)-dimethylformamide, at a suitable temperature such as room temperature, for example about 20°C, in the presence of a coupling reagent such as 0-(7-azabenzotriazol-1-yl)-\( N,N,N',N' \)-tetramethyluronium hexafluorophosphate, and in the presence of a suitable base such as \( \text{N},\text{N-diisopropylethylamine} \). Alternatively, (ii) may be carried out by acylation with a suitable acylating agent such as an acid chloride, in a suitable solvent such as dichloromethane, in the presence of a suitable base such as \( N,N \)-diisopropylamine, and at a suitable temperature such as room temperature, for example about 20°C.

The compound of formula (IV) may be prepared from the compound of formula (V)

by treatment with a reducing agent such as iron filings and ammonium chloride, in a suitable solvent such as ethanol and water, and at a suitable temperature such as from 60 to 100°C, for example about 80°C.

The compound of formula (V) may be prepared from the compound of formula (VI) (which is commercially available)
by treatment with 3,4-dihydro-2H-pyran, in the presence of a suitable acid catalyst such as pyridinium p-toluene sulfonate, in a suitable solvent such as dichloromethane, and at a suitable temperature such as reflux temperature.

5 **Process b**

Compounds of formula (I) wherein \( R^1 \) and \( R^2 \) are as defined above, and salts thereof, may also be prepared by a process comprising deprotection of suitably protected derivatives of compounds of formula (IA) wherein \( R^1 \) and \( R^2 \) are as defined above and \( P \) is a protecting group. Examples of suitable protection groups and the means of their removal can be found in T. W. Greene and P. G. M. Wuts ‘Protective Groups in Organic Synthesis’ (3rd Ed., J. Wiley and Sons, 1999).

As an example of this, compounds of formula (I) may be prepared from compounds of formula (IA) where the indazole ring nitrogen is protected (P), for example with 1-phenylsulphonyl, by deprotection under appropriate conditions, such as treating with a base, for example aqueous sodium hydroxide.

Compounds of formula (IA), wherein \( R^1 \) and \( R^2 \) are as defined above, may be prepared from compounds of formula (VII)
wherein $R^2$ is as defined above, by treatment with a suitable halide such as 5-bromo-3-pyridinamine, in the presence of a suitable palladium catalyst such as tetrakis(triphenylphosphine) palladium (0), in a suitable solvent such as $N,N$-dimethylformamide, and at a suitable temperature such as from 80 to 150°C, for example about 120°C.

Compounds of formula (VII) wherein $R^2$ is as defined above, may be prepared from the compound of formula (VIII)

![Chemical structure of compound VIII](image)

by (i) treatment with an acid of formula $R^2$COOH, wherein $R^2$ is as defined above, or (ii) by treatment with an acid chloride of formula $R^2$COCl, wherein $R^2$ is as defined above. Suitable conditions for (i) include stirring in a suitable solvent such as $N,N$-dimethylformamide, at a suitable temperature such as room temperature, for example about 20°C, in the presence of a coupling reagent such as $0$-(7-azabenzotriazol-1-yl)-$\Lambda$.$\Lambda$.$\Lambda$.'-$\Lambda$'-tetramethyluronium hexafluorophosphate, and in the presence of a suitable base such as $\Lambda$.$\Lambda$-/V-diisopropylethylamine. Alternatively, (ii) may be carried out by treatment with an acylating agent such as an acid chloride, in a suitable solvent such as dichloromethane, in the presence of a suitable base such as $\Lambda$.$\Lambda$-/V-diisopropylethylamine, and at a suitable temperature such as room temperature, for example about 20°C.

The compound of formula (VIII) wherein may be prepared from the compound of formula (IX)
by treatment with a suitable stannane such as hexamethyldistannane, under microwave irradiation, in the presence of a suitable palladium catalyst such as tetrakis(triphenylphosphine)palladium (0), in a suitable solvent such as toluene, in the presence of a suitable base such as triethylamine, and at a suitable temperature such as from 80 to 150°C, for example about 120°C.

Process c

Compounds of formula (I) wherein \( R^2 \) is as defined above and \( R^1 \) is pyridinyl substituted by \(-\text{NHCO}_2\text{R}^0\) and optionally a second substituent \( R^{1a} \) which is halo or \(-\text{OR}^4\), and salts thereof, may be prepared from compounds of formula (X)

\[
\text{(X)}
\]

wherein \( R^2 \) is as defined above, \( R^{1a} \) is pyridinyl substituted by \(-\text{NH}_2\) and optionally a second substituent \( R^{1a} \) which is halo or \(-\text{OR}^4\), and wherein \( P \) is a protecting group, for example tetrahydropyran, by a process comprising treatment with a chloridocarbonate of formula \( \text{CIC}_2\text{R}^0\), in the presence of a suitable base such as DIPEA, in a suitable solvent such as DCM and at a suitable temperature such as room temperature, for example about 20°C.

As the skilled person will appreciate, in the compound of formula (X), the protecting group \( P \) may be on the 1 or 2 position of the indazole. Following reaction with the
chloridocarbonate, the protecting group P may be removed by deprotection under appropriate conditions.

Compounds of formula (X) wherein R¹, R² and P are as defined above, may be prepared from compounds of formula (XI)

\[
\text{(XI)}
\]

wherein R² and P are as defined above, by a process comprising treatment with a suitable halide, under microwave irradiation, in the presence of a suitable catalyst such as Pd(dppf)Cl₂, in a suitable solvent such as aqueous 1,4-dioxane, in the presence of a suitable base such as sodium carbonate, and at a suitable temperature such as from 60 to 150°C, for example about 140°C.

Compounds of formula (XI) wherein R² and P are as defined above, may be prepared from compounds of formula (XII)

\[
\text{(XII)}
\]

wherein R² and P are as defined above, by treatment with a suitable boronate such as 4,4',4,6,6',6'-octamethyl-2,2'-bi-1,3,2-dioxaborinane, under microwave irradiation, in the presence of a suitable catalyst such as Pd(dppf)Cl₂, in a suitable solvent such as 1,4-dioxane, in the presence of a suitable base such as potassium acetate, and at a suitable temperature such as from 60 to 150°C, for example about 80°C.
Thus, in one embodiment, the invention provides a process for preparing a compound of the invention comprising:

a) reacting a compound of formula (II)

\[
\begin{align*}
\text{R}^2 & \quad \text{NH} \\
\text{B} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

(II)

wherein \( \text{R}^2 \) is as defined above, with a suitable halide, followed by deprotection;

b) deprotection of a suitably protected derivative of a compound of formula (IA)

\[
\begin{align*}
\text{O} & \quad \text{NH} \\
\text{R}^2 & \quad \text{B} \\
\text{N} & \quad \text{N} \quad \text{P} \\
\text{R}^1 &
\end{align*}
\]

(IA)

wherein \( \text{R}^1 \) and \( \text{R}^2 \) are as defined above and \( \text{P} \) is a protecting group; or

c) for a compound of formula (I) wherein \( \text{R}^2 \) is as defined above and \( \text{R}^1 \) is pyridinyl substituted by \(-\text{NHC0}_2\text{R}^9\) and optionally a second substituent \( \text{R}^{1\text{b}} \) which is halo or \(-\text{OR}^4\), and salts thereof, reacting a compound of formula (X)

\[
\begin{align*}
\text{R}^2 & \quad \text{NH} \\
\text{B} & \quad \text{O} \\
\text{N} & \quad \text{N} \quad \text{P} \\
\text{R}^{1\text{a}} &
\end{align*}
\]

(X)
wherein $R^2$ is as defined above, $R^{i^8}$ is pyridinyl substituted by -NH$_2$ and optionally a second substituent $R^{i^8}$ which is halo or -OR$^4$, and wherein P is a protecting group, for example tetrahydropyran, with a chloridocarbonate of formula CI$_2$OR$^6$, followed by deprotection.

5 Methods of Use

The compounds of the invention are inhibitors of PI3-kinase activity. Compounds which are PI3-kinase inhibitors may be useful in the treatment of disorders wherein the underlying pathology is (at least in part) attributable to inappropriate PI3-kinase activity, such as asthma and chronic obstructive pulmonary disease (COPD). "Inappropriate PI3-kinase activity" refers to any PI3-kinase activity that deviates from the normal PI3-kinase activity expected in a particular patient. Inappropriate PI3-kinase may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of PI3-kinase activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase leading to inappropriate or uncontrolled activation. Accordingly, in another aspect the invention is directed to methods of treating such disorders.

Such disorders include respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD); allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; cystic fibrosis; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trama), trigeminal neuralgia and central pain.

The methods of treatment of the invention comprise administering a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need thereof. Individual embodiments of the invention include methods of treating any one of the above-mentioned disorders by administering a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need thereof.
As used herein, "treat" in reference to a disorder means: (1) to ameliorate or prevent the disorder or one or more of the biological manifestations of the disorder, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the disorder or (b) one or more of the biological manifestations of the disorder, (3) to alleviate one or more of the symptoms or effects associated with the disorder, or (4) to slow the progression of the disorder or one or more of the biological manifestations of the disorder.

As indicated above, "treatment" of a disorder includes prevention of the disorder. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a disorder or biological manifestation thereof, or to delay the onset of such disorder or biological manifestation thereof.

As used herein, "safe and effective amount" in reference to a compound of formula (I) or a pharmaceutically acceptable salt thereof or other pharmaceutically-active agent means an amount of the compound sufficient to treat the patient's condition but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the disorder being treated; the severity of the disorder being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

As used herein, "patient" refers to a human (including adults and children) or other animal. In one embodiment, "patient" refers to a human.

The compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration and rectal administration. Parenteral administration refers to routes of administration other than enteral or transdermal, and is typically by injection or infusion. Parenteral administration
includes intravenous, intramuscular, and subcutaneous injection or infusion. Topical administration includes application to the skin as well as intraocular, otic, intravaginal, inhaled and intranasal administration. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. In one embodiment, the compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered orally. In another embodiment, the compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered by inhalation. In a further embodiment, the compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered intranasally.

The compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. In one embodiment, a dose is administered once per day. In a further embodiment, a dose is administered twice per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of formula (I) or a pharmaceutically acceptable salt thereof depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of formula (I) or a pharmaceutically acceptable salt thereof depend on the disorder being treated, the severity of the disorder being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Typical daily dosages may vary depending upon the particular route of administration chosen. Typical daily dosages for oral administration range from 0.001 mg to 50 mg per kg of total body weight, for example from 1 mg to 10 mg per kg of total body weight. For example, daily dosages for oral administration may be from 0.5 mg to 2 g per patient, such as 10 mg to 1 g per patient.

Additionally, the compounds of formula (I) may be administered as prodrugs. As used herein, a "prodrug" of a compound of formula (I) is a functional derivative of the compound
which, upon administration to a patient, eventually liberates the compound of formula (I) in vivo. Administration of a compound of formula (I) as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the activity of the compound in vivo; (b) modify the duration of action of the compound in vivo; (c) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleavable in vivo. Such modifications, which include the preparation of phosphates, amides, esters, thioesters, carbonates, and carbamates, are well known to those skilled in the art.

The invention thus provides a method of treating a disorder mediated by inappropriate PI3-kinase activity comprising administering a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need thereof.

In one embodiment, the disorder mediated by inappropriate PI3-kinase activity is selected from the group consisting of respiratory diseases (including asthma and chronic obstructive pulmonary disease (COPD)); allergic diseases (including allergic rhinitis and atopic dermatitis); autoimmune diseases (including rheumatoid arthritis and multiple sclerosis); inflammatory disorders (including inflammatory bowel disease); cardiovascular diseases (including thrombosis and atherosclerosis); hematologic malignancies; cystic fibrosis; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain (including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trama), trigeminal neuralgia and central pain).

In one embodiment, the disorder mediated by inappropriate PI3-kinase activity is a respiratory disease. In a further embodiment, the disorder mediated by inappropriate PI3-kinase activity is asthma. In a further embodiment, the disorder mediated by inappropriate PI3-kinase activity is chronic obstructive pulmonary disease (COPD).

In one embodiment, the disorder mediated by inappropriate PI3-kinase activity is pain.

In one embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in medical therapy. In another embodiment, the invention provides a compound of formula (I) or a pharmaceutically
acceptable salt thereof for use in the treatment of a disorder mediated by inappropriate PI3-kinase activity. In a further embodiment, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate PI3-kinase activity.

Compositions

The compounds of formula (I) and pharmaceutically acceptable salts thereof will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. Accordingly, in another aspect the invention is directed to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically-acceptable excipients.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof can be extracted and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a compound of formula (I) or a pharmaceutically acceptable salt thereof. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically may contain, for example, from 0.5mg to 1g, or from 1mg to 700mg, or from 5mg to 100mg of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions of the invention typically contain one compound of formula (I) or a pharmaceutically acceptable salt thereof.

As used herein, "pharmaceutically-acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of formula (I) or a pharmaceutically acceptable salt thereof when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must of course be pharmaceutically-acceptable eg of sufficiently high purity.
The compound of formula (I) or a pharmaceutically acceptable salt thereof and the pharmaceutically-acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols, solutions, and dry powders; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of formula (I) or pharmaceutically acceptable salts thereof once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: Diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other excipients are present in the formulation.
Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

Accordingly, in another aspect the invention is directed to process for the preparation of a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically-acceptable excipients which comprises mixing the ingredients. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof may be prepared by, for example, admixture at ambient temperature and atmospheric pressure.

In one embodiment, the compounds of formula (I) or pharmaceutically acceptable salts thereof will be formulated for oral administration. In another embodiment, the compounds of formula (I) or pharmaceutically acceptable salts thereof will be formulated for inhaled administration. In a further embodiment, the compounds of formula (I) or pharmaceutically acceptable salts thereof will be formulated for intranasal administration.

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid,
and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a
lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate,
and talc.

Where appropriate, dosage unit formulations for oral administration can be
microencapsulated. The composition can also be prepared to prolong or sustain the
release as for example by coating or embedding particulate material in polymers, wax or
the like.

The compounds of formula (I) or pharmaceutically acceptable salts thereof may also be
coupled with soluble polymers as targetable drug carriers. Such polymers can include
polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol,
polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with
palmitoyl residues. Furthermore, the compounds of formula (I) or pharmaceutically
acceptable salts thereof may be coupled to a class of biodegradable polymers useful in
achieving controlled release of a drug, for example, polylactic acid, polecpsilon
caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropropyran,
polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

In another aspect, the invention is directed to a liquid oral dosage form. Oral liquids such
as solution, syrups and elixirs can be prepared in dosage unit form so that a given
quantity contains a predetermined amount of a compound of formula (I) or a
pharmaceutically acceptable salt thereof. Syrups can be prepared by dissolving the
compound of formula (I) or a pharmaceutically acceptable salt thereof in a suitably
flavored aqueous solution, while elixirs are prepared through the use of a non-toxic
alcoholic vehicle. Suspensions can be formulated by dispersing the compound of formula
(I) or a pharmaceutically acceptable salt thereof in a non-toxic vehicle. Solubilizers and
emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers,
preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or
other artificial sweeteners, and the like can also be added.

In another aspect, the invention is directed to a dosage form adapted for administration to
a patient by inhalation, for example, as a dry powder, an aerosol, a suspension, or a
solution composition. For example, the invention is directed to a dry powder composition
adapted for inhalation comprising compound of formula (I) or a pharmaceutically
acceptable salt thereof.
Dry powder compositions for delivery to the lung by inhalation typically comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof as a finely divided powder together with one or more pharmaceutically-acceptable excipients as finely divided powders. Pharmaceutically-acceptable excipients particularly suited for use in dry powders are known to those skilled in the art and include lactose, starch, mannitol, and mono-, di-, and polysaccharides. The finely divided powder may be prepared by, for example, micronisation and milling. Generally, the size-reduced (eg micronised) compound can be defined by a D$_{50}$ value of about 1 to about 10 microns (for example as measured using laser diffraction).

The dry powder may be administered to the patient via a reservoir dry powder inhaler (RDPI) having a reservoir suitable for storing multiple (un-metered doses) of medicament in dry powder form. RDPIs typically include a means for metering each medicament dose from the reservoir to a delivery position. For example, the metering means may comprise a metering cup, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

Alternatively, the dry powder may be presented in capsules (e.g. gelatin or plastic), cartridges, or blister packs for use in a multi-dose dry powder inhaler (MDPI). MDPIs are inhalers wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple defined doses (or parts thereof) of medicament. When the dry powder is presented as a blister pack, it comprises multiple blisters for containment of the medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of the medicament therefrom. For example, the blisters may be arranged in a generally circular fashion on a disc-form blister pack, or the blisters may be elongate in form, for example comprising a strip or a tape. Each capsule, cartridge, or blister may, for example, contain between 20µg-10mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Aerosols may be formed by suspending or dissolving a compound of formula (I) or a pharmaceutically acceptable salt thereof in a liquified propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquified gases. Representative propellants include: trichlorofluoromethane (propellant 11), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (HFA-134a), 1,1-
difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12),
heptafluoropropane (HFA-227a), perfluoropropane, perfluorobutane, perfluoropentane,
butane, isobutane, and pentane. Aerosols comprising a compound of formula (I) or a
pharmaceutically acceptable salt thereof will typically be administered to a patient via a
metered dose inhaler (MDI). Such devices are known to those skilled in the art.

The aerosol may contain additional pharmaceutically-acceptable excipients typically used
with MDIs such as surfactants, lubricants, cosolvents and other excipients to improve the
physical stability of the formulation, to improve valve performance, to improve solubility, or
to improve taste.

There is thus provided as a further aspect of the invention a pharmaceutical aerosol
formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt
thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon as propellant,
optionally in combination with a surfactant and/or a cosolvent.

According to another aspect of the invention, there is provided a pharmaceutical aerosol
formulation wherein the propellant is selected from 1,1,1,2-tetrafluoroethane,
1,1,1,2,3,3-heptfluoro-n-propane and mixtures thereof.

The formulations of the invention may be buffered by the addition of suitable buffering
agents.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatine, may
be formulated containing a powder mix for inhalation of a compound of formula (I) or a
pharmaceutically acceptable salt thereof and a suitable powder base such as lactose or
starch. Each capsule or cartridge may generally contain from 20µg to 10mg of the
compound of formula (I) or pharmaceutically acceptable salt thereof. Alternatively, the
compound of formula (I) or pharmaceutically acceptable salt thereof may be presented
without excipients such as lactose.

The proportion of the active compound of formula (I) or pharmaceutically acceptable salt
thereof in the local compositions according to the invention depends on the precise type
of formulation to be prepared but will generally be within the range of from 0.001 to 10%
by weight. Generally, for most types of preparations, the proportion used will be within the
range of from 0.005 to 1%, for example from 0.01 to 0.5%. However, in powders for
inhalation or insufflation the proportion used will normally be within the range of from 0.1 to 5%.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains from 2C^g to 10mg, preferably from 2C^g to 200C^g, more preferably from about 2C^g to 50C^g of a compound of formula (I). Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range from 10C^g to 10mg, preferably from 20C^g to 200C^g. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double that delivered with aerosol formulations.

In the case of suspension aerosol formulations, the particle size of the particulate (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and in particular in the range of from 1 to 10 microns, such as from 1 to 5 microns, more preferably from 2 to 3 microns.

The formulations of the invention may be prepared by dispersal or dissolution of the medicament and a compound of formula (I) or a pharmaceutically acceptable salt thereof in the selected propellant in an appropriate container, for example, with the aid of sonication or a high-shear mixer. The process is desirably carried out under controlled humidity conditions.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product. Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

The stability of the suspension aerosol formulations according to the invention may be measured by conventional techniques, for example, by measuring flocculation size distribution using a back light scattering instrument or by measuring particle size
distribution by cascade impaction or by the "twin impinger" analytical process. As used herein reference to the "twin impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopoeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the "respirable fraction" of the aerosol formulations to be calculated. One method used to calculate the "respirable fraction" is by reference to "fine particle fraction" which is the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above.

The term "metered dose inhaler" or MDI means a unit comprising a can, a secured cap covering the can and a formulation metering valve situated in the cap. MDI system includes a suitable channelling device. Suitable channelling devices comprise for example, a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient such as a mouthpiece actuator.

MDI canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example, aluminium or an alloy thereof which may optionally be anodised, lacquer-coated and/or plastic-coated (for example incorporated herein by reference WO96/32099 wherein part or all of the internal surfaces are coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers), which container is closed with a metering valve. The cap may be secured onto the can via ultrasonic welding, screw fitting or crimping. MDIs taught herein may be prepared by methods of the art (e.g. see Byron, above and WO96/32099). Preferably the canister is fitted with a cap assembly, wherein a drug-metering valve is situated in the cap, and said cap is crimped in place.

In one embodiment of the invention the metallic internal surface of the can is coated with a fluoropolymer, more preferably blended with a non-fluoropolymer. In another embodiment of the invention the metallic internal surface of the can is coated with a polymer blend of polytetrafluoroethylene (PTFE) and polyethersulfone (PES). In a further embodiment of the invention the whole of the metallic internal surface of the can is coated with a polymer blend of polytetrafluoroethylene (PTFE) and polyethersulfone (PES).
The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as, for example, low density polyethylene, chlorobutyl, bromobutyl, EPDM, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK357) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser™).

In various embodiments, the MDIs may also be used in conjunction with other structures such as, without limitation, overwrap packages for storing and containing the MDIs, including those described in U.S. Patent Nos. 6,119,853; 6,179,118; 6,315,112; 6,352,152; 6,390,291; and 6,679,374, as well as dose counter units such as, but not limited to, those described in U.S. Patent Nos. 6,360,739 and 6,431,168.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large-scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method for preparing suspension aerosol formulations, a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquefied propellant together with the optional excipients is pressure filled through the charge vessel into a manufacturing vessel. The drug suspension is mixed before recirculation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister. In one example of a bulk manufacturing method for preparing solution aerosol formulations, a metering valve is crimped onto an aluminium can to form an empty canister. The liquefied propellant together with the optional excipients and the dissolved medicament is pressure filled through the charge vessel into a manufacturing vessel.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold to ensure the formulation does not vaporise, and then a metering valve crimped onto the canister.

Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.
Suspensions and solutions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof may also be administered to a patient via a nebulizer. The solvent or suspension agent utilized for nebulization may be any pharmaceutically-acceptable liquid such as water, aqueous saline, alcohols or glycols, e.g., ethanol, isopropylalcohol, glycerol, propylene glycol, polyethylene glycol, etc. or mixtures thereof. Saline solutions utilize salts which display little or no pharmacological activity after administration. Both organic salts, such as alkali metal or ammonium halogen salts, e.g., sodium chloride, potassium chloride or organic salts, such as potassium, sodium and ammonium salts or organic acids, e.g., ascorbic acid, citric acid, acetic acid, tartaric acid, etc. may be used for this purpose.

Other pharmaceutically-acceptable excipients may be added to the suspension or solution. The compound of formula (I) or pharmaceutically acceptable salt thereof may be stabilized by the addition of an inorganic acid, e.g., hydrochloric acid, nitric acid, sulphuric acid and/or phosphoric acid; an organic acid, e.g., ascorbic acid, citric acid, acetic acid, and tartaric acid, etc., a complexing agent such as EDTA or citric acid and salts thereof; or an antioxidant such as antioxidant such as vitamin E or ascorbic acid. These may be used alone or together to stabilize the compound of formula (I) or pharmaceutically acceptable salt thereof. Preservatives may be added such as benzalkonium chloride or benzoic acid and salts thereof. Surfactant may be added particularly to improve the physical stability of suspensions. These include lecithin, disodium dioctylsulphosuccinate, oleic acid and sorbitan esters.

In a further aspect, the invention is directed to a dosage form adapted for intranasal administration.

Formulations for administration to the nose may include pressurised aerosol formulations and aqueous formulations administered to the nose by pressurised pump. Formulations which are non-pressurised and adapted to be administered topically to the nasal cavity are of particular interest. Suitable formulations contain water as the diluent or carrier for this purpose. Aqueous formulations for administration to the lung or nose may be provided with conventional excipients such as buffering agents, tonicity modifying agents and the like. Aqueous formulations may also be administered to the nose by nebulisation.
The compounds of formula (I) or pharmaceutically acceptable salts thereof may be formulated as a fluid formulation for delivery from a fluid dispenser, for example a fluid dispenser having a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity. A fluid dispenser of the aforementioned type is described and illustrated in WO05/044354, the entire content of which is hereby incorporated herein by reference. The dispenser has a housing which houses a fluid discharge device having a compression pump mounted on a container for containing a fluid formulation. The housing has at least one finger-operable side lever which is movable inwardly with respect to the housing to cam the container upwardly in the housing to cause the pump to compress and pump a metered dose of the formulation out of a pump stem through a nasal nozzle of the housing. In one embodiment, the fluid dispenser is of the general type illustrated in Figures 30-40 of WO05/044354.

Pharmaceutical compositions adapted for intranasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the patient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.
Ointments, creams and gels, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as polyethylene glycol.

5 Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

10 Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions may be applied as a topical ointment or cream. When formulated in an ointment, the compound of formula (I) or a pharmaceutically acceptable salt thereof may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the compound of formula (I) or pharmaceutically acceptable salt thereof may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous
injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

The compound and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M₁/M₂/M₃ receptor antagonist), β₂-adrenoreceptor agonists, antiinfective agents, such as antibiotics or antiviral, or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent, such as a corticosteroid or an NSAID, an anticholinergic agent, a β₂-adrenoreceptor agonist, an antiinfective agent, such as an antibiotic or an antiviral, or an antihistamine. One embodiment of the invention encompasses combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a β₂-adrenoreceptor agonist, and/or an anticholinergic, and/or a PDE-4 inhibitor, and/or an antihistamine.

Certain compounds of the invention may show selectivity for PI3K5 over other PI3-kinases. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof which is selective for PI3K5 together with a compound or pharmaceutically acceptable salt thereof which is selective for another PI3-kinase, for example PI3Kγ.

One embodiment of the invention encompasses combinations comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

In one embodiment, the invention encompasses a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a β₂-adrenoreceptor agonist.
Examples of β₂-adrenoreceptor agonists include salmeterol (which may be a racemate or a single enantiomer such as the R-enantiomer), salbutamol (which may be a racemate or a single enantiomer such as the R-enantiomer), formoterol (which may be a racemate or a single diastereomer such as the R,J-diastereomer), salmefamol, fenoterol, carmoterol, etanerol, naminterol, clenbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalencarboxylate) salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. In one embodiment, long-acting β₂-adrenoreceptor agonists, for example, compounds which provide effective bronchodilation for about 12 hrs or longer, are preferred.


Examples of β₂-adrenoreceptor agonists include:

3-(4-[(6-{[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino})
   hexyl] oxy) butyl benzenesulfonamide;

3-(3-{[(7-{[(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl]-amino})
   heptyl] oxy) propyl benzenesulfonamide;

4-{(1R)-2-[(6-{2-[6-dichlorobenzyl] oxy} ethoxy) hexyl] amino]-1-hydroxyethyl}2-
   (hydroxymethyl) phenol;

4-{(1/?)-2-{[6-[4-{3-cyclopentylsulfonyl)phenyl]butoxy]hexyl]amino}-1-hydroxyethyl}2-
   (hydroxymethyl)phenol;

N-[2-hydroxy-5-{[(1 R)-1-hydroxy-2-[2-4-{[(2R)-2-hydroxy-2-

N-2[2-4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl]-2-hydroxy-2-(8-hydroxy-2(1/-)
   quinolinon-5-yl)ethylamine; and

5-{[(R)-2-{(2-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl]-ethylamino})-1-
   hydroxy-ethyl]-8-hydroxy-1 H-quinolin-2-one.

The β₂-adrenoreceptor agonist may be in the form of a salt formed with a pharmaceutically acceptable acid selected from sulphuric, hydrochloric, fumaric, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), cinnamic, substituted
cinnamic, triphenylacetic, sulphamic, sulphanilic, naphthaleneacrylic, benzoic, 4-methoxybenzoic, 2-or 4-hydroxybenzoic, 4-chlorobenzoic and 4-phenylbenzoic acid.

Suitable anti-inflammatory agents include corticosteroids. Suitable corticosteroids which may be used in combination with the compounds of formula (I) or pharmaceutically acceptable salts thereof are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6a,9a-difluoro-17a-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-4,14-diene-17β-carbothioic acid S-fluoromethyl ester, 6a,9a-difluoro-17a-[(2-furanylcarbonyl)oxy]-17β-hydroxy-16a-methyl-3-oxo-androsta-4,14-diene-17β-carbothioic acid S-fluoromethyl ester (fluticasone furoate), 6a,9a-difluoro-17a-oxo-16a-methyl-3-oxo-17a-propionyloxy-androsta-4,14-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, 6α,9α-difluoro-17β-hydroxy-l 6a-methyl-3-oxo-17a-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-4,14-diene-17β-carbothioic acid S-cyanomethyl ester and 6a,9a-difluoro-17β-hydroxy-16a-methyl-17a-(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-4,14-diene-17β-carbothioic acid S-fluoromethyl ester, beclometasone esters (for example the 17-propionate ester or the 17,21-diisopropionate ester), budesonide, flunisolide, mometasone esters (for example mometasone furoate), triamcinolone acetonide, rofleponide, ciclesonide (16a,17-[(R)-cyclohexylmethyl]ene)b(is(oxy))-1β,21-dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6a,9a-difluoro-17a-oxo-16a-methyl-17a-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-4,14-diene-17β-carbothioic acid S-fluoromethyl ester, 6a,9a-difluoro-17a-[(2-furanylcarbonyl)oxy]-17β-hydroxy-16a-methyl-3-oxo-androsta-4,14-diene-17p-carbothioic acid S-fluoromethyl ester, 6α,9α-difluoro-17β-hydroxy-l 6a-methyl-3-oxo-17a-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-4,14-diene-17β-carbothioic acid S-cyanomethyl ester and 6a,9a-difluoro-17β-hydroxy-16a-methyl-17a-(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-4,14-diene-17β-carbothioic acid S-fluoromethyl ester. In one embodiment the corticosteroid is 6α,9α-difluoro-17a-[(2-furanylcarbonyl)oxy]-1β-hydroxy-l 6a-methyl-3-oxo-androsta-4,14-diene-17β-carbothioic acid S-fluoromethyl ester.

Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful in combination therapy include those covered in the following patents: WO03/082827, W098/54159, WO04/005229, WO04/009017, WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899, WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294, WO04/026248, WO03/061651 and WO03/08277. Further non-steroidal compounds are covered in: WO2006/000401, WO2006/000398 and WO2006/015870.

Examples of anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAID's).

Examples of NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (for example, theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (for example montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (for example chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-lipoxygenase inhibitors. An iNOS (inducible nitric oxide synthase inhibitor) is preferably for oral administration. Examples of iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021, W095/34534 and W099/62875. Examples of CCR3 inhibitors include those disclosed in WO02/26722.

In one embodiment, the invention provides the use of the compounds of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor, especially in the case of a formulation adapted for inhalation. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family, such as PDE3 and PDE5, as well as PDE4.

Compounds include c/s-4-cyano-4-(3-cyclopentyl-4-methoxyphenyl)cyclohexane-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and c/s-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1 -ol]. Also, c/s-4-cyano-4-[3-(cyclopentyl)oxy]-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomilast) and its salts,
esters, pro-drugs or physical forms, which is described in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference.

Other compounds include AWD-12-281 from Elbion (Hofgen, N. _et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-1 68787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-1 1294A from Napp (Landells, L.J. _et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 2B): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a phthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR’,106S’)-9-ethoxy-1,2,3,4,4a, 10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. _et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Further compounds are disclosed in the published international patent application WO04/024728 (Glaxo Group Ltd), WO04/056823 (Glaxo Group Ltd) and WO04/1 03998 (Glaxo Group Ltd) (e.g. Example 399 or 544 disclosed therein). Further compounds are also disclosed in WO2005/058892, WO2005/090348, WO2005/090353, and WO2005/090354, all in the name of Glaxo Group Limited.

Examples of anticholinergic agents are those compounds that act as antagonists at the muscarinic receptors, in particular those compounds which are antagonists of the M1 or M3 receptors, dual antagonists of the M1/M3 or M2/M3 receptors or pan-antagonists of the M1/M2/M3 receptors. Exemplary compounds for administration via inhalation include ipratropium (for example, as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium (for example, as the bromide, CAS 30286-75-0) and tiotropium (for example, as the bromide, CAS 136310-93-5, sold under the name Spiriva). Also of interest are revatropate (for example, as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO01/041 18. Exemplary compounds for oral administration include pirenzepine (CAS 28797-61-7), darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5,
sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

Additional compounds are disclosed in WO 2005/037280, WO 2005/046586 and WO 2005/104745, incorporated herein by reference. The present combinations include, but are not limited to:

10 (3-enc/o)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane iodide;
(3-enc/o)-3-(2-cyano-2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
4-[hydroxy(diphenyl)methyl]-1-[2-[(phenylmethyl)oxy]ethyl]-1-azoniabicyclo[2.2.2]octane bromide; and

Other anticholinergic agents include compounds which are disclosed in US patent application 60/487981 including, for example:

20 (3-enc/o)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-enc/o)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-enc/o)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane 4-methylbenzenesulfonate;
(3-enc/o)-8,8-dimethyl-3-[2-phenyl-2-(2-thienyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide; and/or
25 (3-enc/o)-8,8-dimethyl-3-[2-phenyl-2-(2-pyridinyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide.

Further anticholinergic agents include compounds which are disclosed in US patent application 60/511009 including, for example:

30 (enc/o)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane iodide;
3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;
(enc/o)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;
35 3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;
(enc/o)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide; 3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol; /V-benzyl-3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide; (enc/o)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; 1-benzyl-3-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea; 1-ethyl-3-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea; /V-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide; /V-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide; 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile; (endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; /V-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide; 3-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea; /V-[3-((enc/o)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide; and/or (endo)-3-[2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl]-8, 8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

Further compounds include:  
(enc/o)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; (enc/o)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; (enc/o)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide; (enc/o)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; (enc/o)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and/or (enc/o)-3-[2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl]-8, 8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

In one embodiment the invention provides a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an H1 antagonist.

Examples of H1 antagonists include, without limitation, amlexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine,
descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine. In a further embodiment the invention provides a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an H3 antagonist (and/or inverse agonist). Examples of H3 antagonists include, for example, those compounds disclosed in WO2004/035556 and in WO2006/045416. Other histamine receptor antagonists which may be used in combination with the compounds of the present invention include antagonists (and/or inverse agonists) of the H4 receptor, for example, the compounds disclosed in Jablonowski et al., J. Med. Chem. 46:3957-3960 (2003).

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a β2-adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a non-steroidal GR agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a PDE4 inhibitor and a β2-adrenoreceptor agonist.
The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic and a PDE-4 inhibitor.

In a preferred aspect, the invention provides a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a corticosteroid.

In a further preferred aspect, the invention provides a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a β2-adrenoreceptor agonist.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will readily be appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a β2-adrenoreceptor agonist.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a corticosteroid.
The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a non-steroidal GR agonist.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an antihistamine.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a PDE4 inhibitor and a $\beta_2$-adrenoreceptor agonist.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic and a PDE4 inhibitor.

In a preferred aspect, the invention provides a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a corticosteroid.

In a further preferred aspect, the invention provides a pharmaceutical composition comprising a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a $\beta_2$-adrenoreceptor agonist.

The invention will now be illustrated by way of the following non-limiting examples.

**EXAMPLES**

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention.
While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

5 General Methods

LCMS methods

Method A

The HPLC analysis was conducted on a Sunfire C18 column (30mmx4.6mm i.d. 3.5μm packing diameter) at 30 degrees centigrade.
Solvent A = 0.1% v/v solution of Formic Acid in Water.
Solvent B = 0.1% v/v solution of Formic Acid in Acetonitrile.
The gradient employed was:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Flow Rate (ml/min)</th>
<th>% A</th>
<th>% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>0.1</td>
<td>3</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>4.2</td>
<td>3</td>
<td>0</td>
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</tr>
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<td>4.8</td>
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<tr>
<td>4.9</td>
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<td>3</td>
</tr>
<tr>
<td>5.0</td>
<td>3</td>
<td>97</td>
<td>3</td>
</tr>
</tbody>
</table>

The UV detection was an averaged signal from wavelength of 210nm to 350nm and mass spectra were recorded on a mass spectrometer using alternate-scan positive and negative mode electrospray ionization.

Method B

The HPLC analysis was conducted on a Acquity UPLC BEH C18 column (50mmx2.1mm i.d. 1.7μm packing diameter) at 40 degrees centigrade.
Solvent A = 0.1% v/v solution of Formic Acid in Water.
Solvent B = 0.1% v/v solution of Formic Acid in Acetonitrile.
The gradient employed was:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Flow Rate (ml/min)</th>
<th>% A</th>
<th>% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1.9</td>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>
The UV detection was an averaged signal from wavelength of 210nm to 350nm and mass spectra were recorded on a mass spectrometer using alternate-scan positive and negative mode electrospray ionization.

Method C

Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100 - 1000 amu.

UV wavelength: 215 - 330 nm

Column: 3.3 cm x 4.6 mm i.d., 3 μιι ABZ+PLUS

Flow Rate: 3 ml/min

Injection Volume: 5 μιι

Solvent A: 95% MeCN + 0.05% of a 1% v/v solution of formic acid in water

Solvent B: 0.1% v/v solution of formic acid in 10 mmol ammonium acetate (aq)

Gradient: Mixtures of Solvent A and Solvent B are used according to the following gradient profiles (expressed as % Solvent A in the mixture): 0% A; 0.7 mins, 0 - 100% A; 3.5 mins, 100% A; 0.4 mins, 100 - 0% A; 0.2 mins.

Method D

Column: Acquity UPLC BEH C₁₈ 1.7 μιι, 2.1 mm x 50 mm. Column oven at 40 °C

Solvent A: 0.1% formic acid in water containing 10 mmol ammonium acetate

Solvent B: MeCN:Water (95:5, v/v) containing 0.05% formic acid

Injection volume: 0.5 μιι

Injection technique: Partial loop overfill

UV detection: 220 - 330 nm

UV sampling rate: 40 points/s

MS scan range: 100 - 1000 amu

MS scanning rate: 0.2 s/scan with a 0.1 s inter scan delay

MS scan function: Electrospray with pos neg switching

Cycle time: 150 s

Flow rate: 1 ml/min

Gradient:

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>0.1</td>
<td>97</td>
<td>3</td>
</tr>
</tbody>
</table>
Method E

Column; Waters Sunfire C18, 3.5 µM, 2.1 mm i.d. x 30 mm.

Mobile Phase
A: 0.1 % formic acid (aq).
B: 0.1 % formic acid in MeCN

Flow rate; 1 ml/min

Gradient:

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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<tr>
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<td>0</td>
</tr>
<tr>
<td>4.5</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

MDAP methods

Mass Directed Automated Preparative HPLC and MS Conditions

Method A

Stationary phase

The stationary phase used for this purification was Sunfire C18 with a particle size of 5 µm.

Small scale preparative column

Column Dimension : 100mm x 19mm i.d.

Large scale preparative column
Column Dimension : 150mm x 30mm i.d.

Eluent

The eluents employed were:
A = 0.1% v/v solution of formic acid in water.
B = 0.1% v/v solution of formic acid in acetonitrile.

Methods for small scale prep for up to 30 mg of crude sample

There are ten focused small scale preparative methods available for use. The choice of method is dependent on two factors

1. The retention time (RT) of the component/s of interest on the generic analytical LCMS method.
2. The presence of closely eluting impurities to the component/s of interest.

From the analytical RT the choice of one of five small scale focused prep methods is made. Small scale prep methods contain a 10 minute gradient over a specified organic range, followed by a 5 minute flush, except the most polar method which contains a 7 minute gradient over a specified organic range followed by an 8 minute flush. The total run time is 15 minutes.

If there are closely eluting impurities to the component/s of interest then there are five extended small scale focused prep methods available. Extended small scale prep methods contain a 20 minute gradient over the specified organic range followed by a 5 minute flush, except the most polar method which contains a 14 minute gradient over the specified organic range followed by an 11 minute flush. The total run time is 25 minutes.

Flow rates for all small scale methods are 20 ml/min and the purification is performed at ambient temperature.

The injection volume for small scale prep is 500 µl.

The 10 small scale prep methods and the organic ranges of the gradients are shown below. The gradients are the same for normal or extended runs.
In the flush step eluent B is raised to 99% in 0.5 minutes then held there for a further 4.5 minutes.

**Methods for large scale prep for up to 90mg of crude sample**

There are ten focused large scale prep methods available for use. The choice of method is dependent on the same two factors as for small scale prep. The run times (gradient and flush) are the same as for small scale prep methods.

Flow rates for all large scale methods are 40 ml/min and the purification is performed at ambient temperature.

The injection volume for large scale prep is 980 µl.

The 5 large scale method names and the organic ranges of the gradients are shown below. The gradients are the same for either normal or extended runs.

In the flush step eluent B is raised to 99% in 0.5 minutes then held there for a further 4.5 minutes.

**UV detection**

The UV detection for all methods is an averaged signal from all wavelengths from 210nm to 350nm.
MS conditions

MS: Waters ZQ

Ionisation mode: Alternate-scan positive and negative electrospray

Scan range: 100 to 1000 amu
Scan time: 0.50 seconds
Inter scan delay: 0.20 seconds

Method B

Column Details: XBRI DGE C\textsubscript{18} column (100 mm x 19 mm i.d., 5 \(\mu\)m packing diameter)

Solvents:

A: 10 mmol ammonium bicarbonate (aq) adjusted to pH 10 with ammonia (aq)
B: MeCN

The UV detection was an averaged signal from wavelength of 210 nm to 350 nm and mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

Method C

Sunfire, Low pH

Column Details: SUNFIRE C\textsubscript{18} column (100 mm x 19 mm id. 5 \(\mu\)m)

The solvents employed were:

A=0.1% v/v solution of Formic Acid in Water.
B= 0.1% v/v solution of Formic Acid in Acetonitrile.

Method A

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230 nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

Method B

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230 nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

Method C

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

Method D

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

Method E

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

Mass Directed Automated Preparative HPLC column, conditions and eluent

Method D
Column Details: SUNFIRE C18 column (100 mm x 19 mm id. 5 um)

The solvents employed were:
A = 0.1% v/v solution of Trifluoroacetic Acid in Water.
B = 0.1% v/v solution of Trifluoroacetic Acid in Acetonitrile.

Methods below are selected based on the analytical retention time of the compounds being purified.

**Method 1**

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

**Method 2**

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Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm.
Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.
**Method 3**

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Collection was triggered by uv, ms or a combination of the two. The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm. Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

**Method 4**

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Collection was triggered by uv, ms or a combination of the two. The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm. Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

**Method 5**

<table>
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</table>
Collection was triggered by uv, ms or a combination of the two.
The UV detection was at a selected wavelength generally 230nm, 210 nm or 254 nm. Mass spectra were recorded on a mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

5 **Intermediates and Examples**

When the name of a commercial supplier is given after the name of a compound or a reagent, for instance "compound X (Aldrich)" or "compound X/Aldrich", this means that compound X is obtainable from a commercial supplier, such as the commercial supplier named. If not referenced herein the compound or reagent can be purchased from a standard supplier such as Sigma Aldrich, Lancaster, Fluorochem, TCI etc.

Similarly, when a literature or a patent reference is given after the name of a compound, for instance compound Y (EP 0 123 456), this means that the preparation of the compound is described in the named reference.

The names of the Examples have been obtained using a compound naming programme which matches name to structure (e.g. ACD/Name Batch v 9.0).

20 **Intermediate 1**

\[ \text{yV-[6-Bromo-2-(tetrahydro-2H-pyran-2-yl)-2H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide} \]

6-Bromo-2-(tetrahydro-2H-pyran-2-yl)-2H-indazol-4-amine (2.77 g) dissolved in DCM (120 ml) was treated with pyridine (1.135 ml). After a few minutes 2-methyl-1,3-thiazole-4-carbonyl chloride (2.267 g) was added and the reaction was stirred at RT for 1 h. The reaction was extracted between DCM and saturated sodium bicarbonate (aq). The organic layer was dried down. The residue was dissolved in DCM and adsorbed onto florisil before purification by solid loading on ISCO companion using a silica column (40 g) and a gradient of 40 % - 100 % ethyl acetate in cyclohexane. Appropriate fractions were combined and evaporated to dryness to give the title compound, 2.66 g. LC/MS (Method B) \( R_t = 1.17 \text{ min}, M \text{H}^+ = 423. \)
Intermediate 2

2-Methyl-W-[2-(tetrahydro-2H-pyran-2-yl)-6-(4,4,6,6-tetramethyl-1,3,2-dioxaborinan-2-yl)-2H-indazol-4-yl]-1,3-thiazole-4-carboxamide

To 2 separate microwave vials was weighed N-[6-bromo-2-(tetrahydro-2H-pyran-2-yl)-2H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide (1.13 g), potassium acetate (799 mg), 4,4',4',6,6,6',6'-octamethyl-2',2'-bi-1,3,2-dioxaborinane (2.0 g) and PdCl$_2$(dppf) (348 mg). To this was added 1,4-dioxane (17 ml) and the reaction was heated for 30 min at 80 °C in the microwave. Heated vial 2 again for 30 min at 80 °C using microwave. Hence combined reaction mixtures were washed through a silica cartridge (10 g) with methanol, preconditioned with methanol. The solution was dried down. The solid was separated between DCM and water and the DCM layer was dried down. The material was dissolved in DCM and methanol (few drops) and adsorbed onto florisil then purified on the ISCO companion, silica column (80 g) using 40 % - 100 % ethyl acetate in cyclohexane. Fractions collected were analysed for product and the appropriate ones were combined to give the title compound, 1.25 g.

LCMS (method B) $R_t = 1.35$ min, $MH^+ = 483$.

Intermediate 3

6-Bromo-4-nitro-2-(tetrahydro-2H-pyran-2-yl)-2H-indazole

To 6-bromo-4-nitro-1/-indazole (10 g) in dihydropyran (100 ml) was added TFA (0.068 ml) and the reaction was heated for 1.5 h at reflux. After cooling, DCM (180 ml) and saturated sodium bicarbonate solution (50 ml) was added and stirred for 10 min. The DCM was separated from the aqueous which was re-washed with DCM (70 ml). The combined organic layers were passed through a hydrophobic frit and evaporated to dryness. The residual solid was triturated with ether then filtered. The solid material was dissolved in DCM and purified by chromatography on silica on the ISCO Companion, using an isocratic gradient of DCM. Purified fractions were combined and evaporated to dryness to afford the title compound, 7.78 g.
Intermediate 4

**6-Bromo-2-(tetrahydro-2H-pyran-2-yl)-2H-indazol-4-amine**

![Chemical Structure](image)

6-Bromo-4-nitro-2-(tetrahydro-2H-pyran-2-yl)-2H-indazole (6 g), iron filings (3.29 g) and ammonium chloride (0.492 g) were weighed to a 250 ml round-bottomed flask and ethanol (60 ml) then water (18 ml) were added. The reaction was heated to 80 °C for 2.5 h. The reaction mixture was cooled. Ethyl acetate (100 ml) and water (50 ml) were added. There was no visible separation of layers so the reaction was concentrated to remove the ethyl acetate and ethanol. Ethyl acetate (250 ml) was then added and the organic layer was washed with water (50 ml), before passing through a hydrophobic frit. The organic layer was evaporated to dryness. The residue was purified by column chromatography on silica (120 g silica column, ISCO Companion) eluting with a gradient of 1 - 2 % methanol in DCM over 25 min. Fractions containing desired material were combined and evaporated to dryness to afford the title compound, 3.95 g.

**LCMS (method C); R_t = 3.51 min, M^+ = 326/328.**

Intermediate 5

**2-Methyl-1,3-thiazole-4-carbonyl chloride**

![Chemical Structure](image)

To 2-methyl-1,3-thiazole-4-carboxylic acid (1 g) was added thionyl chloride (5 ml). The mixture was heated at 80 °C for 8 h. Thionyl chloride (5 ml) was added and the mixture heated for 2 h at 80 °C. Further thionyl chloride (5 ml) was added and the mixture heated for 2 h. The mixture was concentrated in vacuo and azeotroped with toluene to give the title compound, 1.12 g.

**^1H NMR (DSMO) δ 8.34 (s, 1H), 2.80 (s, 3H)**

Intermediate 6

**1-(Phenylsulfonyl)-6-(trimethylstannanyl)-1H-indazol-4-amine**
A mixture of 6-bromo-1-(phenylsulfonyl)-1 H-indazol-4-amine (1.3 g), hexamethylditin (2.4 g), triethylamine (1 ml) and Pd(PPh3)4 (0.2 g) in toluene (15 ml) was heated under microwave irradiation at 120 °C for 1 h. The reaction was applied to a silica cartridge using light petroleum 40 - 60 °C as eluent. This was changed to ether/light petroleum 40 - 60° C. The appropriate fractions were evaporated to give the title compound, 1.2 g.

LCMS (method A); Rt = 3.3 min, MH+ = 438.

**Intermediate 7**

6-Bromo-1-(phenylsulfonyl)-1 H-indazol-4-amine

6-Bromo-1 H-indazol-4-amine (5 g) was dissolved in DMF (20 ml) and cooled in an ice bath. 60 % Sodium hydride in mineral oil (0.94 g) was added portionwise and the reaction was left under an ice bath for 30 min. Benzenesulfonyl chloride (3 ml) in DMF (5 ml) was added slowly over 15 min and the reaction was left to warm up to RT overnight. Water (100 ml) was added and the reaction stirred for 20 min. Ethyl acetate (120 ml) was added and the water was separated, washed with ethyl acetate (50 ml x 2) and the combined organics were washed with 7.5 % lithium chloride (aq) (50 ml x 2) then water (50 ml) before being separated and passed through a hydrophobic frit. The ethyl acetate was evaporated and the residue passed through a silica cartridge, eluting with DCM (ca. 300 ml) followed by diethyl ether (ca. 400 ml). Product containing pure fractions were combined and evaporated to dryness to give the title compound, 5.9 g.

LCMS (method B); Rt = 1.12 min, MH+ = 354.

**Intermediate 8**

2-Methyl-/V-[1-(phenylsulfonyl)-6-(trimethylstannanyl)-1 H-indazol-4-yl]-1 ,3-thiazole-4-carboxamide
2-Methyl-1,3-thiazole-4-carbonyl chloride (350 mg) in DCM (4 ml) was added dropwise to 1-(phenylsulfonyl)-6-(trimethylstannanyl)-1H-indazol-4-amine (300 mg) in DCM (15 ml) and pyridine (0.167 ml). The reaction was stirred at RT overnight. Saturated sodium bicarbonate (aq) (25 ml) was added and the reaction vigorously stirred for 15 min. The DCM was passed through a hydrophobic frit then evaporated to dryness. The residue was dissolved in DCM and purified on a silica cartridge, preconditioned with cyclohexane, washing with cyclohexane followed by elution with ether. The ether was evaporated to give the title compound, 373 mg.

**Intermediate 9**

**W-(5-Bromo-2-chloro-3^-yridinyl)-W-methylbenzenesulfonamide**

N-(5-Bromo-2-chloro-3-pyridinyl)benzenesulfonamide (300 mg) was dissolved in DMF (8 ml) and cooled to 0 °C. Sodium hydride (60 % in mineral oil) (41 mg) was added in one portion. The reaction was left for 15 min then methyl iodide (0.108 ml) was added slowly. The reaction was left for 10 min then warmed to RT. The reaction was quenched with water (20 ml) then ethyl acetate (40 ml) was added followed by more water (20 ml). The ethyl acetate was separated and the water was washed with further ethyl acetate. The combined organics were washed with brine, separated then passed through a hydrophobic frit before evaporating to dryness. The residue was purified through a 40g silica cartridge eluting with 60 - 100 % DCM in cyclohexane. Appropriate fractions were combined and evaporated to dryness to give the title compound, 192 mg.

**Intermediate 10**

LCMS (Method B) *R*ₜ = 1.16 min, *MH*⁺ = 404.
yV-(5-Bromo-2-chloro-3-pyridinyl)benzenesulphonamide

Benzenesulfonyl chloride (2.24 ml) was added dropwise over 5 - 10 min to a solution of 5-bromo-2-chloro-3-pyridinamine (2.5 g) and pyridine (1.5 ml) in DCM (25 ml). The reaction was stirred for 18 h at RT before evaporation to dryness in vacuo. The residue was split in two and purified by silica gel chromatography, eluting with 0 - 100 % DCM in cyclohexane. Appropriate fractions were combined and evaporated to give the title compound, 1.81 g.

LCMS (Method D) R<sub>t</sub> = 1.09 min, M<sup>+</sup>H<sup>-</sup> = 347.

Intermediate 11
5-Bromo-2-chloro-3-[(phenylsulfonyl)methyl]pyridine

(5-Bromo-2-chloro-3-pyridinyl)methyl methanesulfonate (644 mg) was dissolved in DMF (10 ml) and sodium benzenesulfinate (1179 mg) was added. The reaction was stirred at RT overnight. Saturated sodium bicarbonate (20 ml) was added, followed by water (20 ml) and ethyl acetate (20 ml). The aq was separated and washed with further ethyl acetate. The combined organics were washed with brine then passed through a hydrophobic frit. The crude material was washed through a 5g silica cartridge with DCM. The material was purified on a 40g silica cartridge eluting with cyclohexane:DCM (60 - 100 %). Purified fractions were combined and evaporated to give the title compound, 480 mg.

LCMS (Method B) R<sub>t</sub> = 1.06 min, M<sup>+</sup>H<sup>-</sup> = 346.

Intermediate 12
(5-Bromo-2-chloro-3-pyridinyl)methyl methanesulfonate

Triethylamine (0.564 ml) and DCM (12 ml) were added to (5-bromo-2-chloro-3-pyridinyl)methanol (600 mg). The reaction was cooled to 0 °C and methanesulfonyl
chloride (0.219 ml) was added dropwise. The reaction was left for 30 min then warmed to RT. The reaction was extracted with saturated sodium bicarbonate (aq) (20 ml) and the DCM was separated and passed through a hydrophobic frit then evaporated to dryness. The residue was purified through a 5g silica cartridge, washing with cyclohexane, then cyclohexane:DCM (50:50, v/v) then DCM. The fractions containing product were combined, evaporated to dryness, and then dried on the high vacuum to give the title compound, 644 mg.

LCMS (Method B) \( R_t = 0.93 \) min, \( MH^+ = 302 \).

**Intermediate 13**

\[
\text{N-}[6-(5-Amino-6-chloro-3^yridinyl)-2^y\text{trahydro-2H-pyran-2-yl}]\text{-2H-indazol-4-yl]}\text{-2-methyl-1,3-thiazole-4-carboxamide}
\]

2-Methyl-N-[2-(tetrahydro-2H-pyran-2-yl)-6-(4,4,6,6-tetramethyl-1,3,2-dioxaborinan-2-yl)-]

2H-indazol-4-yl]-1,3-thiazole-4-carboxamide (0.75 g), 5-bromo-2-chloro-3-pyridinamine (0.39 g), sodium carbonate (0.66 g) and Pd(dppf)Cl\(_2\) (0.114 g) were weighed to a 10 - 20 ml microwave vial and 1,4-dioxane (8 ml) then water (8 ml) were added. The reaction was heated at 140 °C for 20 min. The reaction was passed through a 10 g silica cartridge, washing with methanohDCM (1:1, v/v). The solvent was evaporated and the residue was purified on a 40 g ISCO companion silica cartridge, eluting with 1.5 - 7.5% methanol in DCM (containing 1% ammonia) at 40 ml/min. Pure fractions were combined and evaporated to dryness to give the title compound (335 mg).

LCMS (Method D) \( R_t = 1.05 \) min, \( MH^+ = 469/471 \).

**Intermediate 14**

5-Bromo-2-chloro-3-[fluoro(phenylsulfonyl)methyl]pyridine
5-Bromo-2-chloro-3-[(phenylsulfonyl)methyl]pyridine (309 mg) was dissolved in 2-methyltetrahydrofuran (20 ml) and cooled to -78 °C. Sodium bis(trimethylsilyl)amide (0.594 ml) was added dropwise. After 15 min, N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (281 mg) was added portionwise. The reaction was stirred for 1 h. The reaction was quenched with saturated ammonium carbonate (aq) (10 ml) and allowed to warm to RT. The aqueous was separated and the organic was washed with saturated sodium bicarbonate (aq) (15 ml) before being passed through a hydrophobic frit and evaporated to dryness. The residue was triturated with methanol then filtered. The filtrate was evaporated to dryness then dried on the high vacuum to give the title compound, as a white solid, 221 mg.

LCMS (Method B) R_t = 1.17 min, M+H = 366.

**Intermediate 15**

2-Methyl-yV-[6-[3-(methylsulfonyl)-1H-pyrazolo[3,4-fe]pyridin-5-yl]-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide

![Intermediate 15 structure](image)

2-Methyl-N-[1 -(phenylsulfonyl)-6-(trimethylstannanyl)-1 H-indazol-4-yl]-1 ,3-thiazole-4-carboxamide (200 mg) and 5-bromo-3-(methylsulfonyl)-1 H-pyrazolo[3,4-b]pyridine (98 mg) and Pd(PPh_3)_4 (41 mg) were placed in DMF (2 ml) and the mixture heated at 120 °C for a total of 75 min in the microwave. The reaction mixture was purified by MDAP (method A). The product-containing fractions were blown down under a stream of nitrogen to give the title compound, 17 mg.

LCMS (Method B) R_t = 1.03 min, MH^+ = 592.

**Intermediate 16**

5-Bromo-3-(methylsulfonyl)-1H-pyrazolo[3,4-b]pyridine

![Intermediate 16 structure](image)
To a solution of N-{5-bromo-3-[(methylsulfonyl)methyl]-2-pyridinyl}acetamide (3.71 g) in a 250 ml round-bottom flask in DMF (100 ml) was added potassium acetate (1.185 g), acetic acid (1.037 ml) and acetic anhydride (1.151 ml). The solution was stirred at RT before addition of tert-butyl nitrite (4.31 ml) over 15 min. The reaction was heated to 60 °C for 2.5 h. Tert-butyl nitrite (1.43 ml) was added. After 1 h, potassium acetate (0.65 g) and acetic anhydride (0.6 ml) were added. After 1 h, the reaction was cooled and water was added (250 ml), the pH adjusted to 8 using saturated sodium bicarbonate (aq), then partitioned with ethyl acetate and the aqueous layer extracted well with ethyl acetate (3 x 300 ml). The aqueous phase was re-extracted with ethyl acetate (3 x 150 ml). The combined organics were washed with saturated sodium bicarbonate (aq), lithium chloride (aq) (4 x 100 ml), brine, dried (MgSO₄), filtered and evaporated. The aqueous phase was salted out with LiCl and NaCl and re-extracted with ethyl acetate. The organics were combined, evaporated then put under high vacuum overnight. The residue was dissolved in DCM, filtered and purified on a 120 g Companion XL silica cartridge, eluting with 0 - 100 % ethyl acetate in cyclohexane over 12 column volumes to give the title compound, 384 mg.

LCMS (Method B) Rₓ = 0.7 min, MH⁺ = 278.

**Intermediate 17**

**W-{5-Bromo-3-[(methylsulfonyl)methyl]-2-pyridinyl}acetamide**

To 5-bromo-3-[(methylsulfonyl)methyl]-2-pyridinamine (4.7 g) in a 1 L round-bottom flask under nitrogen in acetic acid (100 ml) was added acetic anhydride (3.35 ml) and the reaction was heated to 80 °C. After 3 h acetic anhydride (3.35 ml) was added and the reaction was heated overnight. The reaction was cooled and partitioned between ethyl acetate (200 ml) and water (400 ml) and the aqueous layer extracted well with ethyl acetate. The combined organics were washed with water, and then stirred whilst saturated sodium bicarbonate (aq) was added in a large conical flask, followed by 2M NaOH (aq) to pH 8. The organics were washed with brine, dried over MgSO₄, filtered and evaporated. The acidic aqueous phase from above was taken to pH 8 and extracted with ethyl acetate and the isolated material was combined with the previous material, ethyl acetate was added and then filtered to give the title compound, 3.86 g.
Intermediate 18
5-Bromo-3-[(methylsulfonyl)methyl]-2-pyridinamine

To bis(1,1-dimethylethyl) {5-bromo-3-[(methylsulfonyl)methyl]-2-pyridinyl}imidodicarbonate (8.82 g) in a 1 L round-bottom flask under nitrogen in methanol (200 ml) was added 1M HCl in diethyl ether (190 ml). The reaction was left for 70 min, and then 1M HCl in diethyl ether (95 ml) was added. The reaction was left for 3.5 h, 1M HCl in diethyl ether (95 ml) was added and the reaction was left overnight. Further 1M HCl in diethyl ether was added (60 ml) and the reaction left for 45 min. The reaction volume was reduced to -200 ml and 4M HCl in dioxane (70 ml) was added. The reaction was left for 3.75 h then evaporated to dryness. A portion of the solid obtained was partitioned between ethyl acetate and saturated sodium bicarbonate and the aqueous layer extracted well with ethyl acetate. The combined organics were washed with brine, dried (MgSO₄), filtered and evaporated to give the free base. The remainder of the material was similarly treated, combined then evaporated to dryness to give the title compound, 4.85 g.

LCMS (Method B) Rₜ = 0.46 min, MH⁺ = 267.

Intermediate 19
Bis(1,1-dimethylethyl) {5-bromo-3-[(methylsulfonyl)methyl]-2-pyridinyl}imidodicarbonate

To a solution of bis(1,1-dimethylethyl) {5-bromo-3-[(methylthio)methyl]-2-pyridinyl}imidodicarbonate (19.6 g, 61% pure) in a 500 ml round-bottom flask in MeCN (150 ml) was added oxone (59.6 g) and water (120 ml). The mixture was stirred at RT for 2.25 h. The mixture was partitioned between ethyl acetate and water and the aqueous layer extracted well with ethyl acetate. The combined organics were washed with brine,
dried (MgSO₄), filtered and evaporated. The material was purified on a 330 g Companion XL silica cartridge, eluting with 0-40% ethyl acetate in cyclohexane over 12 column volumes. Pure fractions were evaporated to give the title compound, 8.82 g.

LCMS (Method B) \( R_t = 1.12 \text{ min}, M\text{H}^+ = 367 \) (loss of one boc group).

**Intermediate 20**

Bis(1,1-dimethylethyl) [5-bromo-3-[(methylthio)methyl]-2-pyridinyl]imidodicarbonate

![Chemical Structure](image)

To bis(1,1-dimethylethyl) [5-bromo-3-(bromomethyl)-2-pyridinyl]imidodicarbonate (26.1 g, 64% pure) in a 50 ml round-bottom flask under nitrogen in THF (300 ml) was added sodium thiomethoxide (3.78 g). The reaction was stirred at RT for 80 min before addition of sodium thiomethoxide (1.9 g). After 2.25 h the reaction was partitioned between ethyl acetate and water and the aqueous layer extracted well with ethyl acetate. The combined organics were washed with water, brine, dried (MgSO₄), filtered and evaporated. The residue was purified on a 750 g Companion XL silica cartridge, eluting with 0 - 20 % ethyl acetate in cyclohexane over 12 column volumes. Product-containing fractions were evaporated to give crude the title compound used directly in next step, 19.6 g.

LCMS (Method B) \( R_t = 1.34 \text{ min}, M\text{H}^+ = 435 \).

**Intermediate 21**

Bis(1,1-dimethylethyl) [5-bromo-3-(bromomethyl)-2-pyridinyl]imidodicarbonate

![Chemical Structure](image)

To bis(1,1-dimethylethyl) (5-bromo-3-methyl-2-pyridinyl)imidodicarbonate (27.33 g) in a 1 L round-bottom flask under nitrogen in carbon tetrachloride (600 ml) was added N-bromosuccinimide (13.19 g) in 4 equal portions, every 15 min, whilst the reaction was illuminated with a 300 W white spotlight. After 1.25 h, benzoyl peroxide (1.71 g) was added. After 2.5 h, the mixture was filtered then partitioned with water. The organics were washed with sodium thiosulphate (aq), brine, dried (MgSO₄), filtered and evaporated. The
residue was purified on a 330 gm Companion XL silica cartridge, eluting with 0 - 25 % ethyl acetate in cyclohexane over 12 column volumes. Product-containing fractions were evaporated to give crude the title compound used directly in next step, 23.8 g.

LCMS (Method A) \( R_t = 3.41 \text{ min}, \text{MH}^+ = 467 \).

Impure fractions were combined and repurified using a 120 g Companion XL silica cartridge, eluting with 0 - 25 % ethyl acetate in cyclohexane over 10 column volumes. The cleanest product-containing fractions were evaporated to give crude the title compound used directly in next step, 2.3 g.

LCMS (Method B) \( R_t = 1.33 \text{ min}, \text{MH}^+ = 467 \).

Intermediate 22

Bis(1,1-dimethylethyl) (5-bromo-3-methyl-2-pyridinyl)imidodicarbonate

\[
\begin{align*}
&\text{Br} & \text{N} & \text{O} & \text{O} \\
\text{N} & \text{O} & \text{O} & \text{C} \\
& \text{N} & \text{O} & \text{O} & \text{C}
\end{align*}
\]

To 5-bromo-3-methyl-2-pyridinamine (14.78 g) in a 500 ml round-bottom flask was added DCM (300 ml) followed by DIPEA (30.4 ml), DMAP (9.65 g) and bis(1,1-dimethylethyl) dicarbonate (36.7 ml). The reaction was stirred at RT under nitrogen for 1 h 50 min. The reaction was partitioned between DCM and water and the aqueous layer extracted well with DCM. The combined organics were washed with 0.5 M HCl (aq), water, brine, dried (MgSO\(_4\)), filtered and evaporated. The residue was triturated with ether (-120 ml), some cyclohexane was added and the solid collected by vacuum filtration. This was combined with the evaporated filtrate and purified on a 330 g Companion XL silica cartridge, eluting with 0 - 50 % ethyl acetate in cyclohexane over 10 column volumes, to give the title compound, 27.33 g.

LCMS (Method B) \( R_t = 1.3 \text{ min}, \text{MH}^+ = 389 \).

Intermediate 23

yV-(6-Bromo-1H-indazol-4-yl)-2-methyl-1,3-thiazole-4-carboxamide

\[
\begin{align*}
&\text{S} & \text{N} & \text{O} & \text{NH} \\
& \text{O} & \text{NH} & \text{N} & \text{N} \\
& \text{N} & \text{N} & \text{N} & \text{N}
\end{align*}
\]

2-Methyl-1,3-thiazole-4-carboxylic acid (4.59 g), HATU (13.4 g) and DIPEA (16.8 ml) were
stirred in DMF (140 ml) for 30 min at 20 °C. 6-Bromo-1H-indazol-4-amine (3.40 g) was added and the reaction stirred at 20 °C for 2 days. The solvent was reduced to 40 ml and the reaction mixture applied to 5 x 70 g aminopropyl SPE cartridges and left to stand for 3 h. The cartridges were eluted with DCM:MeOH (1:1, v/v) and the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography, eluting with 0 - 15% methanol (containing 1% Et3N) in DCM. Appropriate fractions were evaporated to give the title compound, 1.02 g.

LC/MS (Method D) Rₜ = 0.96 min, MH⁺ = 339.

Intermediate 24
4-Chloro-N-[5-chloro-2-(methyloxy)-3^-yridinyl]-3-(trifluoromethyl)benzene-sulfonamide

4-Chloro-3-(trifluoromethyl)benzenesulfonyl chloride (56 mg) was dissolved in pyridine (1 ml) and DMAP (2 mg) was added. 5-Chloro-2-(methyloxy)-3-pyridinamide (32 mg) was added and the reaction was heated to 100 °C for 2 h. The reaction was purified by HPLC using 20 - 80% MeCN:water:TFA to give the title compound, 72 mg.

LC/MS (Method E) Rₜ = 3.13 min, MH⁺ = 401.

Example 1
W-[6-[5-Amino-6-(methyloxy)-3^-yridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide

2-Methyl-N-[2-(tetrahydro-2H-pyranyl-2-yl)-6-(4,4,6,6-tetramethyl-1,3,2-dioxaborinan-2-yl)-2H-indazol-4-yl]-1,3-thiazole-4-carboxamide (50 mg), 5-bromo-2-(methyloxy)-3-pyridinamine (21 mg) and Pd(dpdpf)Cl₂ (8 mg) were combined in a microwave vial. 1,4-Dioxane (0.5 ml) was added followed by sodium carbonate (44 mg) dissolved in water (0.5 ml). The reaction was heated in the microwave at 140 °C for 20 min. The reaction
was filtered through a silica cartridge (1 g) washing with DCM:methanol (3:1). The solvent was then removed under a stream of nitrogen. The residue was dissolved in DMSO (1.2 ml) and methanol (0.4 ml) and purified using MDAP (method D). The product-containing fractions were left overnight to deprotect. The residue was dissolved in 1,4-dioxane:water (2 ml, 1:1, v/v) and freeze-dried. The residue was dissolved in DCM, a few drops of TFA were added and the reaction left overnight. The residue was further purified by MDAP (method A) then dried under nitrogen blowdown to give the title compound, 10 mg.

LCMS (method B) R_t = 0.85 min, MH^+ = 381.

Similarly prepared from the boronic ester and the appropriate bromide were the following:

<table>
<thead>
<tr>
<th>Example No</th>
<th>Structure</th>
<th>Name</th>
<th>R_t</th>
<th>MH^+</th>
<th>Bromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="Structure" /></td>
<td>5-(4-[[2-methyl-1,3-thiazol-4-yl]carbonyl][amino]-1H-indazol-6-yl)-3-pyridinecarboxylic acid</td>
<td>0.71</td>
<td>380</td>
<td>5-bromo-3-pyridine-carboxylic acid</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure" /></td>
<td>2-methyl-N-(6-phenyl-1H-indazol-4-yl)-1,3-thiazole-4-carboxamide</td>
<td>1.06</td>
<td>335</td>
<td>bromobenzene</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure" /></td>
<td>N-[6-[3-(cyanomethyl)phenyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>0.99</td>
<td>374</td>
<td>(3-bromophenyl)-acetonitrile</td>
</tr>
</tbody>
</table>

**Example 5**

W-[6-(5-Amino-3^yridinyl)-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide
2-Methyl-N-[1-(phenylsulfonyl)-6-(trimethylstannanyl)-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide (1 g) was dissolved in DMF (4 ml) and 400 µl was dispensed to 5-bromo-3-pyridinamine (0.18 mmol) in DMF (400 µl) in a microwave vessel. Solvias catalyst (4 mg) was added and the reaction was heated in the Anton Parr microwave using initial 700 W to 135 °C for 20 min. The solution was loaded onto C18 SPE (pre-conditioned with 0.1 % TFA in MeCN) and flushed through with 0.1 % TFA in MeCN (3 ml). The solvent was removed under nitrogen blowdown. The sample was dissolved in DMSO (0.5 ml) and purified by MDAP (method C). The solvent was evaporated in vacuo using the Genevac.

The sample was dissolved in IPA (300 µl) and 2M NaOH (aq) (300 µl) was added. The reaction was left overnight. The sample was dissolved in DMSO (0.6 ml) and purified by MDAP (method C). The solvent was evaporated in vacuo using the Genevac to give the title compound, 4 mg.

LCMS (method B) R<sub>t</sub> = 0.55 min, MH<sup>+</sup> = 351.

Similarly prepared from the appropriate bromide were the following;

<table>
<thead>
<tr>
<th>Example No</th>
<th>Structure</th>
<th>Name</th>
<th>Rt</th>
<th>MH&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Bromide Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image.png" alt="Structure" /></td>
<td>N-[6-[3-(hydroxymethyl)phenyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>0.83</td>
<td>365</td>
<td>(3-bromophenyl)-methanol</td>
</tr>
</tbody>
</table>
Example 8

\[ \text{[(3-(4-[(2-Methyl-1,3-thiazol-4-yl)carbonyl]amino)-1H-indazol-6-yl)phenyl]oxy} \text{acetic acid} \]

Similarly prepared from the appropriate bromide were the following:

<table>
<thead>
<tr>
<th>Example No</th>
<th>Structure</th>
<th>Name</th>
<th>Rt</th>
<th>MH⁺</th>
<th>Bromide Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N-{6-[5- (hydroxymethyl)-3-pyridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>0.56</td>
<td>366</td>
<td>(5-bromo-3-pyridinyl)methanol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
<td>pKa</td>
<td>MW</td>
<td>Notes</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-----------------</td>
<td>-----</td>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>9*</td>
<td><img src="image1.png" alt="Image" /></td>
<td>N-[6-(5-amino-6-chloro-3-pyridinyl)-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>0.87</td>
<td>385</td>
<td>5-bromo-2-chloro-3-pyridinamine</td>
</tr>
<tr>
<td>10</td>
<td><img src="image2.png" alt="Image" /></td>
<td>N-[6-[6-chloro-5-(hydroxymethyl)-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>0.85</td>
<td>400</td>
<td>(5-bromo-2-chloro-3-pyridinyl)methanol</td>
</tr>
<tr>
<td>11</td>
<td><img src="image3.png" alt="Image" /></td>
<td>N-[6-{6-chloro-5-methyl(phenylsulfonyl)-amino]-3-pyridinyl]-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>1.1</td>
<td>539</td>
<td>N-(5-bromo-2-chloro-3-pyridinyl)-N-methylbenzene-sulfonamide</td>
</tr>
<tr>
<td>12*</td>
<td><img src="image4.png" alt="Image" /></td>
<td>N-[6-(2-amino-4-pyridinyl)-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide hydrochloride</td>
<td>0.66</td>
<td>351</td>
<td>4-bromo-2-pyridinamine</td>
</tr>
<tr>
<td>13</td>
<td><img src="image5.png" alt="Image" /></td>
<td>N-[6-(5-amino-6-chloro-3-pyridinyl)-1 H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide</td>
<td>1.04</td>
<td>524</td>
<td>5-bromo-2-chloro-3-[(phenylsulfonyl)methyl]pyridine</td>
</tr>
<tr>
<td>14*</td>
<td><img src="image6.png" alt="Image" /></td>
<td>2-chloro-5-{4-[[2-methyl-1,3-thiazol-4-y1]carbonyl]amino]-1 H-indazol-6-yl}-3-pyridine carboxylic acid</td>
<td>0.82</td>
<td>414</td>
<td>5-bromo-2-chloro-3-pyridine carboxylic acid</td>
</tr>
</tbody>
</table>
**Example 16**

Phenylmethyl [2-chloro-5-([2-methyl-1,3-thiazol-4-yl]carbonyl)amino]-1 H-indazol-6-yl)-3-pyridinyl]carbamate

DCM (2 ml) and DIPEA (0.037 ml) were added to N-[6-(5-amino-6-chloro-3-pyridinyl)-2-(tetrahydro-2H-pyran-2-yl)-2H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide (50 mg) and the reaction stirred. Phenylmethyl chloridocarbonate (0.023 ml) was added and the reaction was stirred at RT overnight. The reaction was evaporated to dryness. Pyridine (1 ml) was added followed by phenylmethyl chloridocarbonate (0.023 ml) and the reaction was stirred at RT for 4 h. DMAP (3 mg) was added followed by phenylmethyl chloridocarbonate (0.023 ml) and the reaction was stirred at RT. Phenylmethyl chloridocarbonate (0.05 ml) was added and the reaction was left overnight. Phenylmethyl chloridocarbonate (0.05 ml) was added and the reaction was stirred at RT for 1 h. Phenylmethyl chloridocarbonate (0.05 ml) was added and the reaction stirred at RT for 2 h. 2M HCl (aq) and DCM were added. The DCM was separated, passed through a hydrophobic frit and evaporated to dryness. The residue was dissolved in DMSO:methanol (1 ml, 7:3, v/v) and purified by MDAP (method A). Fraction containing product was evaporated to dryness and methanol (3 ml) and a few drops of 2M HCl (aq) were added and the reaction stirred for 1 h. The reaction was evaporated to dryness to give the title compound, 13 mg.

LCMS (method B) \( R_t = 1.17 \) min, \( M^+ = 519 \)

---

**Example 17**
**Example 18**

2-Methyl-N-[6-[3-(methylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide

To a suspension of 2-methyl-N-[6-[3-(methylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-1H-indazol-4-yl]-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide (20 mg) in IPA (0.5 ml) was added 2M NaOH (aq) (0.5 ml) and the mixture stirred at 20 °C for 3 h. The IPA was removed under a stream of nitrogen and the aqueous was neutralised with 2M HCl (aq), then extracted with DCM which was separated using a hydrophobic frit. The aqueous
layer was extracted with ethyl acetate and the organic extracts were combined and the solvent was removed in vacuo, then under a stream of nitrogen to give the title compound, 9 mg.

LCMS (method B) $R_t = 0.77$ min, $\text{MH}^+ = 452.$

**Example 19**

2-Methyl-W-[[6-{5-(4-morpholinylsulfonyl)-3\text{yridinyl}]-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide

\[
\text{\begin{tikzpicture}
\end{tikzpicture}}
\]

2-Methyl-N-[1-(phenylsulfonyl)-6-(trimethylstannanyl)-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide (50 mg) was placed in a microwave vial with $\text{Pd(PPh}_3\text{)}_4$ (10 mg) and 4-[(5-bromo-3-pyridinyl)sulfonyl]morpholine (30 mg). DMF (2 ml) was added and the reaction was heated in the microwave for 15 min at 120 °C. To the residue was added IPA (2 ml) and 2M NaOH (aq) (1 ml) and the mixture stirred at RT for 3 h. The solvent was blown off under nitrogen and the residue purified by MDAP (method A) to give the title compound as a white solid, 17 mg.

LCMS (method B) $R_t = 0.86$ min, $\text{MH}^+ = 485.$

**Example 20**

2-Methyl-N-[6-(1H-pyrazol-4-yl)-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide

\[
\text{\begin{tikzpicture}
\end{tikzpicture}}
\]

To 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (23 mg) in 1,4-dioxane (1 ml) was added N-(6-bromo-1H-indazol-4-yl)-2-methyl-1,3-thiazole-4-carboxamide (36 mg) dissolved in 1,4-dioxane (1 ml). Potassium carbonate (18 mg) dissolved in water (0.2 ml) and Pd(dppf)Cl$_2$ (10 mg) were added and the reaction was heated in the microwave to 150 °C for 30 min. The solvent was evaporated in vacuo using the Genevac. The residue was loaded in methanol to a C18 cartridge (500 mg) and eluted using MeCN:0.1 % TFA
The appropriate fractions were combined and dried under a stream of nitrogen. The sample was dissolved in MeOH:DMSO (0.5 ml, 1:1) and purified by MDAP (method B). The solvent was evaporated in vacuo using the Genevac to give the title compound, 0.3 mg.

5 LCMS (method B) R_t = 0.67 min, MH^+ = 325.

Similarly prepared from the appropriate bromide were the following:

<table>
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<tr>
<th>Example No</th>
<th>Structure</th>
<th>Name</th>
<th>R_t</th>
<th>MH^+</th>
<th>Bromide Name</th>
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<tr>
<td>21</td>
<td><img src="image" alt="Structure" /></td>
<td>2-methyl-N-[6-[5-(4-morpholinylcarbonyl)-3-pyridinyl]-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide</td>
<td>0.71</td>
<td>449</td>
<td>4-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-pyridinyl]carbonyl]morpholine</td>
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<tr>
<td>22</td>
<td><img src="image" alt="Structure" /></td>
<td>2-methyl-N-[6-[1-(phenylmethyl)-1H-pyrazol-4-yl]-1H-indazol-4-yl]-1,3-thiazole-4-carboxamide</td>
<td>0.96</td>
<td>415</td>
<td>1-(phenylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole</td>
</tr>
</tbody>
</table>

10 Example 23

\[\text{N-[6-(1-Acetyl-2,3-dihydro-1H-indol-4-yl)-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide}\]

![Structure](image)

2-Methyl-N-[2-(tetrahydro-2H-pyran-2-yl)-6-(4,4,6,6-tetramethyl-1,3,2-dioxaborinan-2-yl)-2H-indazol-4-yl]-1,3-thiazole-4-carboxamide (53 mg) in 1,4-dioxane (0.4 ml) was added to 1-acetyl-4-bromo-2,3-dihydro-1H-indole (24 mg). 1,4-Dioxane (0.4 ml) was added followed by Solvias catalyst (2 mg) (heaped microspatula) and tripotassium phosphate
(212 mg) in water (0.2 ml). The reaction was heated in the microwave to 110 °C for 20 min. The solution was then loaded onto C18 SPE (pre-conditioned with MeCN:0.1 % TFA) and flushed through with MeCN:0.1 % TFA (3 ml). The solvent was removed in under nitrogen blowdown. The residue was dissolved in methanol (500 µl) and loaded onto SCX-2 SPE (1 g), pre-conditioned with methanol. The compound was left on the column for 1 h then eluted with 2M ammonia in methanol. The sample was dissolved in DMSO (0.5 ml) and purified by MDAP (method B). The solvent was evaporated in vacuo using the Genevac to give the title compound, 8 mg.

LCMS (method B) $R_t = 0.9$ min, $M^+ = 418$.

**Example 24**

W-[6-5-[[4-Chloro-3-(trifluoromethyl)phenyl]sulfonyl]amino]-6-(methylxy)-3-pyridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide trifluoroacetate

![Chemical structure](image)

2-Methyl-N-[2-(tetrahydro-2H-pyran-2-yl)-6-(4,4,6,6-tetramethyl-1,3,2-dioxaborinan-2-yl)-2H-indazol-4-yl]-1,3-thiazole-4-carboxamide (50 mg), Pd(dppf)Cl$_2$ (8 mg) and sodium carbonate (44 mg) were added to a microwave vial. 4-Chloro-N-[5-chloro-2-(methylxy)-3-pyridinyl]-3-(trifluoromethyl)benzenesulfonamide (42 mg) was added followed by 1,4-dioxane (0.5 ml) and water (0.5 ml). The reaction was heated at 140 °C for 30 min. The material was passed through a 1 g silica cartridge with DCM:methanol, then evaporated to dryness. The residue was dissolved in DMSO:methanol (1.6 ml, 1:1, v/v), passed through a 1 g C18 cartridge washing with MeCN and evaporated under nitrogen blow down. The residue was dissolved in DMSO:methanol (1.6 ml, 1:1, v/v) and purified by MDAP (method D). The pure fractions were combined, blown down, suspended in 1,4-dioxane:water (ca. 3ml, 1:1, v/v) and freeze-dried to give the title compound, 7 mg.

LCMS (method B) $R_t = 1.21$ min, $M^+ = 623$.

**BIOLOGICAL DATA**

**PI3K Alpha, Beta, Delta and Gamma Assays**
**Assay principle**

The assay readout exploits the specific and high affinity binding of PIP3 to an isolated pleckstrin homology (PH) domain in the generation of a signal. Briefly, the PIP3 product is detected by displacement of biotinylated PIP3 from an energy transfer complex consisting of Europium (Eu)-labelled anti-GST monoclonal antibody, a GST-tagged PH domain, biotin-PIP3 and Streptavidin-APC. Excitation of Eu leads to a transfer of energy to APC and a sensitized fluorescence emission at 665nm. PIP3 formed by PI3kinase activity competes for the binding site on the PH domain, resulting in a loss of energy transfer and a decrease in signal.

**Assay protocol**

Solid compounds are typically plated with 0.1 µl of 100% DMSO in all wells (except column 6 and 18) of a 384-well, v bottom, low volume Greiner plate. The compounds are serially diluted (4-fold in 100% DMSO) across the plate from column 1 to column 12 and column 13 to column 24 and leave column 6 and 18 containing only DMSO to yield 11 concentrations for each test compound.

The assays are run using specific PI3 kinase kits from Millipore (Cat# 33-001)

The assay kit consist of the following:

- 4x PI3K reaction buffer (Contains 200mM Hepes pH 7, 600mM NaCl, 40mM MgCl₂, <1% Cholate (w/v), <1% Chaps (w/v), 0.05% Sodium Azide (w/v))
- PIP2 (1mM)
- 3xBiotin PIP3 (50µM)
- Detection Mix C (Contains 267mM KF)
- Detection Mix A (Contains 60µg/ml streptavidin-APC)
- Detection Mix B (Contains 36µg/ml Europium-anti-GST(Anti-GST-K) and 1g/ml GST-GRP1-PH-Domain and 1mM DTT)
- Stop Solution (Contains 150mM EDTA)

Manually add 3µl of Reaction buffer (contains 1mM DTT) to column 18 only for 100% inhibition control (no activity)

Manually add 3µl of 2X Enzyme solution to all wells except column 18. Preincubate with compound for 15minut.es.
Manually add 3 µl of 2X Substrate solution to all wells. (column 6 represents 0% inhibition control)

Leave plate for 1hr (cover from light) (In the case of Gamma only a 50 min incubation is required)

Manually add 3 µl Stop/Detection solution to all wells

Leave plate for 1 hour (cover from light)

The assay is read upon the BMG Rubystar and the ratio data is utilised to calculate 11 point curves.

NB The substrate solution (concentrations) differ with each isoform (see below)

**Alpha**
2x substrate solution containing 500 µM ATP, 16 µM PIP2 and 0.030 µM 3X biotin-PIP3.

**Beta**
2x substrate solution containing 800 µM ATP, 16 µM PIP2 and 0.030 µM 3X biotin-PIP3.

**Delta**
2X substrate solution containing 160 µM ATP, 10 µM PIP2 and 0.030 µM 3X biotin-PIP3.

**Gamma**
2X substrate solution containing 30 µM ATP, 16 µM PIP2 and 0.030 µM 3X biotin-PIP3.

**Analysis Method**
Data processed through the XC50 4-parameter logistic curve fit algorithm in Activity Base.

Normalise to % inhibition between the high and low controls (0% and 100% inhibition respectively)

Primary Module fit: Slope, Min and Max asymptotes varies

Secondary Module fits: (1) Fix Min asymptote, (2) Fix Max asymptote, (3) Fix Min and Max asymptotes

Curve Fit QC: pXC50 95% CL ratio >10
-20 < Min asymptote < 20
80 < Max asymptote < 120

The compounds of Examples 1 to 24 were tested in one or more of the PI3K Alpha, Beta, Delta and/or Gamma assays above or similar assays and were found to have a mean plC50 of 5 or greater.
What is claimed is:

1. A compound of formula (I)

   ![](image)

   (I)

   wherein

   \[ R^1 \] is phenyl optionally substituted by \(-\text{OR}^3\), \(-\text{CH}_2\text{OR}^4\) or \(-\text{CH}_2\text{CN}\); 5-membered heteroaryl wherein the 5-membered heteroaryl contains one or two heteroatoms independently selected from oxygen, nitrogen and sulphur and is optionally substituted by \(-\text{CH}_2\text{phenyl}\); pyridinyl wherein the pyridinyl is substituted by one substituent selected from \(-\text{NH}_2\), \(-\text{CH}_2\text{OR}^5\), \(-\text{CO}_2\text{R}^6\), \(-\text{CONR}^7\text{R}^8\), \(-\text{NHCO}_2\text{R}^9\), \(-\text{XS}_2\text{R}^{10}\), \(-\text{S}_2\text{NR}^1\text{R}^2\) and \(-\text{NHS}_2\text{R}^3\), and is optionally substituted by a second substituent selected from halo and \(-\text{OR}^{14}\); 9- or 10-membered bicyclic heteroaryl wherein the 9- or 10-membered bicyclic heteroaryl contains from one to three heteroatoms independently selected from oxygen and nitrogen and is substituted by \(-\text{S}_2\text{R}^{15}\); or phenyl fused to pyrrolidinyl wherein the pyrrolidinyl is substituted by \(-\text{COR}^{16}\);

   \[ R^2 \] is 5-membered heteroaryl wherein the 5-membered heteroaryl contains one or two heteroatoms independently selected from oxygen, nitrogen and sulphur and is optionally substituted by \(\text{C}_{1-6}\text{alkyl}\);

   \[ R^3 \] is \(\text{C}_{1-6}\text{alkyl}\) substituted by \(-\text{CO}_2\text{R}^{17}\);

   \[ R^4, R^5, R^6, R^{14} \text{ and } R^{15} \] are each independently hydrogen or \(\text{C}_{1-6}\text{alkyl}\);

   \[ R^7 \text{ and } R^8 \] are each hydrogen, or \(R^7 \text{ and } R^8\), together with the nitrogen atom to which they are attached, are linked to form a 6-membered heterocyclyl optionally containing an oxygen atom;

   \[ R^9 \] is \(\text{C}_{1-6}\text{alkyl}\) optionally substituted by phenyl;
R^0 and R^15 are each independently C<sub>1-6</sub> alkyl or phenyl;

R^11 and R^12, together with the nitrogen atom to which they are attached, are linked to form a 6-membered heterocyclyl optionally containing an oxygen atom;

R^13 is phenyl substituted by -CF<sub>3</sub> and halo;

R^16 is C<sub>1-6</sub> alkyl; and

X is -CH<sub>2</sub>-, -CHF- or -N(CH<sub>3</sub>)<sub>2</sub>;

or a salt thereof.

2. A compound according to claim 1 wherein R^1 is phenyl substituted by -OR<sup>3</sup> or -CH<sub>2</sub>OR<sup>5</sup>; pyridiny1 wherein the pyridiny1 is substituted by one substituent selected from -NH<sub>2</sub>, -CH<sub>2</sub>OR<sup>5</sup> and -NHSO<sub>2</sub>R<sup>13</sup>, and is optionally substituted by a second substituent selected from halo and -OR<sup>14</sup>; or 9- or 10-membered bicyclic heteroaryl wherein the 9- or 10-membered bicyclic heteroaryl contains from one to three heteroatoms independently selected from oxygen and nitrogen and is substituted by -SO<sub>2</sub>R<sup>15</sup>.

3. A compound according to claim 1 wherein R^1 is pyridiny1 wherein the pyridiny1 is substituted by one substituent selected from -NH<sub>2</sub> and -NHSO<sub>2</sub>R<sup>13</sup>, and is optionally substituted by a second substituent which is -OR<sup>14</sup>; or 9-membered bicyclic heteroaryl wherein the 9-membered bicyclic heteroaryl contains three nitrogen atoms and is substituted by -SO<sub>2</sub>R<sup>15</sup>.

4. A compound according to claim 1 or claim 2 wherein R^2 is 5-membered heteroaryl wherein the 5-membered heteroaryl contains one or two heteroatoms independently selected from nitrogen and sulphur and is optionally substituted by C<sub>1-6</sub> alkyl.

5. A compound which is:
/V-{6-[5-amino-6-(methyloxy)-3-pyridinyl]-1 H-indazol-4-yl}-2-methyl-1,3-thiazole-4-carboxamide;

5-(4-[(2-methyl-1,3-thiazol-4-yl)carbonyl]amino)-1 H-indazol-6-yl)-3-pyridinecarboxylic acid;
2-methyl-N-(6-phenyl-1 H-indazol-4-yl)-1,3-thiazole-4-carboxamide;
N-{6-[3-(cyanomethyl)phenyl]-1H-indazol-4-yl}-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-(5-amino-3-pyridinyl)-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-[3-(hydroxymethyl)phenyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-[5-(hydroxymethyl)-3-pyridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-[3-(4-[[(2-methyl-1,3-thiazol-4-yl)carbonyl]amino]-1H-indazol-6-yl)phenyl]oxy]acetic acid;  
N-[6-(5-amino-6-chloro-3-pyridinyl)-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-[6-chloro-5-(hydroxymethyl)-3-pyridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-(2-amino-4-pyridinyl)-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-{6-chloro-5-[methyl(phenylsulfonyl)-amino]-1H-indazol-4-yl}-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-(2-amino-4-pyridinyl)-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
N-[6-{6-chloro-5-[(phenylsulfonyl)methyl]-3-pyridinyl}-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
2-chloro-5-(4-[[2-methyl-1,3-thiazol-4-yl]carbonyl]amino)-1H-indazol-6-yl)-3-pyridinecarboxylic acid;  
5-(4-[[2-methyl-1,3-thiazol-4-yl]carbonyl]amino)-1H-indazol-6-yl)-3-pyridinecarboxamide;  
phenylmethyl [2-chloro-5-(4-[[2-methyl-1,3-thiazol-4-yl]carbonyl]amino]-1H-indazol-6-yl]-3-pyridinyl)carbamate;  
/V-(6-[6-chloro-5-[fluoro(phenylsulfonyl)]methyl]-3-pyridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
2-methyl-N-[6-{6-chloro-5-[methylsulfonyl]-1H-pyrazolo[3,4-b]pyridin-5-yl]-1H-indazol-4-yl]-1H,3-thiazole-4-carboxamide;  
2-methyl-N-[6-[5-(4-morpholinylsulfonyl)-3-pyridinyl]-1H-indazol-4-yl]-1H,3-thiazole-4-carboxamide;  
2-methyl-N-[6-{1-(phenylmethyl)-1H-pyrazol-4-yl}-1H-indazol-4-yl]-1H,3-thiazole-4-carboxamide;  
2-methyl-N-[6-{1-(acetyl-2,3-dihydro-1H-indol-4-yl)-1H-indazol-4-yl}-2-methyl-1H,3-thiazole-4-carboxamide;  
/N-[6-{1-[4-chloro-3-(trifluoromethyl)phenyl]sulfonyl]amino)-6-(methylxy)-3-pyridinyl]-1H-indazol-4-yl]-2-methyl-1,3-thiazole-4-carboxamide;  
or a salt thereof.
6. A compound according to any one of claims 1 to 5 in the form of a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

8. A compound as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in medical therapy.

9. A compound as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder mediated by inappropriate PI3-kinase activity.

10. Use of a compound as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate PI3-kinase activity.

11. A method of treating a disorder mediated by inappropriate PI3-kinase activity comprising administering a safe and effective amount of a compound as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

12. A method according to claim 11 wherein the disorder mediated by inappropriate PI3-kinase activity is a respiratory disease; an allergic disease; an autoimmune disease; an inflammatory disorder; a cardiovascular disease; a hematologic malignancy; cystic fibrosis; a neurodegenerative disease; pancreatitis; multiorgan failure; kidney disease; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injury; or pain.

13. A method according to claim 11 wherein the disorder mediated by inappropriate PI3-kinase activity is asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, thrombosis, atherosclerosis, hematologic malignancy, cystic fibrosis, neurodegenerative disease, pancreatitis, multiorgan failure, kidney disease, platelet aggregation, cancer, sperm motility, transplantation rejection, graft rejection, lung injury, pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory
pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trama), trigeminal neuralgia or central pain.

14. A method according to claim 11 wherein the disorder mediated by inappropriate PI3-kinase activity is asthma.

15. A method according to claim 11 wherein the disorder mediated by inappropriate PI3-kinase activity is COPD.
#### A. CLASSIFICATION OF SUBJECT MATTER

- **I.N.V.**
  - C07D4/17/ 12
  - C07D47/14
  - C07D47/1/04
  - A61K3/146
  - A61P11/00
  - A61P29/00
  - A61P37/0Q
  - A61P25/00
  - A61P9/00

#### 8. FIELDS SEARCHED

- Minimum documentation searched (classification system followed by classification symbols)
  - C07D
  - A61 K
  - A61 P

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

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

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X, P</td>
<td>wo 2009/147 187 AI (GLAXO GROUP LTD [GB]; BALDWIN IAN ROBERT [GB]; DOWN KENNETH DAVI D [GB]) 10 December 2009 (2009 - 12 - 10) page 9 - page 22</td>
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- Special categories of cited documents:
  - "X" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- "U" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- "V" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- "W" document member of the same patent family

**Date of the actual completion of the international search**

- 11 February 2011

**Date of mailing of the international search report**

- 23/02/2011

**Name and mailing address of the ISA**

- European Patent Office, P.B. 5818 Patentlaan 2
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- Fax: (+31-70) 340-3016

**Authorized officer**

- Fazz, Raffael
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