Abstract: The invention provides a compound of Formula (I): or salts, solvates or tautomers thereof, for use: a) in the prophylaxis or treatment of a disease state or condition mediated by a kinase, or a mutated form thereof, which isa member of the AXL family, or the PKC family, or the CSF-1/PDGFR receptor subfamily, or the Mitogen- and stress-activated kinase family, or the DAP kinase-related apoptosis-inducing protein kinase family; or is a Salt-inducible kinase; or is a member of the 90kDa ribosomal S6 kinase family, or the p21 activated kinase (PAK) family, or the Brain specific kinase family, or the Tousled-like kinase (TLK) family; or b) as an antibacterial agent; or c) as a neuroprotective agent, an immunosuppressive agent or anti-osteolytic agent; or d) in the prophylaxis or treatment of a disease or condition selected from the following: pain; coronary artery disease, myocardial contraction, cardiomyopathy, cardiac remodelling, and heart failure, hypertension, systemic vascular diseases and a range of lung conditions, lung injury; disease states or conditions resulting in excessive bone formation/diseases; and diseases in which bone resorption mediates morbidity; proliferative vitreoretinopathy, liver fibrosis, renal failure, irritable bowel syndrome, oxidative stress-related neurodegenerative disorders and diabetic nephropathy; cerebro ischemia, Coffin-Lowry syndrome, Borna disease, spinocerebellarataxia type 14, schizophrenia, transplant rejection, organ transplantation, resistance to transplantation, graft vs. host disease, pancreatitis and metal poisoning; pancreatic adenocarcinoma, gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from various cancers; adenopathy, hepatosplenomegaly, and circulating lymphoblasts; and allodynia and hyperalgesia.
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
This invention relates to new therapeutic uses including the antibacterial use of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and its salts and crystalline forms.

This application is related to United Kingdom patent application number 080873 1.4 filed 14 May 2008 and United Kingdom patent application number 0809774.3 filed 30 May 2008; the contents of each of which are incorporated herein by reference in their entirety.

**Background of the Invention**

The compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base and various salts thereof are disclosed in our earlier International patent application filed 30th December 2005 claiming priority from USSN 60/640,475 and GB0428552.4 as being inhibitors of Cyclin Dependent Kinases (CDK kinases), Aurora kinases and Glycogen Synthase Kinase-3 (GSK3). This was published as WO 2006/070195 on 6th July 2006.

The compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base and various salts thereof are further disclosed in our earlier International patent application filed 29th December 2006 claiming priority from USSN 60/755,339 and GB0526607.7 filed on 30th December 2005 and USSN 60/806,218 filed on 29th June 2006 as being inhibitors of various further kinases. This was published as WO 2007/077435 on 12th July 2007.

**Protein Kinases**


Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-
protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

Mer

The c-Mer receptor tyrosine kinase (RTK) is a member of the Axl RTK subfamily which is characterized by an N-CAM-like extracellular domain and a common ligand, Gas6 (growth arrest-specific protein 6). Protein S, another vitamin K-dependant ligand has also been observed to bind to Sky and Mer. The family comprises of three members, Axl, Mer and Sky. Human Mer, or c-Mer, is so named after its original reported expression pattern (monocytes and epithelial and reproductive tissues). Mer has been shown to be required for ingestion of apoptotic cells by professional phagocytes such as monocytes/macrophages, retinal pigment epithelial cells and dendritic cells. Mer has also been shown to activate the STAT transcription factor pathway, which was associated with Mer-induced transformation. Upregulation of STATs is found in a wide range of cancer types.

There is a large body of evidence linking this family of tyrosine kinases to carcinogenesis. Axl was initially identified as an NIH3T3 transforming gene, and Mer is the human ortholog of the transforming retroviral oncogene, v-eyk. Overexpression of Axl, Mer, and Sky has been reported in various cancer types. Mer overexpression has been found in solid tumours and leukaemias including prostate, acute lymphoblastic leukemia and mantle cell lymphoma. Mice overexpressing Mer were found to develop adenopathy (lymphadenopathy).
hepatosplenomegaly, and circulating lymphoblasts (Oncogene (2006) 25, 6092-6100). Overexpression of any two of the three kinases was found to be a predictor of poor prognosis for gastric cancer, suggesting these kinases synergize with each other in gastric carcinogenesis. Mer protein kinase seems to play an important role in gastric cancer progression, gastric adenocarcinoma and metastasis and may be a useful prognostic marker in gastric adenocarcinoma. Activation of Mer in the prostate cancer cell line DU145 was found to cause induction of endocrine factors including interleukin (IL)-8 and several other angiogenic CXC chemokines as well as bone morphogenic factors. The dramatic increase of IL-8 expression is seen at both transcriptional and posttranscriptional levels. (Wu et al., Cancer Research 2004; 64, 7311-7320; Hafizi and Dahlback, Cytokine & Growth Factor Rev. 2006; 17(4), 295-304).

**MSK1/2**

Mitogen- and stress-activated kinase (MSK) 1 and MSK2 (also named RSKB or RLPK) belong to a family of dual protein kinases that are activated by either extracellular signal-regulated kinase (ERK) or p38 mitogen-activated protein kinases in response to stress or mitogenic extracellular stimuli. MSK1 and 2 have been shown to play key roles in the transcriptional regulation of immediate early genes including the inflammatory gene interleukin-6 and immediate early response genes, such as c-fos.

Mice with knockouts of MSK1, MSK2, or both MSK1 and MSK2 were viable and fertile and showed no obvious health defects but potential target rationales for MSK1 inhibition in cancer are now emerging. MSK1 gene silencing in human tumour cells leads to severe mitotic aberrations and impaired proliferation. Persistent activation of the Ras-MAPK pathway and MSK1 resulting in the elevation of phosphorylated H3 levels may contribute to the aberrant gene expression observed in oncogene-transformed cells (Strelkov and Davie Cancer Research 2002; 62(1): 75-78).

It has also been shown that MSK1 can enhance ER81-dependent transcription, both through direct phosphorylation as well as indirectly by stimulating the co-activating factors CBP and p300. ER81 has been shown to be involved in oncogenesis and breast tumour formation. The oncogene HER2/Neu has been shown to trigger ER81 through MAPK pathways and is frequently overexpressed in breast tumours and correlates with adverse prognosis. Pharmacological inhibitors of MSK1 may therefore benefit breast cancer treatment. (Janknecht Oncogene 2003; 22: 746-755).
In disease areas other than oncology, analysis of psoriatic skin has shown that MAPK pathways are activated. Reports have now also shown that at least two of these downstream kinases, MAPKAP-K2 and MSK1, are activated in psoriatic skin compared to normal skin. Immunostaining experiments suggested that this activation of MSK occurred mainly in keratinocytes in the psoriatic skin. This implies MSK 1 and/or 2 inhibition in potential treatments for several inflammatory diseases, including arthritis and psoriasis. (Funding et al., 2006; Invest. Dermatology 126:1784-1791).

MSK-I and -2 may have a critical role in linking cellular signalling pathways to chromatin modification and modulation of transcription factor complexes and have potential therapeutic utility. Indeed, it has been demonstrated that MSK-I mediates excitotoxicity-induced death of hippocampal neurones and that inhibitors of MSK-I and -2 may, therefore, be of use in the treatment of diseases involving ischaemic injury (E.A. Irving and M. Bamford, J. Cereb. Blood Flow Metab. 22 (2002), p. 631). Since inhibitors of the p38 pathway and the ERK pathway are reported to be neuroprotectants, MSK-I and -2 inhibitors are also of interest in this regard.

MSK inhibitors may also be of interest to pharmacologically precondition the heart against ischemia reperfusion injury so called cardioprotective effects or ischemic preconditioning (IPC).

Inhibitors of kinases in the Erk MAPK cascade have been suggested for use in the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events, including cerebral ischemia after cardiac arrest, stroke and multi-infarct dementia and also after cerebral ischemic events such as those resulting from head injury, surgery and/or during childbirth. Since Msks are activated by Erk MARK, Msk inhibitors could serve a similar use. Inhibition of cytokines offers modest protection from injury in animal models of lung ischemia-reperfusion. Inhibition of MSK may also provide protection from injury and has the potential benefit of reducing lung reperfusion injury severity.

Msks are reported to be localized exclusively to the nucleus, and are responsible for the phosphorylation and activation of the transcription factor CREB in response to certain stress stimuli. In macrophage and monocyte cells, Mskl is involved in CREB-mediated transcriptional regulation of IL-1 p and Cox2 in response to bacterial 2.5 lipopolysaccharide.

Although Msks are only one of a number of Erk substrates, CREB is involved in many different transcriptional activities, and Msk-mediated CREB phosphorylation could play a role in some cancers. In addition, through modulation of production of pro-inflammatory cytokines such as IL-1 p and prostaglandins, inhibitors of Msks could be of use in treatments for neuroinflammatory diseases such as stroke, multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis and inflammatory pain, as well as other inflammatory
diseases such as rheumatoid arthritis, irritable bowel syndrome, inflammatory bowel disease and asthma.

**DRAK1**

DRAK1 (DAP kinase-related apoptosis-inducing protein kinase 1) and DRAK2 were first cloned by Sanjo et al. in 1998 as novel serine/threonine kinases and are novel members of the ser/thr protein kinase family, which mediate apoptosis through catalytic activity. The kinase activity of DRAK1 is significantly stronger than that of DRAK2. DRAK1 messenger RNA appears to be ubiquitously expressed in human tissues. The DRAK1 protein is located in the nucleus and the messenger RNA is ubiquitously expressed in human tissues. Overexpression of DRAK1 induces apoptosis. Sanjo, et al.; J. Biol. Chem 1998; 273: 29066.

DRAK1 may be a useful therapeutic target for the prevention of diseases involving cell death. During pathological conditions associated with neuronal cell death such as cerebral ischemia or epilepsy, DAP-kinase expression is increased, thus defining this enzyme as a potential neuroprotective drug target for the treatment of CNS diseases. A small molecule inhibitor with an IC₅₀ of 13μM has been reported, that showed neuroprotective effects in animal hypoxia-ischemia models, even when administered 6 hours following injury supporting the hypothesis that targeting protein kinases which function early in programmed cell death pathways could identify new therapeutic approaches to acute brain injury. (Velentza et al., Bio-org. Med. Chem. 2003; 13(20): 3465-3470).

DRAK1 has also been found to be associated with rheumatoid arthritis (RA). DRAK1 expression showed an age-associated ascending trend with significantly greater transcripts of RANKL and DRAK1 in females (p < 0.01). Compared with age-matched controls, RA patients exhibited increased RANKL, PPAR-Gamma, and DRAK1 mRNA levels (p < 0.05) (Jiang et al., J Orthop. Res. 2008; ePub).

DRAK1 is strongly expressed in bone marrow tissues. Moreover, DRAK1 is expressed weakly or not at all in osteoblasts; however, it is expressed strongly in osteoclasts, multinucleated giant cells with the resorbing activity of calcified tissues. These results suggest that DRAK1 is closely involved in the regulation of osteoclastogenesis and osteoclast apoptosis. Patients with conditions resulting in excessive bone formation may derive therapeutic benefit from inhibition of osteoblast apoptosis and increased bone resorption. (Kojima et al., J. Biol. Chem. 2001; Vol. 276, (22): 19238-19243).
SIK

Salt-inducible kinase (SIK) belongs to a family of AMP-activated protein kinase, a serine/threonine protein kinase which plays important roles in regulating metabolism of cells under the stress. SIK was identified as a specific kinase induced by Adrenocorticotropic hormone (ACTH) in the adrenal glands of rats fed a high-salt diet. ACTH is the major stimulant for biosynthesis of steroid hormones in the adrenocortical cells.

ACTH induced nuclear to cytosolic translocation of SIK in a PKA-dependent manner and this intracellular localisation of SIK was thought to be an important factor in determining the time-dependent change in the level of steroidogenic gene expression including CYPl IA, StAR, CYPl IB1, CYPl 1B2 and SIK itself in ACTH-stimulated cells. (Takemori et al., J. Biol. Chem 2002; 277(44): 42334-42343).

Subsequently, two additional SIK isoforms and identified. The previously characterized adrenal-specific enzyme was named SIKL, adipose-specific isoform SIK2 that regulates the early phase of insulin-signaling in the adipose tissue of type 2 diabetic animals and a ubiquitously expressed isoform SIK3. (Katoh et al., Mol. Cell. Endocrinology 2004; 217(1-2): 109-12).

FMS

The Fms proto-oncogene is a protein tyrosine-kinase transmembrane receptor also known as macrophage colony-stimulating factor 1 receptor (M-CSF-IR) and belongs to the CSF-1/PDGF receptor subfamily. It is expressed in bone marrow and in differentiated blood mononuclear cells. Binding of the ligand CSF-I to this receptor induces receptor dimerisation, activation and autophosphorylation of cytoplasmic tyrosine residues used as docking sites for SH2-domain containing signalling proteins. There 5 major autophosphorylation sites including PY723 and PY809.

Imatinib has also been described as an effective inhibitor of the FMS receptor and that mutation of Asp 802 of FMS to Val confers imatinib resistance. This suggests that Fms inhibitors may also prove effective for the treatment of diseases whose progression is dependent upon FMS receptor and ligand activity. These include inflammatory conditions such as rheumatoid arthritis and cancers such as breast and ovarian cancers. The FMS receptor and ligand have also been shown to be important in the biology of breast cancer and regulate tumor cell invasion by
a urokinase-dependent mechanism in breast cancer. Activated FMS receptor has been associated with enhanced invasive and metastatic potential whilst expression of the FMS receptor and ligand together predict a highly significant decrease in survival and increased risk of recurrence which may serve to identify high-risk ovarian cancer patients. (Dewar et al., Blood 2005; 105(8): 3127-3132).

Breast, prostate, and lung cancers are frequently associated with bone metastasis. In bone metastatic lesions, osteoclasts play a key role in the development of osteolysis. Pharmacological agents have been described that inhibit osteolytic bone destruction through the suppression of CSF-I-induced osteoclast accumulation in vivo in bone metastasis rat models. This implies that FMS inhibitors may be also useful therapeutic agents for osteolytic disease associated with bone metastasis and other bone diseases in patients. (Ohno et al., Mol. Cancer Ther. 2006; 5(11): 2634-43).

Increased tumor-associated macrophage numbers have been associated with tumor progression. Macrophage numbers present within target tissues have been strongly correlated with disease severity in rheumatoid arthritis and immune nephritis. In some solid tumors, such as breast cancer, elevated macrophage numbers are thought to contribute to disease progression and poor survivability. Binding of CSF-I to its exclusive receptor, colony-stimulating factor-1 receptor (FMS), induces receptor dimerization and autophosphorylation which leads to the phosphorylation of downstream signaling proteins, and the subsequent differentiation and activation of cells in the macrophage lineage. Animal studies with CSF-I deficient mice suggest that CSF-I/FMS is a crucial component of a positive cycle that drives chronic inflammation. Thus, the inhibition of FMS has great potential in treating human diseases such as rheumatoid arthritis as well as certain cancers where macrophages are pathogenic. Inhibitors of the c-Fms tyrosine kinase might also act as anti-inflammatory or anti-osteolytic agents against arthritis.

RSK1-4

The 90kDa ribosomal S6 kinases (RSK1-4) are a family of widely expressed serine/threonine kinases characterised by two functional kinase domains and a C-terminal docking site for ERKs. They are activated by ERK or PDK1 and act as downstream effectors of mitogen-activated protein kinase (MAPK). Rsk has been shown to directly promote cell survival by regulating the expression and activation of pro-survival proteins such as CREB (cyclic adenosine monophosphate response element binding protein). The combination of promoting
cell survival and prevention of apoptosis causes excessive cell survival, eventually leading to
diseases such as cancer and autoimmune disorders. RSKs have been implicated in a number of
cancer types including prostate and breast cancers, osteosarcomas and angiogenesis.

RSK2 regulates the expression of PSA, an important diagnostic marker for prostate cancer.

RSK regulates the growth and is elevated in some human prostate cancer cell lines such as
LNCaP cells. RSK levels are higher in 30% of human prostate tumors compared to normal
prostate tissue suggest that RSK is an important drug target for prostate cancer.

RSK was shown to be overexpressed in 50% of human breast cancer tissue samples, suggesting
that regulation of RSK has been compromised. RSK has a role in proliferation of transformed
cells and may be a useful new target for chemotherapeutic agents. An RSK inhibitor was
shown to inhibit proliferation of the human breast cancer cell line MCF-7 but not the normal
human breast cell line MCF-IOA, although it still inhibited RSK in these cells. This further
supports the proliferative requirement of RSK activity for some breast cancer cells. (Smith et

RSK-dependent stabilization of c-Fos through phosphorylation was found to be essential for
osteosarcoma formation in mice and may also be important for human osteosarcomas. (David

In addition to cancer targets, RSK has also been suggested as a potential therapeutic target for
liver fibrosis as it has a contributory role in the development of the disease.

In addition to its involvement in various cancers, inappropriate RSK activity has been
implicated in the etiology of a number of other diseases including cardiomyopathy, infection,
and lead poisoning. Evidence also shows PKC-MEK-p42/44 MAPK was a common signal
component for the expression of TNF upon exposure to lead (Pb). Further, elevated activity of
MAPK, the immediate upstream RSK activator, has also been shown in various neural and
heart pathologies, inflammation, and Borna disease and so an RSK inhibitor may be useful in
the treatment of these disorders. Therefore, it is possible to envision a number of potential
clinical uses for RSK inhibitors. However, RSK2 is important in normal development and has
been associated with Coffin-Lowry syndrome. In this syndrome patients have an X-linked
mental retardation condition and skeletal abnormalities. Some of the pathology associated with
this syndrome may be due to the fact that the patients express truncated mutants of RSK2.
These mutants may have functions that differ from wild-type RSK2. In a RSK2 mouse
knockout model MAPK activity is elevated and it is thought that RSK2 may act as a negative
regulator of MAPK activity. Results suggest that it may be possible to inhibit RSK activity
without deleterious consequences and it is possible that an inhibitor of RSK activity may be well tolerated in vivo.

The RSKs are implicated in a range of cancers in particular sarcomas, prostate cancer, and breast cancer. Furthermore, it is known that RSK levels are higher in human breast and prostate tumors compared to normal tissue. Evidence from other laboratories has demonstrated that RSK is involved in osteosarcoma formation and in non-small cell lung carcinoma. Taken together, these results suggest that RSK could serve as an important novel drug target in some types of cancers. In addition, inhibitors of Rsk can also be used as therapeutic interventions in non-terminal diseased states or neurological diseases such as epilepsy in which the MAPK signaling pathway is improperly regulated.

PKC family

The PKC family of enzymes are serine-threonine kinases involved in multiple cell signaling pathways and the control of many cellular processes. Activation leads to a variety of cellular responses such as secretion, gene expression, proliferation and muscle contraction. The family consists of at least 12 isozymes and are classified, based on their interactions with calcium and diacylglycerol as cofactors. Conventional or classic isoforms including α, βI, βII, and γ require both calcium and diacylglycerol for activation. Novel isoforms such as δ, ε, η, and θ are independent of calcium but require diacylglycerol for activation. Atypical isoforms including λ and ζ, are calcium and diacylglycerol independent. Most of the PKC isoforms are ubiquitously expressed although some of them are restricted to certain organs or cell types. PKCγ has been shown to be specifically expressed in neuronal tissue, whereas PKCβ is preferentially expressed in pancreatic islets, monocytes and brain. There is evidence demonstrating altered activity of some PKC isoforms in the neurons of brains of Alzheimers Disease (AD) sufferers and other neurodegenerative disorders.

PKCµ (also known as Protein Kinase D or PKD) is implicated in the regulation of multiple cellular processes including Golgi organization and membrane transport in epithelial cells. PKCµ is phosphorylated on serine 742 in the activation loop in a PKC-dependent pathway by other PKC isoforms. This is critical for its catalytic activity, substrate phosphorylation and role in activating the ERK1 MAP Kinase signalling cascade growth factor-induced signalling processes and proliferative effects in cells such as keratinocytes. PKCµ is thought to be involved in the function of invadopodia formed by breast cancer cells during invasion of the surrounding tissues. Particularly in the context of breast cancer, PKCµ and its upstream
activating kinase PKC ε seemed to be involved in triggering cellular adhesion processes. Antiapoptotic effects have also been reported such as PKCµ mediated pancreatic adenocarcinoma cell resistance. (Trauzold et al., Oncogene 2003; 22: 8939-8947)

Increasing evidence now points toward important roles for PKCµ-mediated signaling pathways in the cardiovascular system, particularly in the regulation of myocardial contraction, hypertrophy and remodeling. (Avkiran et alh, Circulation Research 2008; 102: 157). An inhibitor of Protein Kinase C-mu (PKD) can be used to block phosphorylation of histone deacetylases (HDACs) which has an important role of in disease progression, and is a key factor in cardiac disease. Inhibitors of PCK-mu can therefore be used in the treatment of heart disease and its manifestations, including coronary artery disease, myocardial infarction, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

Decreasing PKD activity in the heart cells of a subject may serve as a treatment for myocardial infarct, prevention of cardiac hypertrophy and dilated cardiomyopathy, inhibition of progression of cardiac hypertrophy, treatment of heart failure, inhibition of progression of heart failure, increasing exercise tolerance in a subject with heart failure or cardiac hypertrophy, reducing hospitalization in a subject with heart failure or cardiac hypertrophy, improving quality of life in a subject with heart failure or cardiac hypertrophy, and decreasing morbidity or mortality in subjects with heart failure or cardiac hypertrophy.

Hypertension is a frequent precursor of congestive heart failure (CHF). When heart failure occurs, the left ventricle usually is hypertrophied and dilated and indices of systolic function, such as ejection fraction, are reduced. The treatment may improve one or more symptoms of pathologic cardiac hypertrophy or heart failure such as providing increased exercise capacity, increased cardiac ejection volume, decreased left ventricular end diastolic pressure, decreased pulmonary capillary wedge pressure, increased cardiac output or cardiac index, lowered pulmonary artery pressures, decreased left ventricular end systolic and diastolic dimensions, decreased left and right ventricular wall stress, decreased wall tension and wall thickness, increased quality of life, and decreased disease-related morbidity and mortality.

It is also desirable to develop pharmacological strategies to attenuate diseases such as hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as asthma, bronchiolitis, interstitial lung disease and lung injury.
PKCγ is mainly expressed in neuronal tissues however cell transformation of mammary epithelial cells following PKCγ over-expression has been described but whether this contributes also to breast cancer formation is not known. (Martiny-Baron et al., Pharmacological Research 2007; 55, (6): 477-486.) PKCγ mutations resulting in increased kinase activity have been found in neurodegenerative disorders such spinocerebellar ataxia type 14 (SCA14).

In addition PKCγ has been found to have a role in pain. Thus, inhibitors of PKC-gamma have use in the management and/or lessening of pain in particular chronic pain. Chronic pain, unlike normal pain, does not abate. A number of physiological changes in the spinal cord, dorsal root ganglia (DRG), and the brain have been observed, which correspond to the state of chronic pain. Chronic neuropathic pain results from aberrant sensory processing in either the peripheral and/or the central nervous system (CNS), typically caused by an initial inflammatory, immunological, or viral episode, or by ischemic or mechanical insult to a nerve. Neuropathic pain is characterized by an altered pain perception that can manifest as allodynia, a response to a normally non-noxious stimulus (e.g., the touch of clothing becomes painful), or as hyperalgesia, a decreased threshold to noxious stimuli (e.g., warm water on burned skin). PKCγ deficient mice show greatly reduced hyperalgesia following an inflammatory nerve injury. PKC gamma along with two other isozymes (β1 and ε) have been shown to participate in the sensation of pain (the nociception pathway) (Igwe O. J., et al., Neuroscience 104(3):875-890 (2001); Martin W. J., et al., Neuroscience 88(4):1267-1274 (1999); Khasar S. G., et al., Neuron 24(1):253-60 (1999)). Nociception is the term commonly used to refer to the perception of pain. Nociception is the unconscious afferent activity produced in the peripheral and central nervous system by stimuli that have the potential to damage tissue. As such compounds inhibiting PKC-mu will be useful for the treatment or prevention of pain. It is desirable to have an agent for the palliative treatment of pain, i.e. the direct relief of pain in addition to the relief of pain as the result of amelioration of the underlying disease or medical condition, which is the cause of the pain.

Withdrawal from addictive substances is often associated with heightened sensory sensitivity and pain. On withdrawal from opioids or alcohol many patients experience a heightened sensitivity to stimuli and an exaggerated pain response. PKCgamma mediates ethanol withdrawal hyper-responsiveness in spinal motor neurons. Inhibitory PKC-gamma-specific peptides attenuated mechanical allodynia and thermal hyperalgesia in EtOH-withdrawal rats (J Pain. 2005 Aug;6(8):535-49). Further, thermal hyperalgesia during spontaneous opiate withdrawal was inhibited by PKC gamma inhibitors (Pain. 2004 Jul;110(1-2):28 1-9). These studies implicate a role for PKC gamma inhibitors alldynia and hyperalgesia, in particular in EtOH or opiate withdrawal-associated alldynia and hyperalgesia.
PKCβ can contribute in several ways to tumor formation, with direct effects on tumor cells and with involvement in tumor host mechanisms such as inflammation and angiogenesis. PKCβ is also involved in other disease areas. Hyperglycemia has been shown to lead to PKCβ activation and contribute to diabetic microvascular complications. In vivo studies have shown that inhibition of PKCβ can delay or even reverse diabetic retinopathy, nephropathy and neuropathy. Thus PKCβ inhibitors are currently in clinical trials to treat diabetic induced vascular abnormalities.

Small molecules that target specific sites within the PKC isoforms, including the diacylglycerol binding site are in development. These include inhibitors of single or multiple PKC isoforms. In addition peptide fragments that act as inhibitors or activators of translocation as well as antisense and siRNA approaches are also being pursued. The role of PKC in tumorigenesis and apoptosis suggests that combining PKC inhibitors with conventional cytotoxics may be also be an effective way to inhibit tumor growth.

PAK5

The p21 activated kinase (PAK) family of kinases has become increasingly of interest as effectors of Rho family of small G proteins and as an upstream regulator of MAPK signalling pathways during cellular events such as re-arrangement of the cytoskeleton and apoptosis.

p21-activated kinase 5 (Pak5) is an effector for the small GTPase Cdc42, known to activate cell survival signaling pathways but these GTPases do not regulate Pak5 kinase activity, which is constitutive and stronger than any other Pak. Pak5 is highly expressed in mammalian brain and is not expressed in most other tissues. It is however found in some at lower levels such as prostate, testes and adrenal gland and at relatively high levels in the pancreas. (Li and Minden Mol Cell Biol. 2003; 23(20): 7134-7142). Overexpression of Pak5 activates the JNK kinase pathway but not p38 or ERK pathways. Pak5s have also been shown to be upstream in pathways leading to activation of both the JNK (Bagrodia, S., et al. (1995) J. Biol. Chem. 270: 22731-22737) and ERK kinase pathways (Brown, J., et al. (1996). CurrBiol. 6: 598-605). Pak5 has been shown to induce resistance to apoptosis by several mechanisms including phosphorylation of BAD on serine residues, in particular serine 112 as well as inhibition of PARP and caspase 3 cleavage. Over expression of the kinase dead mutant was shown not to protect against apoptosis. (Cotteret et al., Mol. Cell. Biol. 2003; 23(16), 5526-5539) In MiaPa-Ca-2 pancreatic carcinoma cells inhibiting Pak5 expression was found to induce a 7-fold increase in apoptosis and has been suggested as a potential therapeutic target where the link to
tumour cell survival was confirmed. PAK5 may also have a mitogenic role, and be linked to cancer, based on its expression profile (elevated RNA and protein levels in a wide variety of tumor cell lines), its interaction with cdc42 via its PBD, and the ability of a kinase-dead allele (Lys350, 351 Ala) to block ras transformation of NIH3T3 cells. A small molecule inhibitor of PAK5 kinase activity may yield compounds with therapeutic potential for intervention in cancer derived from a wide variety of tissue types.

PAK5 may also play a role in HIV pathogenesis as potential mediators of Nef signaling, since none of the known PAKs correspond to the PAK-like kinase shown to interact with, and be activated by, the HIV nef protein (Lu, X. et al. (1996) Current Biology 6: 1677-1684).

Inhibitors of PAK5 may have a role in the treatment of rheumatoid arthritis, atherosclerosis, autoimmune disorders, organ transplantation, myocardial infarction, cardiomyopathies, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer. Inhibitors of PAK5 are also useful for the treatment of diabetic nephropathy, and inhibition of dendritic spine formation and neurite outgrowth in primary neurons and neuroblastoma cells through the activation of Rac/Cdc42-PAK signaling pathways.

**BrSK 1 and 2**

Brain serine/threonine kinase (BRSK, also known as brain-specific kinase) is a kinase expressed in the human brain in two isoforms (BRSK1 and BRSK2). Brain specific kinases 1 and 2 (BRSK1/2) are AMPK-related kinases that are highly expressed in mammalian forebrain. It is required for the polarization of forebrain neurons which endows axons and dendrites with distinct properties, possibly by locally regulating phosphorylation of microtubule-associated proteins. Information regarding the potential downstream targets for BRSK1/2 is very limited, however a number of AMPK-related kinases, including BRSK1 and BRSK2, phosphorylate Tau, a microtubule-associated protein that regulates stability of the microtubule network.

Although BrSK1 and 2 are predominantly expressed in the brain, it has been reported recently that low-level expression of BRSK2 and low but significant activity of both isoforms have been found in pancreas as has been described for other traditionally neuronal kinases such as PAK5. (Bright et al., J Biol. Chem. 2008; ePub).

Alzheimer's disease (AD) is the most common cause of dementia in the elderly and is characterised by a decline in cognitive function that progresses slowly and results in symptoms such as memory loss and disorientation. Death occurs, on average, 9 years after diagnosis. The
incidence of AD increases with age, so that while about 5% of people over the age of 70 are sufferers, this figure increases to 20% of those over 80 years old.

Existing treatments exclusively target the primary symptoms of AD. Diseased neurons may release insufficient or excessive amounts of particular neurotransmitters, and so current drugs are aimed at increasing neurotransmitter levels or at reducing the stimulation of nerve cells by neurotransmitters. Although these drugs provide some improvement in the symptoms of AD, they fail to address the underlying cause of the disease.

The classic clinical and neuropathological features of AD, first described in 1907, consist of senile or neuritic plaques and tangled bundles of fibers (neurofibrillary tangles) (Verdile et al., Pharm. Res. 2004; 50: 397-409). In addition, there is a severe loss of neurons in the hippocampus and the cerebral cortex. Neuritic plaques are extracellular lesions, consisting mainly of deposits of β-amyloid peptide (Aβ), surrounded by dystrophic (swollen, damaged and degenerating) neurites and glial cells activated by inflammatory processes. In contrast, neurofibrillary tangles (NFTs) are intracellular clusters composed of a hyperphosphorylated form of the protein Tau, which are found extensively in the brain (e.g. mainly in cortex and hippocampus in AD). Tau is a soluble cytoplasmic protein which has a role in microtubule stabilisation. Excessive phosphorylation of this protein renders it insoluble and leads to its aggregation into paired helical filaments, which in turn form NFTs.

There has been considerable interest in the use of kinase inhibitors to control the hyperphosphorylation of Tau to treat or prevent AD other conditions involving Tau phosphorylation. The microtubule affinity regulating kinase (MARK) is one such example since phosphorylation of Tau's microtubule-binding domain by the protein kinase MARK primes Tau for hyperphosphorylation by the kinases GSK-3 and Cdk5, which in turn triggers the aggregation of Tau into filaments and tangles. Toxic consequences for the neuron might be exacerbated by tangle formation but are already evident during the early steps of the process. (Drewes. Trends Biochem. Sci 2004; 29: 548-555).

Tiki and 2

The Tousled-like kinases are an evolutionarily conserved family of Serine/threonine protein kinases implicated in regulation of chromatin assembly in human cells named for their homology to the Tousled gene from Arabidopsis thaliana, essential for flower development. In mammals, TLks are regulated in a cell cycle-dependent manner with maximal activity in S phase, and their link to chromatin assembly was established by the identification of the human
chromatin assembly factors Asfla and Asflb (hAsfl) as TIk substrates. The two known human
TLks, Tiki and TLk2, are 84% similar at the amino acid sequence level, ubiquitously expressed.
Both kinases are inactivated by the generation of double strand breaks (DSBs), DNA-damaging
agents and inhibitors of DNA replication, such as aphidicolin. This is dependent on intact
checkpoints rather than inhibition of DNA synthesis itself, specifically the S-phase DNA
damage checkpoint. DNA-damage during S-phase leads to ATM- and Chkl-dependent
inhibition of TLk activity through phosphorylation.

TLK1 has been found to be overexpressed in some breast cancers but not in benign breast
specimens from non-cancer patients. The degree of TLK1 elevation is correlated with the
degree of IF4E overexpression. (Norton et al, J Surg Res. 2004; 116(1): 98-103). In cell lines,
TLKIB overexpression has been recently associated with resistance to radiation.

Antibacterial Infections
Since the introduction of antibiotics in the 1940s many previously lethal infections can now be
treated. However, as each new antibiotic is introduced bacterial resistance arises to it. This
combined with the increase in elderly and immune-suppressed populations has meant that
bacterial infections remain common and deadly causes of human disease. In addition, multi-
drug-resistant bacteria pose a grave and growing threat to public health. In the US alone 2
million people a year acquire infections whilst in hospital and 90 000 die as a result.

Antibiotic resistance arises following the introduction of every new drug and is seen as an
inevitable result of the selective pressure that arises on widespread antibiotic use. It has been
shown that bacterial pathogens can acquire resistance to multiple antibiotics and resistance can
be transferred between unrelated bacterial species. (Stuart B. Levy, The Challenge of
406, 775-781; Schluger, N. (2000) Int. J. Tuberculosis Lung Disease 4, S71 -S75; Raviglione et
and novel approaches to drug development are necessary to combat the ever increasing number
of antibiotic-resistant pathogens and to keep one step ahead of evolving resistance (Leeb M

In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative
pathogens, so named because of their reaction to the Gram-stain, which stains the bacterial cell
wall. Gram-negative bacteria have an extra outer membrane surrounding the cell wall which
protects the cell wall from the stain. Gram-negative bacteria include pathogens such as
Salmonella (e.g. Salmonella typhimurium), Escherichia (e.g. Escherichia coli), Klebsiella (e.g.
Klebsiella pneumoniae), Actinobacteria (including Brachybacterium, Actinomyces, Corynebacterium, Micrococcus, monocyogenes, and Streptomyces species), Helicobacter (e.g. Helicobacter pylori), Legionella (e.g. L. pneumophila), Moraxella (e.g. Moraxella catarrhalis), Neisseria (e.g. Neisseria meningitidis, Neisseria gonorrhoeae), Haemophilus (e.g. Haemophilus influenzae, H. ducreyi), Enterobacter (e.g. Enterobactericeae pneumococci, Enterobacterfaecalis), Pseudomonas (e.g. Pseudomonas aeruginosa, P. pseudomallei), Proteus (e.g. Proteus mirabilis) and Shigella (e.g. Shigella dysenteriae). The additional protective cell membrane in Gram-negative bacteria often results in them being less susceptible to conventional, topical antibacterial actives.

Gram-positive bacteria include pathogens such as Staphylococci (e.g. Staphylococcus aureus, Staphylococcus epidermidis), Streptococci (e.g. Streptococcus diogenes, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus gordonii, S. pyogenes), Enterococci (e.g. Enterococcusfaecium), Clostridium (e.g. Clostridium perfringens, Clostridium difficile, Clostridium botulinum), Bacillus (e.g. Bacillus anthracis), Listeria (e.g. Listeria monocytogenes) and Mycobacteria (e.g. Mycobacterium tuberculosi, Mycobacterium avium and Mycobacterium leprae).

Resistance to antibiotics can arise due to a number of different mechanisms including blocking the antibiotic’s accumulation (e.g. efflux pumps), modification of the antibiotic (e.g. beta-lactamases) or changes in the antibacterial target itself (e.g. ribosomal modification (erm) strains). Resistance can be inherent to the organism or acquired due to mutation or transfer of genes from other microorganisms.

Resistant strains of Gram-positive and Gram-negative bacteria are prevalent in hospital environments and are both difficult to treat and to eradicate, this being a treatment problem especially in intensive care units. They are also increasingly found as community-acquired infections. Examples of Gram-positive resistant strains are methicillin resistant Staphylococcus aureus (MRSA), methicillin resistant Staphylococcus epidermidis (MRSE), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae, vancomycin-resistant enterococcus (VRE), and multiply resistant Enterococcusfaecium. Gram-negative bacteria can have intrinsic resistance due to their outer membrane barrier and multidrug efflux pumps, which can lead to resistance to almost all antibiotics. The resistant strains also often use enzymes to breakdown antibiotics, e.g. the extended spectrum beta-lactamases, which are often found in Klebsiella pneumoniae, Escherichia coli and Enterobacteriaceae. Pseudomonas aeruginosa, K pneumoniae and Acinetobacter can be resistant to all clinically available antibiotics due to a combination of these mechanisms.
Staphylococcus aureus

Staphylococcus aureus (also known as golden staph), is the most common cause of staphylococcal infections. S. aureus is an aerobic and opportunistic Gram-positive coccus, which appears as grape-like clusters and has large, round, golden-yellow colonies, often causing hemolysis, when grown on blood agar plates. The golden appearance is the etymological root of the bacteria's name: aureus means "golden" in Latin. S. aureus frequently lives on the skin or in the nose of a person and is commensal on the skin of 20-30% of the general population.

S. aureus causes two types of disease, invasive and toxigenic. Invasive infections are characterised by abscess formation of varying severity from minor skin infections, such as pimples, impetigo, boils, cellulitis, folliculitis, furuncles (boils), carbuncles (a collection of furuncles), to life-threatening diseases, such as, osteomyelitis, endocarditis, septic arthritis, pneumonia and meningitis. Toxigenic diseases include Toxic shock syndrome (TSS), food poisoning and scalded skin syndrome (Staphylococcal scalded skin syndrome or SSSS). S. aureus can affects skin, soft tissue, respiratory, bone, joint, endovascular and wound infections. It is a major cause of nosocomial infections, causing infection of surgical wounds and sites of indwelling medical devices (e.g. prosthetic joints), which may lead to sepsis and septicemia.

S. aureus (including Methicillin-resistant Staphylococcus aureus or MRSA) is spread through human-to-human contact. The bacterium is able to transport itself on the hands of medical staff who, for instance, get the bacteria from a seemingly healthy patient carrying a "benign" or commensal strain of the pathogen, and then go into surgery and infect the open incision with staphylococcus.

S. aureus infections can be spread through contact with pus from an infected wound, skin-to-skin contact with an infected person and contact with objects such as towels, sheets, clothing, or athletic equipment used by an infected person. Deeply situated S. aureus infections can be very severe.

S. aureus can also cause disease in animals. For example, it is one of the causal agents of mastitis in dairy cows and can also cause bumblefoot in chickens.

Diagnosis

Depending upon the type of infection present, an appropriate specimen is obtained accordingly and sent to the laboratory for definitive identification by using biochemical or enzyme-based
tests. A Gram stain is first performed, which should show typical Gram-positive bacteria, cocci, in clusters. Secondly, the organism is cultured in Mannitol Salt Agar, which is a selective medium with 7-9% NaCl that allows *S. aureus* to grow producing yellow-colored colonies as a result of salt utilization and subsequent drop in the medium’s pH. Furthermore, for differentiation on the species level, catalase (positive for all species), coagulase (fibrin clot formation), DNAse (zone of clearance on nutrient agar), lipase (a yellow color and rancid odor smell), and phosphatase (a pink color) tests can be performed. For staphylococcal food poisoning, phage typing can be performed to determine if the staphylococci recovered from the food is the source of infection.

Recent genetic advances have enabled reliable and rapid techniques for the identification and characterization of clinical isolates of *S. aureus* in real-time which is important in identifying outbreaks and new strains of *S. aureus*. These are used in infection control strategies to limit bacterial spread and ensure the appropriate use of antibiotics. These techniques include Real-time PCR and Quantitative PCR and are increasingly being employed in clinical laboratories.

Treatment and Antibiotic resistance
*S. aureus* may occur as a commensal on human skin in particular in the nose or throat. The occurrence of *S. aureus* under these circumstances (‘colonisation’) does not always indicate infection and therefore may not require treatment. In addition, as such bacteria play a fundamental role in preventing the colonisation of other, more harmful bacteria and fungi, treatment under these circumstances may be undesirable.

*S. aureus* has become resistant to many commonly used antibiotics. Staphylococcal infection that is not antibiotic resistant can be treated in about a month (depending on severity) using appropriate antibiotics. Methicillin-resistant *S. aureus* (MRSA) is one of the most common resistant bacteria found in hospitals and is a treatment concern especially in intensive care units. When penicillin was first introduced more than 95% of *S. aureus* were susceptible, now less than 10% are, due to the acquisition of beta-lactamases by the bacteria which break down the beta-lactam ring of the penicillin molecule. Methicillin (a penicillin resistant to beta-lactamases) was introduced to overcome this resistance, but now more than 40% of infections are resistant to this antibiotic in some hospitals. The mechanism of resistance to methicillin is by the acquisition of the mecA gene, which codes for an altered penicillin-binding protein (PBP) that has a lower affinity for binding β-lactams (penicillins, cephalosporins and carbapenems). This confers resistance to all β-lactam antibiotics and obviates their clinical use during Methicillin-resistant *S. aureus* (MRSA) infections. MRSA often show multiple resistance to antibiotics being resistant not just to all β-lactams but also to aminoglycosides,
macrolides, clindamycin and sometimes quinolones. The glycopeptides vancomycin and
tecoplanin are increasingly the major clinically effective antibiotics for such infections and
MRSA with intermediate resistance to vancomycin has already been reported. Glycopeptide
resistance is mediated by acquisition of the vanA gene. The vanA gene originates from the
enterococci and codes for an alternative peptidoglycan to which vancomycin will not bind.

Recently, there has been an explosion in MRSA prevalence in hospitals where it is now
endemic and it has been increasingly prevalent in the community too. MRSA infections in both
the hospital and community setting are commonly treated with non-β-lactam antibiotics such as
clindamycin (a lincosamine) and co-trimoxazole (also commonly known as
trimethoprim/sulfamethoxazole). Resistance to these antibiotics has also led to the use of a new
class of broad-spectrum anti-Gram-positive antibiotics the oxazolidinones, e.g. linezolid, but
resistance to this new class of antibiotics has already been reported. The last line of treatment
for serious invasive infections due to MRSA is currently the glycopeptide antibiotics
(vancomycin and teicoplanin). There are number of issues with these antibiotics - the need for
intravenous administration (there is no oral preparation available), toxicity including
nephrotoxicity, and the need to monitor drug levels regularly by means of blood tests. There are
also concerns that glycopeptide antibiotics do not penetrate very well into infected tissues
which is of particular importance with infections of the brain and meninges, and in
endocarditis. Glycopeptides can not be used to treat methicillin-sensitive *S. aureus* as outcomes
are inferior. In addition there are concerns regarding the potential for *S. aureus* to become
widely resistant to vancomycin (vancomycin-resistant *S. aureus* or VRSA).

Because of the high level of resistance to penicillins, and because of the potential for MRSA to
develop resistance to multiple classes of antibiotics including vancomycin, there is a need for
new drugs which are active against *S. aureus*.

*Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* is a Gram-negative, aerobic, rod-shaped bacterium with unipolar
motility. Adaptation to microaerobic or anaerobic environments is necessary for certain
lifestyles of *P. aeruginosa*, for example lung infections in cystic fibrosis patients. An
opportunistic pathogen of immunocompromised individuals, *P. aeruginosa* typically infects the
pulmonary tract, urinary tract, burns, wounds, and also causes blood infections. It is the most
common cause of burn and external ear infections, and is the most frequent colonizer of
medical devices (e.g. catheters). *Pseudomonas* can in rare circumstances cause community
acquired pneumonias, as well as ventilator-associated pneumonias. One in ten hospital-acquired
infections are from *Pseudomonas* and it is responsible for a considerable proportion of
intensive care infections. Cystic fibrosis patients are predisposed to *P. aeruginosa* infection of the lungs. In cystic fibrosis patients thick layers of alginate surrounding bacterial mucoid cells can limit the diffusion of oxygen. *P. aeruginosa* may also be a common cause of "hot-tub rash" (dermatitis), caused by lack of proper, periodic attention to water quality. The most common cause of burn infections is *P. aeruginosa*. *Pseudomonas* is also a common cause of post-operative infection in radial keratotomy surgery patients.

In plants, *P. aeruginosa* induces symptoms of soft rot with Arabidopsis thaliana (Thale cress) and Letuca sativa (Lettuce). It is a powerful pathogen with Arabidopsis and with some animals: Caenorhabditis elegans, Drosophila and Galleria mellonella. The associations of virulence factors are the same for vegetal and animal infections.

**Diagnosis**

An appropriate specimen is collected and sent to the bacteriology laboratory for identification.

First, a Gram stain is performed, which should show Gram-negative rods with no particular arrangement. If the specimen is pure, the organism is grown on MacConkey agar plate to produce colorless colonies (as it doesn't ferment lactose), but if the specimen is not pure, then the use of a selective plate is essential. Cetrimide agar has been traditionally used for this purpose. When grown on it, *P. aeruginosa* expresses the exopigment pyocyanin, which is blue-green in color, and the colonies will appear flat, large, and oval. It also has a characteristic fruity smell. *P. aeruginosa* is catalase, oxidase, nitrase, and lipase positive. When grown on TSI medium it has a K/K/g-/H2S- profile, meaning that the medium will not change color. Finally, serology could help which is based on H & O antigens.

**Treatment and Antibiotic Resistance**

*P. aeruginosa* is frequently isolated from non-sterile sites (mouth swabs, sputum, and so forth) and under these circumstances, it often represents colonisation and not infection. The advice of a microbiologist or infectious diseases physician is usually sought prior to starting treatment upon isolation of *P. aeruginosa* from non-sterile specimens. Often no treatment is needed.

When *P. aeruginosa* is isolated from a sterile site (blood, bone, deep collections), it almost always requires treatment. It is sometimes possible to guide treatment according to laboratory sensitivities, rather than choosing an antibiotic empirically. If antibiotics are started empirically, then cultures should be obtained and the choice of antibiotic used should be reviewed when the culture results are available.
A range of antibiotics have activity against *P. aeruginosa* [aminoglycosides (gentamicin, amikacin, tobramycin); quinolones (ciprofloxacin and levofloxacin but not moxifloxacin); cephalosporins (ceftazidine, cefepime, cefpirome, but not cefuroxime, ceftriaxone, cefotaxime); ureidopenicillins (piperacillin, ticarcillin; *P. aeruginosa* is intrinsically resistant to all other penicillins); carbapenems (meropenem, imipenem, but not ertapenem); polymyxins (polymyxin B and colistin) and monobactams (aztreonam)] but these antibiotics, with the exception of fluoroquinolones, must all be given by injection. For this reason, in some hospitals, fluoroquinolone use is severely restricted in order to avoid the development of resistant strains of *P. aeruginosa*. In the rare occasions where infection is superficial and limited (for example, ear infections or nail infections) topical gentamicin or colistin may be used.

*P. aeruginosa* has inherent resistance to a large range of antibiotics due to low membrane permeability and may also readily acquire resistance after unsuccessful treatment, particularly through multidrug efflux pumps. This evolving resistance has led to clinical isolates emerging that are only susceptible to one class of antibiotic, the polymyxins, an old class of polypeptide cationic antibiotics. Furthermore there are also reports of pan-drug resistant strains of *P. aeruginosa*.

Due to the low antibiotic susceptibility and the rise in acquired resistance to existing agents, new antibacterial agents with activity against *P. aeruginosa* are required.

Accordingly, it is an object of the present invention to provide pharmaceutical compounds which have broad antibacterial activity including activity against Gram-positive and Gram-negative organisms. It is a further object of the present invention to provide pharmaceutical compounds having antibacterial activity that can be used in animal medicine (for example in the treatment of mammals such as humans), or in the treatment of plants (e.g. in agriculture and horticulture), or as general antibacterial agents, for example as preservatives and disinfectants. The antibacterial activity of the compound of the present invention thus comprises an important contribution to therapy for treating infections caused by these difficult to control pathogens.

WO 03/035065 & WO 03/035644 (Aventis) discloses a broad class of benzimidazole derivatives as protein kinase inhibitors.
WO 03/066629 (Vertex) discloses benzimidazolylpyrazole amines as kinase inhibitors.

WO 2005/028624 (Plexxikon) discloses molecular scaffolds for compounds having activity against protein kinases.

**Summary of the Invention**

In a first aspect, the invention provides a compound of Formula (I), or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase, or a mutated form thereof, which is:

- a member of the AXL family, such as AxI, Mer and Sky, in particular Mer.
- a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2
- a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1
- a Salt-inducible kinase (SIK)
- a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor receptor 1 receptor (M-CSF-IR or FMS)
- a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4
- a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and µ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ)
- a member of the p21 activated kinase (PAK) family in particular PAK5
- a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or
- a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2;

wherein the compound of Formula (I) is:

![Chemical Structure](image-url)
In a second aspect, the invention provides a compound of Formula (I), or salts, solvates or tautomers thereof, for use as an antibacterial agent, wherein the compound of Formula (I) is:

(I)

**Description of the Invention**

The compound of formula (I) corresponds to the structure of Examples 24, 65 and 66 disclosed in our International patent application number PCT/GB2005/005097 (WO 2006/070195), the contents of which are incorporated herein by reference.

In a first aspect, the invention provides a compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase, or a mutated form thereof, wherein the kinase is:

- a member of the AXL family, such as AxI, Mer and Sky, in particular Mer.
- a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2
- a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1
- a Salt-inducible kinase (SIK)
- a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS)
- a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4
- a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ)
- a member of the p21 activated kinase (PAK) family in particular PAK5
- a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or
a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

In a second aspect, the invention provides a compound of Formula (I) or salts, solvates or tautomers thereof, for use as an antibacterial agent.

As a result of the activities described above a further aspect of the invention is a compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease or condition selected from the following:

- pain;
- coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF), hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease, lung injury;
- disease states or conditions resulting in excessive bone formation, Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients;
- proliferative vitreoretinopathy, liver fibrosis, renal failure, irritable bowel syndrome (IBS), oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy;
- cerebral ischemia, Coffin-Lowry syndrome, Borna disease, spinocerebellar ataxia type 14 (SCA14), schizophrenia, transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, pancreatitis and metal (e.g. lead) poisoning;
- pancreatic adenocarcinoma, gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases;
- adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts; and
- allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).
In a third aspect the invention provides a compound of Formula (I) or salts, solvates or
tautomers thereof, for use as a neuroprotective agent, as an immunosuppressive agent or as an
anti-osteolytic agent.

In further aspects, the invention provides:

A compound of Formula (I) or salts, solvates or tautomers thereof, for use:

a) in the prophylaxis or treatment of a disease state or condition mediated by a
kinase, or a mutated form thereof, which is a member of the AXL family, or the PKC
family, or the CSF-1/PDGF receptor subfamily, or the Mitogen- and stress-activated
kinase family, or the DAP kinase-related apoptosis-inducing protein kinase family; or
is a Salt-inducible kinase; or is a member of the 90kDa ribosomal S6 kinase family, or
the p21 activated kinase (PAK) family, or the Brain specific kinase family, or the
Tousled-like kinase (TLK) family; or
b) as an antibacterial agent; or

c) as a neuroprotective agent, an immunosuppressive agent or anti-osteolytic
agent; or

d) in the prophylaxis or treatment of a disease or condition selected from the
following: pain; coronary artery disease, myocardial contraction, cardiomyopathy,
cardiac remodelling, and heart failure, hypertension, systemic vascular diseases and a
range of lung conditions, lung injury; disease states or conditions resulting in excessive
bone formation; bone diseases; and diseases in which bone resorption mediates
morbidity; proliferative vitreoretinopathy, liver fibrosis, renal failure, irritable bowel
syndrome, oxidative stress-related neurodegenerative disorders and diabetic nephro-
and neuropathy; cerebral ischemia, Coffin-Lowry syndrome, Borna disease,
spinocerebellar ataxia type 14, schizophrenia, transplant rejection, organ
transplantation, resistance to transplantation, graft vs. host disease, pancreatitis and
metal poisoning; pancreatic adenocarcinoma, gastric adenocarcinomas; invasive and/or
metastatic breast cancer; metastasis from various cancers; adenopathy,
hepatosplenomegaly, and circulating lymphoblasts; and allodynia and hyperalgesia.

A compound of formula (I) or salts, solvates or tautomers thereof, for use in the
prophylaxis or treatment of a disease state or condition mediated by a kinase which is a
member of the AXL family, such as Axl, Mer and Sky, in particular Mer; a member of
the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in
particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein
kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible
kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular
macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of
the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and µ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from a member of the AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and µ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, and a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a member of the AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2)

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from a member of the AXL family (e.g. Mer),
Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1-4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCµ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1-4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCµ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from PKC-mu, BrSK2 and FMS.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from PKC-mu, BrSK2 and FMS.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a
mutated form of a kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

- A compound of formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a member of the AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, wherein the disease or condition is selected from from pain; coronary artery disease; myocardial contraction; cardiomyopathy (e.g. dilated cardiomyopathy); cardiac remodeling; heart failure such as congestive heart failure (CHF); hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders; systemic vascular diseases; bronchiolitis; interstitial lung disease; lung injury; disease state or condition results in excessive bone formation; Paget's disease; prosthesis failure; osteolytic sarcoma; tumor metastasis to bone; osteolytic disease associated with bone metastasis; proliferative vitreoretinopathy; liver fibrosis; renal failure; irritable bowel syndrome (IBS); oxidative stress-related neurodegenerative disorders; diabetic nephro- and neuropathy; cerebral ischemia; Coffm-Lowry syndrome; Borna disease; spinocerebellar ataxia type 14 (SCA14); schizophrenia; transplant rejection; organ transplantation; resistance to transplantation; in graft vs. host disease; pancreatitis; metal (e.g. lead) poisoning; pancreatic adenocarcinoma; gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases; adenopathy (lymphadenopathy); hepatosplenomegaly; circulating lymphoblasts; alldynia including mechanical alldynia and EtOH or opiate withdrawal-associated alldynia, and hyperalgesia, in particular thermal hyperalgesia.
and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia)

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease selected from pain; coronary artery disease; myocardial contraction; cardiomyopathy (e.g. dilated cardiomyopathy); cardiac remodeling; heart failure such as congestive heart failure (CHF); hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders; systemic vascular diseases; bronchiolitis; interstitial lung disease; lung injury; disease state or condition results in excessive bone formation; Paget's disease; prosthesis failure; osteolytic sarcoma; tumor metastasis to bone; osteolytic disease associated with bone metastasis; proliferative vitreoretinopathy; liver fibrosis; renal failure; irritable bowel syndrome (IBS); oxidative stress-related neurodegenerative disorders; diabetic nephropathy; neuropathy; cerebral ischemia; Coffin-Lowry syndrome; Borna disease; spinocerebellar ataxia type 14 (SCA14); schizophrenia; transplant rejection; organ transplantation; resistance to transplantation; in graft vs. host disease; pancreatitis; metal (e.g. lead) poisoning; pancreatic adenocarcinoma; gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases; adenopathy (lymphadenopathy); hepatosplenomegaly; circulating lymphoblasts; allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by Mer.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by Mer; wherein the disease state or condition is gastric adenocarcinoma or adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts, in particular gastric adenocarcinoma.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of gastric adenocarcinoma or adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts, in particular gastric adenocarcinoma.
A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by a kinase which is MSK, in particular Msk2.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by a kinase which is MSK, in particular Msk2; and wherein the disease state or condition is irritable bowel syndrome (IBS).

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of irritable bowel syndrome (IBS).

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by a kinase which is MSK, in particular Msk2; wherein the use is as a neuroprotective agent.

A compound of the formula (I) or salts, solvates or tautomer thereof, for use as a neuroprotective agent.

The use of a compound of the formula (I) or salts, solvates or tautomer thereof, for the manufacture of a medicament for use as a neuroprotective agent.

A method of preventing or reducing damage or injury in a patient in need, which method comprises administering to the patient an effective neuroprotective amount of a compound of the formula (I) or salts, solvates or tautomer thereof.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by DRAK, in particular DRAK2.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by DRAK, in particular DRAK2; and wherein the disease state or condition results in excessive bone formation.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by FMS.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by FMS; and wherein...
the disease state or condition is selected from metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and in proliferative vitreoretinopathy.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition selected from metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and in proliferative vitreoretinopathy.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by a kinase which is RSK1, 2, 3, or 4, in particular RSK2, 3 or 4.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by a kinase which is RSK1, 2, 3, or 4, in particular RSK2, 3 or 4; and wherein the disease state or condition is selected from liver fibrosis, cardiomyopathy, Coffm-Lowry syndrome, Borna disease and lead poisoning.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of liver fibrosis, Coffm-Lowry syndrome, Borna disease and lead poisoning.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by PKC, in particular PKC-gamma or PKC-mu.
A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by PKC-mu, and
wherein the disease state or condition is selected from coronary artery disease,
myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac
remodelling, and heart failure such as congestive heart failure (CHF)

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by PKC-mu, and
wherein the disease state or condition is selected from hypertension including chronic
hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a
range of lung conditions such as bronchiolitis, interstitial lung disease and lung injury.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of hypertension including chronic hypoxic pulmonary
hypertension (PHTN) disorders, systemic vascular diseases and a range of lung
conditions such as bronchiolitis, interstitial lung disease and lung injury

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by PKC-mu, and
wherein the disease state or condition is pancreatic adenocarcinoma.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and
wherein the disease state or condition is spinocerebellar ataxia type 14 (SCAI 4).

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of spinocerebellar ataxia type 14 (SCAI 4).

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and
wherein the disease state or condition is pain.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and
wherein the disease state or condition is allodynia including mechanical allodynia and
EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular
thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known
as EtOH or opiate withdrawal-associated hyperalgesia).
A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by PAK5.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by PAK5, and wherein the disease state or condition is organ transplantation, cardiomyopathies, renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, and pancreatitis.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use as an immunosuppressive agent.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the use as an immunosuppressive agent.

A compound of formula I or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by BrSK1 and 2, in particular BRSK2.

A compound of formula I or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by BrSK1 and 2, in particular BRSK2, and wherein the disease state or condition is schizophrenia or cerebral ischemia.

A compound of formula I or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of schizophrenia or cerebral ischemia.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition mediated by AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1.
receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-
4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-
gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase
family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2) or mutated form
thereof; and wherein the disease state or condition is cancer.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by AXL family (e.g.
Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related
apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK),
CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1
receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-
4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-
gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase
family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2); and wherein the
disease state or condition is selected from cancer.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a disease state or condition mediated by AXL family (e.g.
Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related
apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK),
CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1
receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-
4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-
gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase
family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2); and wherein the
cancer is selected from adenocarcinomas in particular pancreatic adenocarcinomas and
gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from
ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon
cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the
treatment or prophylaxis of a cancer, wherein the cancer is selected from pancreatic
adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer;
metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung
cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone
metastases.
A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, λ, and μ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCµ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.
A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from PKC-mu, BrSK2 and FMS.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition which is a malignancy driven by a mutated form of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5 and wherein the malignancy is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; and metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a cancer which expresses a mutated kinase which is a mutated form of Mer, PKC-mu, or FMS.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a cancer which expresses a mutated kinase which is a mutated form of Mer, PKC-mu, or FMS, and wherein the cancer is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

A compound of the formula (I) or salts, solvates or tautomers thereof, for the treatment or prophylaxis of a disease state or condition which is a malignancy driven by a mutated form of Mer, MSK2, DRAK1, SIK, FMS, RSK2, RSK3, RSK4, PKC-mu (PKC\(\mu\)) or PKC-gamma (PKC\(\gamma\)), PAK5, BrSK2 or TLK2; for example PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease or condition (e.g. cancer) characterized by overexpression of any one or more kinases selected from a member of the AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-
activated kinase family such as MSK 1 and MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (β1 and βII), γ, δ, ε, ζ, η, θ, ι, λ, and µ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

The use of a compound of formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase, or mutated form thereof, which is a member of the AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (β1 and βII), γ, δ, ε, ζ, η, θ, ι, λ, and µ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

The use of a compound of formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a member of the AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF
receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (β1 and βII)), γ, δ, ε, ζ, η, θ, t, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BrSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (β1 and βII)), γ, δ, ε, ζ, η, θ, t, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BrSK1/2), in particular BrSK2, and a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).
The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1-4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCμ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2.

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1-4 (in particular RSK2, RSK3, RSK4), PKC-mu (PKCμ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2.

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from PKC-mu, BrSK2 and FMS.

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from PKC-mu, BrSK2 and FMS.

The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from PKC-mu, BrSK2 and FMS.
condition mediated by a kinase which is a mutated form of a kinase selected from PKC-mu, BrSK2 and FMS.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a mutated form of a kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

- The use of a compound of formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a kinase which is a member of the AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (β1 and βII), γ, δ, ε, ζ, η, θ, τ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, wherein the disease or condition is selected from from pain; coronary artery disease; myocardial contraction; cardiomyopathy (e.g. dilated cardiomyopathy); cardiac remodeling; heart failure such as congestive heart failure (CHF); hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders; systemic vascular diseases; bronchiolitis; interstitial lung disease; lung injury; disease state or condition results in excessive bone formation; Paget's disease; prosthesis failure; osteolytic sarcoma; tumor metastasis to bone; osteolytic disease associated with bone metastasis; proliferative vitreoretinopathy; liver fibrosis; renal failure; irritable bowel syndrome (IBS); oxidative stress-related neurodegenerative disorders; diabetic nephropathy and neuropathy; cerebral ischemia; Coffin-Lowry syndrome; Borna disease; spinocerebellar ataxia type 14 (SCA14); schizophrenia; transplant rejection; organ
transplantation; resistance to transplantation; in graft vs. host disease; pancreatitis; metal (e.g. lead) poisoning; pancreatic adenocarcinoma; gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases; adenopathy (lymphadenopathy); hepatosplenomegaly; circulating lymphoblasts; allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease selected from pain; coronary artery disease; myocardial contraction; cardiomyopathy (e.g. dilated cardiomyopathy); cardiac remodeling; heart failure such as congestive heart failure (CHF); hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders; systemic vascular diseases; bronchiolitis; interstitial lung disease; lung injury; disease state or condition results in excessive bone formation; Paget's disease; prosthesis failure; osteolytic sarcoma; tumor metastasis to bone; osteolytic disease associated with bone metastasis; proliferative vitreoretinopathy; liver fibrosis; renal failure; irritable bowel syndrome (IBS); oxidative stress-related neurodegenerative disorders; diabetic nephro- and neuropathy; cerebral ischemia; Coffin-Lowry syndrome; Borna disease; spinocerebellar ataxia type 14 (SCAI 4); schizophrenia; transplant rejection; organ transplantation; resistance to transplantation; in graft vs. host disease; pancreatitis; metal (e.g. lead) poisoning; pancreatic adenocarcinoma; gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases; adenopathy (lymphadenopathy); hepatosplenomegaly; circulating lymphoblasts; allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by Mer.
The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by DRAK, in particular DRAK2; and wherein the disease state or condition results in excessive bone formation.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of gastric adenocarcinoma or adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts, in particular gastric adenocarcinoma.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of gastric adenocarcinoma or adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts, in particular gastric adenocarcinoma.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by a kinase which is MSK, in particular Msk2.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by a kinase which is MSK, in particular Msk2; and wherein the disease state or condition is irritable bowel syndrome (IBS).

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of irritable bowel syndrome (IBS).

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by a kinase which is MSK, in particular Msk2; wherein the use is as neuroprotective agents.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by DRAK, in particular DRAK2.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by DRAK, in particular DRAK2; and wherein the disease state or condition results in excessive bone formation.
The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by FMS.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by FMS; and wherein the disease state or condition is selected from metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and in proliferative vitreoretinopathy.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition selected from metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and in proliferative vitreoretinopathy.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by a kinase which is RSK1, 2, 3, or 4, in particular RSK2, 3 or 4.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by a kinase which is RSK1, 2, 3, or 4, in particular RSK2, 3 or 4; and wherein the disease state or condition is selected from liver fibrosis, cardiomyopathy, Coffin-Lowry syndrome, Borna disease and lead poisoning.
The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of liver fibrosis, Coffin-Lowry syndrome, Borna disease and lead poisoning.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, thereof for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and wherein the disease state or condition is spinocerebellar ataxia type 14 (SCA14).

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, thereof for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-mu, and wherein the disease state or condition is selected from coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF).

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-mu, and wherein the disease state or condition is selected from hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease and lung injury.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease and lung injury.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-mu, and wherein the disease state or condition is pancreatic adenocarcinoma.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and wherein the disease state or condition is spinocerebellar ataxia type 14 (SCA14).
The use of a compound of the formula (I), or salts, solvates or tautomers or crystalline forms thereof (e.g. a compound of formula (I) or a salt or crystalline forms thereof) for the manufacture of a medicament for the treatment or prophylaxis of spinocerebellar ataxia type 14 (SCA1 4).

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and wherein the disease state or condition is pain.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PKC-gamma, and wherein the disease state or condition is alldynia including mechanical alldynia and EtOH or opiate withdrawal-associated alldynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PAK5.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by PAK5, and wherein the disease state or condition is organ transplantation, cardiomyopathies, renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, and pancreatitis.
The use of a compound of formula I or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by BrSK1 and 2, in particular BRSK2.

The use of a compound of formula I or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by BrSK1 and 2, in particular BRSK2, and wherein the disease state or condition is schizophrenia or cerebral ischemia.

The use of a compound of formula I or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of schizophrenia or cerebral ischemia.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKC\(\mu\)) or PKC-gamma (PKC\(\gamma\)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2) or a mutated form thereof; and wherein the disease state or condition is selected from cancer.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKC\(\mu\)) or PKC-gamma (PKC\(\gamma\)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2); and wherein the disease state or condition is selected from cancer.
The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-μ (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2); and wherein the cancer is selected from adenocarcinomas in particular pancreatic adenocarcinomas and gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a cancer, wherein the cancer is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

The use of a compound of Formula (1) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-μ (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2),
in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKC<sub>&mu;</sub>) or PKC-gamma (PKC<sub>γ</sub>)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKC<sub>&mu;</sub>), PKC-gamma (PKC<sub>γ</sub>), PAK5, BrSK2 and TLK2.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from PKC<sub>&mu;</sub>, BrSK2 and FMS.

- The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a cancer which expresses a mutated kinase which is a mutated form of kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition which is a malignancy driven by a mutated form of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5 and wherein the malignancy is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast...
cancer; and metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a cancer which expresses a mutated kinase which is a mutated form of Mer, PKC-mu, or FMS.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a cancer which expresses a mutated kinase which is a mutated form of Mer, PKC-mu, or FMS, and wherein the cancer is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition which is a malignancy driven by a mutated form of Mer, MSK2, DRAK1, SIK, FMS, RSK2, RSK3, RSK4, PKC-mu (PKCμ) or PKC-gamma (PKCγ), PAK5, BrSK2 or TLK2; for example PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the treatment or prophylaxis of a disease or condition (e.g. cancer) characterized by overexpression of any one or more kinases selected from a member of the AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-1, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.
A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase, or mutated form thereof, which is a member of the AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, τ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is a member of the AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, τ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is a mutated form
of a kinase selected from AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, θ, ι, λ, and μ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, and a member of the Tousled-like kinase (TLK) family such as TLKI or TLK2 in particular TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is a mutated form of a kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like
kinase (TLK) family (e.g. TLK2), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCµ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCµ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase selected from PKC-mu, BrSK2 and FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase selected from PKC-mu, BrSK2 and FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is a mutated form of a kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is a member of the AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSKI -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βl and βll), γ, δ, ε, ζ, θ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, wherein the disease or condition is selected from pain; coronary artery disease; myocardial contraction; cardiomyopathy (e.g. dilated cardiomyopathy); cardiac remodeling; heart failure such as congestive heart failure (CHF); hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders; systemic vascular diseases; bronchiolitis; interstitial lung disease; lung injury; disease state or condition results in excessive bone formation; Paget's disease; prosthesis failure; osteolytic sarcoma; tumor metastasis to bone; osteolytic disease associated with bone metastasis; proliferative vitreoretinopathy; liver fibrosis; renal failure; irritable bowel syndrome (IBS); oxidative stress-related neurodegenerative disorders; diabetic nephro- and neuropathy; cerebral ischemia; Coffm-Lowry syndrome; Borna disease; spinocerebellar ataxia type 14 (SCA14); schizophrenia; transplant rejection; organ transplantation; resistance to transplantation;
in graft vs. host disease; pancreatitis; metal (e.g. lead) poisoning; pancreatic adenocarcinoma; gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases; adenopathy (lymphadenopathy); hepatosplenomegaly; circulating lymphoblasts; allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease or condition in a patient, wherein the disease or condition is selected from pain; coronary artery disease; myocardial contraction; cardiomyopathy (e.g. dilated cardiomyopathy); cardiac remodeling; heart failure such as congestive heart failure (CHF); hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders; systemic vascular diseases; bronchiolitis; interstitial lung disease; lung injury; disease state or condition results in excessive bone formation; Paget's disease; prosthesis failure; osteolytic sarcoma; tumor metastasis to bone; osteolytic disease associated with bone metastasis; proliferative vitreoretinopathy; liver fibrosis; renal failure; irritable bowel syndrome (IBS); oxidative stress-related neurodegenerative disorders; diabetic nephropathy; cerebral ischemia; Coffin-Lowry syndrome; Borna disease; spinocerebellar ataxia type 14 (SCA14); schizophrenia; transplant rejection; organ transplantation; resistance to transplantation; in graft vs. host disease; pancreatitis; metal (e.g. lead) poisoning; pancreatic adenocarcinoma; gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases; adenopathy (lymphadenopathy); hepatosplenomegaly; circulating lymphoblasts; allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

" A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by Mer, which method comprises
administering to the patient a therapeutically effective amount of a compound of the formula (I) and salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by Mer; wherein the disease state or condition is gastric adenocarcinoma or adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts, in particular gastric adenocarcinoma, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of gastric adenocarcinoma or adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts, in particular gastric adenocarcinoma, in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is MSK, in particular Msk2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is MSK, in particular Msk2; and wherein the disease state or condition is irritable bowel syndrome (IBS), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of irritable bowel syndrome (IBS) in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is MSK, in particular Msk2; wherein the use is as neuroprotective agents, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by DRAK, in particular DRAK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by DRAK, in particular DRAK2; and wherein the disease state or condition results in excessive bone formation, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by FMS; and is selected from metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and in proliferative vitreoretinopathy, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is selected from metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and in proliferative
vitreoretinopathy, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is RSK1, 2, 3, or 4, in particular RSK2, 3 or 4, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by a kinase which is RSK1, 2, 3, or 4, in particular RSK2, 3 or 4; and wherein the disease state or condition is selected from liver fibrosis, cardiomyopathy, Coffm-Lowry syndrome, Borna disease and lead poisoning, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a disease state in a patient, wherein the disease state is selected from liver fibrosis, Coffm-Lowry syndrome, Borna disease and lead poisoning, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC, in particular PKC-gamma or PKC-mu, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC-mu, and is selected from coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC-mu, and is selected from hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease and lung injury, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state in a patient, wherein the disease state is selected from hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease and lung injury, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC-mu, and is pancreatic adenocarcinoma, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC-gamma, and is spinocerebellar ataxia type 14 (SCAI 4), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of spinocerebellar ataxia type 14 (SCAI 4) in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC-gamma, and wherein the disease state or condition is pain, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PKC-gamma, and wherein the disease state or condition is allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PAK5, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by PAK5, and wherein the disease state or condition is organ transplantation, cardiomyopathies, renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, and pancreatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by BrSK1 and 2, in particular BRSK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by BrSK1 and 2, in particular BRSK2, and wherein the disease state or condition is schizophrenia or cerebral ischemia, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of schizophrenia or cerebral ischemia in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by AXL family (e.g. Mer), Mitogen-and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2) or a mutated form thereof; and wherein the disease state or condition is selected from cancer, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by AXL family (e.g. Mer), Mitogen-and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2); and wherein the disease state or condition is selected from cancer, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is mediated by AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSKI -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) or Tousled-like kinase (TLK) family (e.g. TLK2); and wherein the cancer is selected from adenocarcinomas in particular pancreatic adenocarcinomas and gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment or prophylaxis of a cancer in a patient, wherein the cancer is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of kinase selected from AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSKI -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, i, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2
(BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of kinase selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCµ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of kinase selected from PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of kinase selected from PKC-mu, BrSK2 and FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of kinase selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5, which method
comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is a malignancy driven by a mutated form of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5 and wherein the malignancy is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; and metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of Mer, PKC-mu, or FMS, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a cancer in a patient, wherein the cancer is one which expresses a mutated kinase which is a mutated form of Mer, PKC-mu, or FMS, and wherein the cancer is selected from pancreatic adenocarcinoma, gastric adenocarcinoma; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment or prophylaxis of a disease state or condition in a patient, wherein the disease state or condition is a malignancy driven by a mutated form of Mer, MSK2, DRAK1, SIK, FMS, RSK2, RSK3, RSK4, PKC-mu (PKCμ) or PKC-gamma (PKCγ), PAK5, BrSK2 or TLK2; for example PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the prophylaxis or treatment of a disease state or condition (e.g. cancer) in a patient, wherein the disease state or condition (e.g. cancer) is characterized by overexpression of any one or more kinases selected from a member of the AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-
activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

"A method for the diagnosis and treatment of a disease state or condition mediated by a kinase which is AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2; which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against the kinase; and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound compound of the formula (I) or salt, solvates and tautomers thereof.

The invention also provides:
A compound of Formula (I), or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition described herein.

A compound of Formula (I), and salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition described herein.

The use of a compound of the formula (I) or salts, solvates and tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against a kinase which is AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSKI /2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against a kinase which is AXL family, such as AxI, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma,
delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, τ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- A method for the diagnosis and treatment of a cancer in which the cancer cells thereof contain a mutant form of one of the following kinases AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, τ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2; which method comprises (i) screening a patient to determine whether a cancer from which the patient is or may be suffering is one in which the cancer cells thereof contain the drug resistant kinase mutation; and (ii) where it is indicated that the cancer cells do contain the drug resistant mutation, thereafter administering to the patient a compound of the formula (I) or salts, solvates or tautomers thereof.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a cancer in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a cancer in which the cancer cells thereof contain a mutant form of one of the following kinases: AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of
the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βl and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a cancer in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a cancer in which the cancer cells thereof contain a mutant form of one of the following kinases AXL family, such as Axl, Mer and Sky, in particular Mer; a member of the Mitogen- and stress-activated kinase family such as MSK1 and MSK2, in particular MSK2; a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1; a Salt-inducible kinase (SIK); a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS); a member of the 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4; PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βl and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ); a member of the p21 activated kinase (PAK) family in particular PAK5; a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a cancer in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a cancer which expresses a mutated molecular target which is a mutated form of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a cancer in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from a cancer which expresses a mutated molecular target which is a mutated form of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5.
A method for the diagnosis and treatment of a cancer which expresses a mutated molecular target which is a mutated form of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5; which method comprises (i) screening a patient to determine whether a cancer from which the patient is or may be suffering is one which expresses the said mutated molecular target; and (ii) where it is indicated that the cancer cells do express the said mutated molecular target, thereafter administering to the patient a compound of the formula (I) or salts, solvates or tautomers thereof.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use as a modulator (e.g. inhibitor) of a kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1,-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

A method of modulating a cellular process (for example cell division) by modulating (e.g. inhibiting) the activity of a kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1,-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) using a compound of the formula (I) or salts, solvates or tautomers thereof.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof for the manufacture of a medicament for modulating (e.g. inhibiting) the activity of a kinase selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1,-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g.
PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of Crohn's disease.

It has now been found that compound of the formula (I) have good activity against PKC-gamma and/or FMS kinases and, on the basis of such activity, the compounds will be useful in the treatment of pain. Therefore, the invention also provides:

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of pain.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of any one or more of nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia, post operative pain, pain due to hypersensivity, headache, inflammatory pain (e.g. rheumatic, dental, dysmenorrhoea or infection), neurological pain, neurogenic pain, skeletal pain (e.g. caused by tumour metatasis or osteoarthritis), musculoskeletal pain, cancer related pain or vascular pain.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of any one or more of nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia, post operative pain, pain due to hypersensivity, headache, inflammatory pain (e.g. rheumatic, dental, dysmenorrhoea or infection), neurological pain, neurogenic pain, skeletal pain (e.g. caused by tumour metatasis or osteoarthritis), musculoskeletal pain, or vascular pain.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory and neurogenic pain.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the reduction or elimination of pain in a patient (e.g. a mammal such as a human) suffering from pain.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in treating any one or more of nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia, post operative pain, pain due to hypersensivity, headache, inflammatory pain (rheumatic, dental, dysmenorrhoea or infection), neurological pain, neurogenic pain, skeletal pain (e.g. caused by tumour metatasis or osteoarthritis), musculoskeletal pain, cancer related pain or vascular pain.
The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment of pain.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the reduction or elimination of pain in a patient (e.g. a mammal such as a human) suffering from pain.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment of any one or more of nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia, post operative pain, pain due to hypersensitivity, headache, inflammatory pain (e.g. rheumatic, dental, dysmenorrhoea or infection), neurological pain, neurogenic pain, skeletal pain (e.g. caused by tumour metatasis or osteoarthritis), musculoskeletal pain, cancer related pain or vascular pain.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment of pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory and neurogenic pain.

A method of treating pain in a patient such as a mammal (e.g. human), which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the reduction or elimination of pain in a patient (e.g. a mammal such as a human) suffering from pain, which method comprises administering to the patient an effective pain-reducing or pain-eliminating amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment of any one or more of nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia, post operative pain, pain due to hypersensivity, headache, inflammatory pain (rheumatic, dental, dysmenorrhoea or infection), neurological pain, neurogenic pain, skeletal pain (e.g. caused by tumour metatasis or osteoarthritis), musculoskeletal pain, cancer related pain or vascular pain, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the treatment of pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory and neurogenic pain, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.
It has now been found that compound of the formula (I) have good activity against PKC-mu and/or RSK and/or PAK5 kinases and, on the basis of such activity, the compounds will be useful in the treatment of certain heart conditions. Therefore, the invention also provides:

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of any one or more of coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of cardiomyopathy including Dilated cardiomyopathy, Restrictive cardiomyopathy, Hypertrophic cardiomyopathy, Coronary artery disease; Congenital heart disease; Ischemic (or ischaemic) cardiomyopathy; Hypertensive cardiomyopathy, Valvular cardiomyopathy; Inflammatory cardiomyopathy; Cardiomyopathy secondary to a systemic metabolic disease and Alcoholic cardiomyopathy, in particular dilated cardiomyopathy.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of congestive heart failure.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the treatment of cardiomyopathy including Dilated cardiomyopathy, Restrictive cardiomyopathy, Hypertrophic cardiomyopathy, Coronary artery disease; Congenital heart disease; Ischemic (or ischaemic)
cardiomyopathy; Hypertensive cardiomyopathy, Valvular cardiomyopathy; Inflammatory cardiomyopathy; Cardiomyopathy secondary to a systemic metabolic disease and Alcoholic cardiomyopathy, in particular dilated cardiomyopathy.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the treatment of congestive heart failure.

- A method for the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF) in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment of any one or more of coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF), in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment of cardiomyopathy including Dilated cardiomyopathy, Restrictive cardiomyopathy, Hypertrophic cardiomyopathy, Coronary artery disease; Congenital heart disease; Ischemic (or ischaemic) cardiomyopathy; Hypertensive cardiomyopathy, Valvular cardiomyopathy; Inflammatory cardiomyopathy; Cardiomyopathy secondary to a systemic metabolic disease and Alcoholic cardiomyopathy, in particular dilated cardiomyopathy, in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

" A method for the treatment of congestive heart failure in a patient, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

It has now been found that compound of the formula (I) have good activity against a number of kinases implicated in bone development and, on the basis of such activity, the compounds will be useful in the treatment of certain bone disorders. Therefore, the invention also provides:

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of bone disorders including Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and
tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use as antiosteolytic agents.

" A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of hypercalcemia, osteoarthritis, or symptomatic treatment of bone metastasis.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment of a condition that results in excessive bone formation.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the treatment of bone disorders including Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use as an antiosteolytic agent.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the treatment of hypercalcemia, osteoarthritis, or symptomatic treatment of bone metastasis.

- The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for use in the treatment of a condition that results in excessive bone formation.

- A method for the treatment of bone disorders including Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method of treating a bone disorder in a patient in need thereof, which method comprises administering to the patient a therapeutically effective antiosteolytic amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

- A method for the treatment of hypercalcemia, osteoarthritis, or symptomatic treatment of bone metastasis in a patient, which method comprises administering to the patient a
therapeutically effective amount of a compound of the formula (I) and salts, solvates or
tautomers thereof.

- A method for the treatment of condition that results in excessive bone formation in a
  patient, which method comprises administering to the patient a therapeutically effective
  amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

As a result of the antibacterial activity described herein further aspects of the invention include:

- A compound of formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a bacterial infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a Gram-positive bacterial infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a Staphylococcus spp., Streptococcus spp., Enterococcus
  spp., Clostridium spp., Bacillus spp., Mycobacteria spp. or Listeria spp. infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a Staphylococcus aureus, Staphylococcus epidermidis,
  Streptococcus diogenes, Streptococcus pneumoniae, Streptococcus mutans,
  Streptococcus gordonii, Streptococcus pyogenes, Enterococcusfaecium, Clostridium
  perfringens, Clostridium difficile, Clostridium botulinum, Bacillus anthracis, Listeria
  monocytogenes, Mycobacterium tuberculosis, Mycobacterium avium or
  Mycobacterium leprae infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a Staphylococcus infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a Staphylococcus aureus infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a drug resistant Staphylococcus aureus infection (e.g.
  MRSA)

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of a Gram-negative bacterial infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
  prophylaxis or treatment of an Escherichia spp., Salmonella spp., Pseudomonas spp.,

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a Salmonella typhimurium, Escherichia coli, Klebsiella pneumoniae, Helicobacter pylori, Legionella pneumophila, Moraxella catarrhalis, Neisseria meningitidis, Neisseria gonorrhoeae, Haemophilus influenzae, Haemophilus ducreyi, Enterobactericeae pneumococci, Enterobacter faecalis, Pseudomonas aeruginosa, Pseudomonas pseudomallei, Proteus mirabilis or Shigella dysenteriae infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a Pseudomonas infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a Pseudomonas aeruginosa infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a drug resistant Pseudomonas aeruginosa infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a systemic bacterial infection.

- A compound of formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a topical bacterial infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a nosocomial bacterial infection.

- A compound of the Formula (I) or salts, solvates or tautomers thereof for use in the prophylaxis or treatment of nosocomial infections for example sepsis and septicemia.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a drug resistant bacterial infection.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Gram-positive bacteria and drug resistant strains thereof.

- A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Gram-positive bacteria.
A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Mycobacteria* spp. or *Listeria* spp., and drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Mycobacteria* spp. or *Listeria* spp.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus diogenes*, *Streptococcus pneumoniae*, *Streptococcus mutans*, *Streptococcus gordonii*, *Streptococcus pyogenes*, *Enterococcus faecium*, *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*, *Bacillus anthracis*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Mycobacterium avium* or *Mycobacterium leprae*, or drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus* spp. and drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus* spp.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus aureus* and drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by *Staphylococcus aureus*.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Gram-negative bacteria and drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Gram-negative bacteria.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Escherichia spp., Salmonella spp., Pseudomonas spp., Helicobacter spp., Legionella spp., Moraxella spp., Neisseria spp., Hemophilus spp., Klebsiella spp., Actinobacteria spp., Proteus, Shigella or Enterobacter spp..

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Salmonella typhimurium, Escherichia coli, Klebsiella pneumoniae, Helicobacter pylori, Legionella pneumophila, Moraxella catarrhalis, Neisseria meningitidis, Neisseria gonorrhoeae, Haemophilus influenzae, Haemophilus ducreyi, Enterobactericeae pneumococci, Enterobacter faecalis, Pseudomonas aeruginosa, Pseudomonas pseudomallei, Proteus mirabilis or Shigella dysenteriae, or drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Pseudomonas spp. and drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Pseudomonas spp..

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Pseudomonas aeruginosa and drug resistant strains thereof.

A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition caused by Pseudomonas aeruginosa.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of infection.

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of infection such as streptococcal infection including strep throat, impetigo, erysipelas, scarlet fever, infections from surgical procedures, hospital acquired lung infection, skin infection, diabetic foot infections, soft tissue infection,
bone infection, joint infection, ear infection including otitis media, eye infection including conjunctivitis and blepharoconjunctivitis, urinary tract infection including catheter infection, venous catheter insertions, prosthesis infection, respiratory tract infection including upper respiratory tract infection, lower respiratory tract infection; tonsillitis; meningitis; cellulitis; diverticulitis; endocarditis; osteomyelitis; pseudomembranous colitis; bronchitis e.g. tracheobronchitis; sinusitis; laryngitis; pneumonia including community acquired pneumonia, bronchopneumonia and legionellosis (Legionnaires' disease); sepsis; septic arthritis; cellulitis; osteomyelitis; epiglottitis; exacerbation of existing chronic obstructive pulmonary disease (COPD); botulism; food poisoning; gonorrhoea; septicaemia including meningococcal septicaemia; typhoid fever; paratyphoid fever; foodborne illness including food poisoning; toxic shock syndrome (TSS); gastrointestinal diseases including diarrhoea, dysentery-like conditions; ankylosing spondylitis; scalded skin syndrome; peptic ulcers; chronic gastritis; duodenitis; gas gangrene; enterotoxemia; tetanus; anthrax; listeriosis; necrotizing fascitis; tuberculosis; bacteraemia, chancroid, shigellosis, leprosy or dysentery.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition caused by a Gram-positive bacteria; wherein the disease state or condition is an infection such as urinary tract infection, or streptococcal infection including strep throat, impetigo, erysipelas, scarlet fever; tonsillitis; meningitis; cellulitis; diverticulitis; endocarditis; pseudomembranous colitis; botulism; food poisoning; bacteraemia; gas gangrene; enterotoxemia; tetanus; anthrax; listeriosis; necrotizing fascitis; bacterial pneumonia; tuberculosis or leprosy.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of urinary tract infection, streptococcal infection including strep throat, impetigo, erysipelas, scarlet fever; tonsillitis; meningitis; cellulitis; diverticulitis; endocarditis; pseudomembranous colitis; botulism; food poisoning; bacteraemia; gas gangrene; enterotoxemia; tetanus; anthrax; listeriosis; necrotizing fascitis; bacterial pneumonia; tuberculosis or leprosy.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition caused by a Gram-negative bacteria; and wherein the disease state or condition is an infection such as infection from surgical procedures, soft tissue infection, joint infection, ear infection including otitis media, eye infection including conjunctivitis and blepharoconjunctivitis, urinary tract infection including venous catheter insertions, respiratory tract infection including
upper respiratory tract infection, and lower respiratory tract infection; bronchitis e.g. tracheobronchitis; sinusitis; laryngitis; pneumonia including bronchopneumonia and legionellosis (Legionnaires' disease); sepsis; cellulitis; osteomyelitis; epiglottitis; exacerbation of existing chronic obstructive pulmonary disease (COPD); gonorrhoea; bacterial meningitis; septicemia including meningococcal septicaemia; typhoid fever; paratyphoid fever; foodborne illness; gastrointestinal diseases including diarrhoea, dysentery-like conditions; ankylosing spondylitis; peptic ulcers; chronic gastritis; duodenitis; bacteremia, chancroid, shigellosis or dysentery.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of an infection such as infection from surgical procedures, soft tissue infection, joint infection, ear infection including otitis media, eye infection including conjunctivitis and blepharoconjunctivitis, urinary tract infection including venous catheter insertions, respiratory tract infection including upper respiratory tract infection, and lower respiratory tract infection; bronchitis e.g. tracheobronchitis; sinusitis; laryngitis; pneumonia including bronchopneumonia and legionellosis (Legionnaires' disease); sepsis; cellulitis; osteomyelitis; epiglottitis; exacerbation of existing chronic obstructive pulmonary disease (COPD); gonorrhoea; bacterial meningitis; septicemia including meningococcal septicaemia; typhoid fever; paratyphoid fever; foodborne illness; gastrointestinal diseases including diarrhoea, dysentery-like conditions; ankylosing spondylitis; peptic ulcers; chronic gastritis; duodenitis; bacteremia, chancroid, shigellosis or dysentery.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of pneumonia, community acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital acquired lung infections, bone and joint infections, mastitis, catheter infection, foreign body, prosthesis infections or peptic ulcer disease.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of nosocomial pneumoniae, community acquired pneumoniae, including concurrent bacteremia, penicillin resistance and sensitive streptococcus pneumoniae, diabetic foot infections, or skin and skin structure infections

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of nosocomial pneumonia caused by *S. aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pneumoniae* (including multidrug-resistant strains (MDRSP)); complicated skin and skin structure infections, including
diabetic foot infections, without concomitant osteomyelitis, caused by *S. aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*; uncomplicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*; vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia; and community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multidrug-resistant strains MDRSP), also in cases with concurrent bacteremia, or caused by *S. aureus* (methicillin-susceptible strains only).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition caused by *S. aureus*; and wherein the disease state or condition is skin infections (in particular pimples, impetigo, boils, cellulitis, folliculitis, furuncles, carbuncles), endocarditis, osteomyelitis, septic arthritis, pneumonia, meningitis, toxic shock syndrome (TSS), food poisoning or scalded skin syndrome (Staphylococcal scalded skin syndrome or SSSS).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of skin infections (in particular pimples, impetigo, boils, cellulitis, folliculitis, furuncles, carbuncles), endocarditis, osteomyelitis, septic arthritis, pneumonia, meningitis, toxic shock syndrome (TSS), food poisoning or scalded skin syndrome (Staphylococcal scalded skin syndrome or SSSS).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of infection of surgical wounds and sites of indwelling medical devices (e.g. prosthetic joints and catheters).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of sepsis or septicemia.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition caused by *P. aeruginosa*; and wherein the disease state or condition is infection of the pulmonary tract, urinary tract, external ear, burns, wounds, blood; intensive care infection; infection of the lungs in cystic fibrosis patients; post-operative infection in radial keratotomy surgery patients; pneumonias such as community acquired pneumonias and ventilator-associated pneumonias; or dermatitis.
A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of infections of the pulmonary tract, urinary tract, external ear, burns, wounds, blood; intensive care infections; infection of the lungs in cystic fibrosis patients; post-operative infection in radial keratotomy surgery patients; pneumonias such as community acquired pneumonias and ventilator-associated pneumonias; or dermatitis

A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of opportunistic infections that occur in debilitated and immunosuppressed patients such as patients with leukemias and lymphomas, people who are receiving immunosuppressive therapy, and patients with predisposing conditions such as diabetes mellitus or AIDS, as well as for non-immunosuppressed patients.

The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition as defined herein.

A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is as defined herein, which method comprises administering to the patient a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is as defined herein, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

A method for the diagnosis and treatment of a disease state or condition caused by bacteria (e.g. a Gram-positive or Gram-negative bacteria); which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having antibacterial activity; and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of the formula (I) or salt, solvates and tautomers thereof.

The use of a compound of the formula (I) or salts, solvates and tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering
from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having antibacterial activity.

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having antibacterial activity.

- A method for the diagnosis and treatment of a disease state or condition caused by bacteria (e.g. a Gram-positive or Gram-negative bacteria); which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against bacteria (e.g. a Gram-positive or Gram-negative bacteria); and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of the formula (I) or salt, solvates and tautomers thereof.

- The use of a compound of the formula (I) or salts, solvates and tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against bacteria (e.g. a Gram-positive or Gram-negative bacteria).

- A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against bacteria (e.g. Gram-positive and/or Gram-negative bacteria).

Further embodiments of the invention provide:

- 1-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and salts, solvates and tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition as defined herein.
l-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or salts, solvates and tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition as defined herein.  

The use of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and salts, solvates and tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition as defined herein.  

The use of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or salts, solvates and tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition as defined herein.  

A method for the prophylaxis of a disease state or condition as defined herein, which method comprises administering to a patient in need thereof, an effective amount of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or salts, solvates or tautomers thereof.  

A method for the prophylaxis of a disease state or condition as defined herein, which method comprises administering to a patient in need thereof, an effective amount of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea lactate or citrate salt (in particular Lactate salt) including crystalline forms thereof, for use in the prophylaxis or treatment of a disease state or condition as defined herein.  

The use of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea lactate or citrate salt (in particular Lactate salt) including crystalline forms thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition as defined herein.  

A method for the prophylaxis of a disease state or condition as defined herein, which method comprises administering to a patient in need thereof, an effective amount of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea lactate or citrate salt (in particular Lactate salt) including crystalline forms thereof.
A compound of the formula (I) and salts, solvates and tautomers thereof, as for use in alleviating or reducing the incidence of a disease state or condition as defined herein.

A compound of the formula (I) or salts, solvates and tautomers thereof, as for use in alleviating or reducing the incidence of a disease state or condition as defined herein.

The use of a compound of the formula (I) and salts, solvates and tautomers thereof, for the manufacture of a medicament for alleviating or reducing the incidence of a disease state or condition as defined herein.

The use of a compound of the formula (I) or salts, solvates and tautomers thereof, for the manufacture of a medicament for alleviating or reducing the incidence of a disease state or condition as defined herein.

A method for alleviating or reducing the incidence of a disease state or condition as defined herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. in a therapeutically effective amount) of the formula (I) and salts, solvates and tautomers thereof.

A method for alleviating or reducing the incidence of a disease state or condition as defined herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. in a therapeutically effective amount) of the formula (I) or salts, solvates and tautomers thereof.

A pharmaceutical composition for use in the treatment of the conditions and diseases described herein.

A medicament for the treatment of the conditions and diseases described herein.

In all of the statements above, in one embodiment the salt is the lactate or citrate salt or mixtures thereof, in particular the lactate salt. In another embodiment, the salt is in a crystalline form. In one embodiment the crystalline form is as described herein and in WO 2006/070195.

Thus, the invention further provides:

A lactate (particularly the L-lactate) or citrate salt of a compound of the formula (I) for use in the prophylaxis or treatment of a disease state or condition described herein.

The use of a lactate (particularly the L-lactate) or citrate salt of a compound of the formula (I) for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition described herein.
A method for the prophylaxis or treatment of a disease state or condition in a patient, wherein the disease state or condition is as described herein, which method comprises administering to a subject in need thereof a therapeutically effective amount of a lactate (particularly the L-lactate) or citrate salt of a compound of the formula (I).

GENERAL PREFERENCES AND DEFINITIONS

As used herein, the term "treatment" and the related terms "treat" and "treating" refer to both prophylactic or preventative treatment as well as curative or palliative treatment of the condition (e.g. pain or infection). Thus, the term encompasses situations where the condition (e.g. pain or infection) is already being experienced by a subject or patient, as well as situations where condition (e.g. pain or infection) is not currently being experienced but is expected to arise. The term "treatment", "treat", "treating" and related terms also cover both complete and partial reduction or prevention of the condition. In addition, the term encompasses inhibiting or killing bacteria. Thus, for example in the context of pain or infection, the compound of the invention may prevent an existing condition from worsening, assist in the management of the condition or reduce or even eliminate the condition. When used in a prophylactic sense, the compound may prevent any condition from developing or it may lessen the extent of condition that may develop. In one embodiment the term means treatment only (i.e. excludes prophylaxis).

As used herein, the term "modulation", as applied to the activity of a kinase, is intended to define a change in the level of biological activity of the protein kinase. Thus, modulation encompasses physiological changes which effect an increase or decrease in the relevant protein kinase activity. In the latter case, the modulation may be described as "inhibition". The modulation may arise directly or indirectly, and may be mediated by any mechanism and at any physiological level, including for example at the level of gene expression (including for example transcription, translation and/or post-translational modification), at the level of expression of genes encoding regulatory elements which act directly or indirectly on the levels of kinase activity. Thus, modulation may imply elevated/suppressed expression or over- or under-expression of a kinase, including gene amplification (i.e. multiple gene copies) and/or increased or decreased expression by a transcriptional effect, as well as hyper- (or hypo-) activity and (de)activation of the protein kinase(s) (including (de)activation) by mutation(s). The terms "modulated", "modulating" and "modulate" are to be interpreted accordingly.
As used herein, the term "mediated", as used e.g. in conjunction with a kinase as described herein (and applied for example to various physiological processes, diseases, states, conditions, therapies, treatments or interventions) is intended to operate limitatively so that the various processes, diseases, states, conditions, treatments and interventions to which the term is applied are those in which the kinase plays a biological role. In cases where the term is applied to a disease, state or condition, the biological role played by a kinase may be direct or indirect and may be necessary and/or sufficient for the manifestation of the symptoms of the disease, state or condition (or its aetiology or progression). Thus, kinase activity (and in particular aberrant levels of kinase activity, e.g. kinase over-expression) need not necessarily be the proximal cause of the disease, state or condition: rather, it is contemplated that the kinase mediated diseases, states or conditions include those having multifactorial aetiologies and complex progressions in which the kinase in question is only partially involved. In cases where the term is applied to treatment, prophylaxis or intervention, the role played by the kinase may be direct or indirect and may be necessary and/or sufficient for the operation of the treatment, prophylaxis or outcome of the intervention. Thus, a disease state or condition mediated by a kinase includes the development of resistance to any particular cancer drug or treatment.

The term "upregulation of a kinase" as used herein is defined as including elevated expression or over-expression of the kinase, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation of the kinase, including activation by mutations and stabilisation.

The term "overexpression" means elevated levels of a kinase in the cell compared to normal levels. This can be due to gene amplification or upregulation of the pathway comprising the gene, or due to elevated levels of the protein in the cell due to stabilisation of the protein or reduction in the rate of destruction of the protein.

As used herein, the term "caused by", as used e.g. in conjunction with a bacteria as described herein (and applied for example to various physiological processes, diseases, states, conditions, therapies, treatments or interventions) is intended to operate limitatively so that the various processes, diseases, states, conditions, treatments and interventions to which the term is applied are those in which the bacteria plays a biological role. In cases where the term is applied to a disease, state or condition, the biological role played by the bacteria may be direct or indirect and may be necessary and/or sufficient for the manifestation of the symptoms of the disease, state or condition (or its aetiology or progression). Thus, bacterial activity need not necessarily be the proximal cause of the disease, state or condition: rather, it is contemplated that the diseases, states or conditions caused by the bacteria include those contributed to by bacteria, and those having multifactorial aetiologies and complex progressions in which the bacteria in
question is only partially involved or to which the bacteria only contributes to the disease state or condition. In cases where the term is applied to treatment, prophylaxis or intervention, the role played by the bacteria may be direct or indirect and may be necessary and/or sufficient for the operation of the treatment, prophylaxis or outcome of the intervention. Thus, a disease state or condition mediated by a bacterium includes the development of resistance to any particular drug or treatment.

References to compound of the invention include the compound of Formula (I) and/or salts (e.g. lactate or citrate salts) thereof.

References to the prophylaxis or treatment of a disease state or condition such as cancer include within their scope alleviating or reducing the incidence of that disease e.g. cancer.

In the compounds shown below that contain an NH moiety (e.g. amide and urea NH groups, benzoimidazole NH groups and pyrazole NH groups), the hydrogen atom may not be explicitly shown. However, in such cases, it is to be understood that the hydrogen atom is present. For example, in many of the compounds, a hydrogen atom is not explicitly shown at the 1-position of the pyrazole ring - i.e. the pyrazole ring appears thus:

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

In such cases, it is to be understood that a hydrogen atom is present at the 1-position, i.e. the above structure is equivalent to:

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{H}
\end{array}
\]

In one embodiment the compound of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea includes its salts, solvates, and tautomers. References to salts include crystalline forms thereof, in particular as described herein.
In another embodiment the compound of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea includes its salts and crystalline forms thereof.

The free base of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea from which the salts are derived has the formula (I):

![Chemical Structure](image)

(I)

The compound of the formula (I) may be referred to in this application by its chemical name, 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea, or, for convenience, as "the compound I", or "the compound of formula (I)". Each of these synonyms refers to the compound shown in formula (I) above and having the chemical name 1-cyclopropyl-S-fS^S-morpholin^-ylmethyl-1H-benzoimidazol^-y^-1H-pyrazol^-yll-urea.

References to the compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base and its acid addition salts include within their scope all solvates, tautomers and isotopes thereof and, where the context admits, N-oxides, other ionic forms and prodrugs. Therefore a reference to the alternative tautomer of formula (I), 1-cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea is to be understood to refer to compound (I).

The compound for the new therapeutic uses of the invention is 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea.

In one embodiment the compound for the new therapeutic uses of the invention is 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or salts (e.g. the lactate or citrate salts or mixtures thereof), solvates and tautomers thereof.

In another embodiment the compound for the new therapeutic uses of the invention is 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and salts (e.g. the lactate or citrate salts or mixtures thereof), solvates and tautomers thereof.

The invention further provides therapeutic uses of the compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and its salts.
The invention provides *inter alia* the lactate and citrate salts of the compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and crystalline forms thereof for the new uses defined herein.

More particularly, the invention provides for the novel uses described herein, a salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea selected from the lactate, citrate and mixtures thereof.

L-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and salts thereof

The acid addition salt of formula (I) may be selected from salts formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), aspartic (e.g. L-aspartic), benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric (e.g. (+) camphoric), camphor-sulphonic, (+)-(15)-camphor-10-sulphonic, capric, caproic, caprylic, carbonic, cinnamic, citric, cyclamic, dodecanoate, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, isobutyric, lactic (e.g. (+)-L-lactic and , (-)-D-lactic), lactobionic, laurylsulphonic, maleic, malic, (-)-L-malic, malonic, (±)-DL-mandelic, methanesulphonic, mucic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, tartaric (e.g. (+)-L-tartaric), thiocyanic, toluenesulphonic (e.g. />-toluenesulphonic), undecylenic and valeric and xinafoic acids, as well as acylated amino acids and cation exchange resins.

One particular group of salts consists of salts formed from hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

One sub-group of salts consists of salts formed from hydrochloric, acetic, adipic, L-aspartic and D- or L-lactic acids.
Another sub-group of salts consists of the acetate, mesylate, ethanesulphonate, D- or L-lactate, adipate, D-glucurionate, D-gluconate and hydrochloride salts. In another embodiment the preferred acid addition salts are mesylate, ethanesulphonate, D- or L-lactate, and hydrochloride salts.

In one particular embodiment the acid addition salt is the DL-lactate, in particular the L-lactate or D-lactate, preferably the L-lactate.

In one embodiment, the salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl]-urea may be the acetate, mesylate, ethanesulphonate, DL-lactate, adipate, D-glucurionate, D-gluconate or hydrochloride salt.

In another embodiment the free base or salt of the compound of Formula (I) is selected from the L-lactate salt, free base dehydrate, esylate salt, free base and hydrochloride salt.

In a further and preferred embodiment, the salt of the compound of Formula (I) is selected from the lactate and citrate salts and mixtures thereof, and more preferably is selected from the L-lactate and citrate salts and mixtures thereof, with the L-lactate salt being particularly preferred.

Particular and preferred embodiments of the invention relating to the L-lactate and citrate salts of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl]-urea are set out and described in more detail below.

In another embodiment, the compound of Formula (I) is a free base.

The salts of the present invention, such as the lactate (e.g. L-lactate) and citrate salts, can be synthesized from the parent compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl]-urea by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the parent compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl]-urea with the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

For example, an acid addition salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl]-urea, such as the lactate (e.g. L-lactate) and citrate salts, can be formed by preparing a solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl]-urea free base in a solvent (typically an organic
solvent) or mixture of solvents, and treating the solution with an acid to form a precipitate of the acid addition salt.

The acid may be added as a solution in a solvent which is miscible with the solvent in which the free base is dissolved. The solvent in which the free base is initially dissolved may be one in which the acid addition salt thereof is insoluble. Alternatively, the solvent in which the free base is initially dissolved may be one in which the acid addition salt is at least partially soluble, a different solvent in which the acid addition salt is less soluble subsequently being added such that the salt precipitates out of solution.

Alternatively an acid addition salt, such as the the lactate (e.g. L-lactate) and citrate salts, can be formed by dissolving 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea in a solvent comprising a volatile acid and optionally a co-solvent, thereby to form a solution of the acid addition salt with the volatile acid, and the resulting solution is then concentrated or evaporated to isolate the salt. A further example of an acid addition salt that can be made in this way is the acetate salt.

The salt is typically precipitated from the organic solvent as it is formed and hence can be isolated by separation of the solid from the solution, e.g. by filtration. One salt form of the invention can be converted to the free base and optionally to another salt form by methods well known to the skilled person. For example, the free base can be formed by passing the salt solution through a column containing an amine stationary phase (e.g. a Strata-NH₂ column). Alternatively, a solution of the salt in water can be treated with sodium bicarbonate to decompose the salt and precipitate out the free base. The free base may then be combined with another acid by one of the methods described above or elsewhere herein.

The preferred salts such as acid addition salts e.g. the lactate (e.g. L-lactate) and citrate salts, have a number of advantages. For example, the salts will enjoy one or more of the following advantages in that they:

- will be more soluble in particular they will have improved solubility in aqueous solution and hence will be better for i.v. administration (e.g. by infusion)
- will allow control of solution pH and are therefore better for i.v. administration;
- may have improved anti-cancer activity; and
- may have an improved therapeutic index.

Further advantages of the salts are that they:

- will have better stability for example thermal stability (e.g. improved shelf life);
• will have advantages for production; and
• will have better physicochemical properties.

The lactate (e.g. L-lactate) salt of the invention is particularly advantageous as it has good solubility in water, and gives better solubility in buffer systems.

Preferred salts for use in the preparation of liquid (e.g. aqueous) pharmaceutical compositions are acid addition salts (such as the lactates) having a solubility in a given liquid carrier (e.g. water) of greater than 1 mg/ml, typically greater than 5 mg/ml of the liquid carrier (e.g. water), more typically greater than 15 mg/ml, more typically greater than 20 mg/ml and preferably greater than 25 mg/ml.

Aqueous solutions of the salts (e.g. in the form of pharmaceutical compositions) represent a further aspect of the invention. Such solutions may be buffered or unbuffered. In solution, the salts will typically dissociate to form 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form together with one or more counter ions. In another aspect, therefore, the invention also provides an aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form together with one or more counter ions and optionally one or more further counter ions (for example counter ions derived from other salts such as sodium chloride or buffering agents).

The salts of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms therefore also form part of the invention.

The compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea may also form N-oxides. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1911, 1, 509-514) in which the amine compound is reacted with ω-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.
The compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and its acid addition salts may exist in a number of different tautomeric forms and references in this application to the compound include all such forms.

More particularly, in the lactate or citrate salts of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea of the invention, the benzoimidazole group may take either of the following two tautomeric forms A and B. For simplicity, the general formula (I) illustrates forms A but the formula is to be taken as embracing all four tautomeric forms.

Moreover, in the context of the lactate or citrate salts of 1-cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea, references to the alternative tautomer, are clearly references to the lactate or citrate salts of the same compound as 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea.

The pyrazole ring may also exhibit tautomerism and can exist in the two tautomeric forms C and D below.

In addition cis and trans conformations of the urea are possible.

References to 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and its salts also include variants with one or more isotopic substitutions,
and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope $^1$H, $^2$H (D), and $^3$H (T). Similarly, references to carbon and oxygen include within their scope respectively $^{12}$C, $^{13}$C and $^{16}$C and $^{18}$O.

The isotopes may be radioactive or non-radioactive. In one embodiment of the invention, the compounds contain no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

Also encompassed by references to 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and its salts are any polymorphic forms, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) thereof.

Solvates

Also encompassed by formula (I) are any polymorphic forms of the compounds, and solvates such as hydrates.

The compound of the invention and its salts and tautomers may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include compounds on the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid or ethanolamine and the like. The compounds of the invention may exert their biological effects whilst they are in solution.

Solvates are well known in pharmaceutical chemistry. They can be important to the processes for the preparation of a substance (e.g. in relation to their purification, the storage of the substance (e.g. its stability) and the ease of handling of the substance and are often formed as part of the isolation or purification stages of a chemical synthesis. A person skilled in the art can determine by means of standard and long used techniques whether a hydrate or other solvate has formed by the isolation conditions or purification conditions used to prepare a given compound. Examples of such techniques include thermogravimetric analysis (TGA),
differential scanning calorimetry (DSC), X-ray crystallography (e.g. single crystal X-ray crystallography or X-ray powder diffraction) and Solid State NMR (SS-NMR, also known as Magic Angle Spinning NMR or MAS-NMR). Such techniques are as much a part of the standard analytical toolkit of the skilled chemist as NMR, IR, HPLC and MS.

Alternatively the skilled person can deliberately form a solvate using crystallisation conditions that include an amount of the solvent required for the particular solvate. Thereafter the standard methods described above, can be used to establish whether solvates had formed.

Furthermore, the compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention.

Lactate and Citrate Salts, Mixtures and Crystals of the compound of formula (I)

As will be apparent from the foregoing sections of the application, preferred salts of Compound (I) are the acid addition salts formed with lactic acid (more preferably L-lactic acid), citric acid or mixtures thereof. For convenience the salts formed from L-lactic acid, and citric acid may be referred to herein as the L-lactate salts and citrate salts respectively.

In one particular embodiment the salt is the L-lactate or D-lactate, preferably L-lactate.

In another embodiment, the salt is a salt formed with citric acid.

More particularly the salts are a mixture of the L-lactate salts and citrate salts.

In the solid state, the lactate (particularly the L-lactate) or citrate salts of the invention can be crystalline or amorphous or a mixture thereof.

In one embodiment, the lactate (particularly the L-lactate) or citrate salts are amorphous.

In an amorphous solid, the three dimensional structure that normally exists in a crystalline form does not exist and the positions of the molecules relative to one another in the amorphous form are essentially random, see for example Hancock et al. J. Pharm. Sci. (1997), 86, 1).

In another embodiment, the lactate (particularly the L-lactate) or citrate salts are substantially crystalline i.e. they may be from 50% to 100% crystalline, and more particularly they may be at least 50% crystalline, or at least 60% crystalline, or at least 70% crystalline, or at least 80% crystalline, or at least 90% crystalline, or at least 95% crystalline, or at least 98% crystalline, or at least 99% crystalline, or at least 99.5% crystalline, or at least 99.9% crystalline, for example 100% crystalline.
In a further embodiment, the lactate or citrate salts are selected from the group consisting of lactate (particularly the L-lactate) or citrate salts that are from 50% to 100% crystalline, for example at least 50% crystalline, at least 60% crystalline, at least 70% crystalline, at least 80% crystalline, at least 90% crystalline, at least 95% crystalline, at least 98% crystalline, at least 99% crystalline, at least 99.5% crystalline, and at least 99.9% crystalline, for example 100% crystalline.

More preferably the lactate (particularly the L-lactate) or citrate salts may be those (or may be selected from the group consisting of those) that are 95% to 100% crystalline, for example at least 98% crystalline, or at least 99% crystalline, or at least 99.5% crystalline, or at least 99.6% crystalline or at least 99.7% crystalline or at least 99.8% crystalline or at least 99.9% crystalline, for example 100% crystalline.

One example of a substantially crystalline salt is a crystalline salt formed with L-lactic acid.

Another example of a substantially crystalline salt is a crystalline salt formed with citric acid.

The salts of the invention, in the solid state, can be solvated (e.g. hydrated) or non-solvated (e.g. anhydrous).

In one embodiment, the salts are non-solvated (e.g. anhydrous).

A further example of a non-solvated salt is the crystalline salt formed with lactic acid (particularly L-lactic acid) as defined herein.

In one embodiment the crystalline form of the salt of Formula (I) is selected from L-lactate salt and citrate salt, in particular the L-lactate salt.

The term "anhydrous" as used herein does not exclude the possibility of the presence of some water on or in the salt (e.g. a crystal of the salt). For example, there may be some water present on the surface of the salt (e.g. salt crystal), or minor amounts within the body of the salt (e.g. crystal). Typically, an anhydrous form contains fewer than 0.4 molecules of water per molecule of compound, and more preferably contains fewer than 0.1 molecules of water per molecule of compound, for example 0 molecules of water.

In another embodiment, the lactate (particularly the L-lactate) or citrate salts are solvated. Where the salts are hydrated, they can contain, for example, up to three molecules of water of crystallisation, more usually up to two molecules of water, e.g. one molecule of water or two molecules of water. Non-stoichiometric hydrates may also be formed in which the number of molecules of water present is less than one or is otherwise a non-integer. For example, where
there is less than one molecule of water present, there may be for example 0.4, or 0.5, or 0.6, or 0.7, or 0.8, or 0.9 molecules of water present per molecule of compound.

Other solvates include alcoholates such as ethanolates and isopropanolates.

In one embodiment, the lactic acid salt (particularly the L-lactate) is solvated for example with water and/or ethanol.

The lactate (particularly the L-lactate) or citrate salts of the present invention can be synthesized from the parent compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the parent compound 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea with the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

A method of preparing a lactate (particularly the L-lactate) or citrate salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea comprises forming a solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea free base in a solvent (typically an organic solvent) or mixture of solvents, and treating the solution with an acid to form a precipitate of the salt.

The acid may be added as a solution in a solvent which is miscible with the solvent in which the free base is dissolved. The solvent in which the free base is initially dissolved may be one in which the salt thereof is insoluble. Alternatively, the solvent in which the free base is initially dissolved may be one in which the salt is at least partially soluble, a different solvent in which the salt is less soluble subsequently being added such that the salt precipitates out of solution.

In an alternative method of forming a salt, 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea is dissolved in a solvent comprising a volatile acid and optionally a co-solvent, thereby to form a solution of the salt with the volatile acid, and the resulting solution is then concentrated or evaporated to isolate the salt.

A method of forming a lactate (particularly the L-lactate) or citrate salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea as defined herein, comprises treating a compound of the formula (I):
with an organic or inorganic acid as defined herein in an organic solvent, and optionally isolating the salt thus formed.

The lactate (particularly the L-lactate) or citrate salt is typically precipitated from the organic solvent as it is formed and hence can be isolated by separation of the solid from the solution, e.g. by filtration.

One salt form of the invention can be converted to the free base and optionally to another salt form by methods well known to the skilled person. For example, the free base can be formed by passing the salt solution through a column containing an amine stationary phase (e.g. a Strata-NH₂ column). Alternatively, a solution of the salt in water can be treated with sodium bicarbonate to decompose the salt and precipitate out the free base. The free base may then be combined with another acid by one of the methods described above or elsewhere herein.

The lactate (particularly the L-lactate) or citrate salts have a number of advantages over the corresponding free base. For example, the salts will enjoy one or more of the following advantages over the free base in that they:

- will be more soluble in particular they will have improved solubility in aqueous solution and hence will be better for i.v. administration (e.g. by infusion)
- will allow control of solution pH and therefore better for i.v. administration;
- will have better stability for example thermal stability (e.g. improved shelf life);
- will have advantages for production;
- will have better physicochemical properties;
- may have improved anti-cancer activity; and
- may have an improved therapeutic index.

The crystalline lactate salt (particularly the L-lactate) of the invention is particularly advantageous as it is:

- non-hygrosopic
- anhydrous and does not form hydrates
- single polymorphic form
- crystalline
• stable to storage
• has sharp melting point and no form changes in DSC experiment.
• has good solubility in water, and gives better solubility in buffer systems.

The term 'stable' or 'stability' as used herein includes chemical stability and solid state (physical) stability. The term 'chemical stability' means that the compound can be stored in an isolated form, or in the form of a formulation in which it is provided in admixture with for example, pharmaceutically acceptable carriers, diluents or adjuvants as described herein, under normal storage conditions, with little or no chemical degradation or decomposition. 'Solid-state stability' means the compound can be stored in an isolated solid form, or the form of a solid formulation in which it is provided in admixture with, for example, pharmaceutically acceptable carriers, diluents or adjuvants as described herein, under normal storage conditions, with little or no solid-state transformation (e.g. hydration, dehydration, solvatisation, desolvatisation, crystallisation, recrystallisation or solid-state phase transition).

Preferred salts for use in the preparation of liquid (e.g. aqueous) pharmaceutical compositions are the salts of the invention (i.e. the lactate or citrate or mixtures thereof as defined herein) having a solubility in a given liquid carrier (e.g. water or buffered systems) of greater than 1 mg/ml, typically greater than 5 mg/ml of the liquid carrier (e.g. water), more typically greater than 15 mg/ml, more typically greater than 20 mg/ml and preferably greater than 25 mg/ml.

In another aspect, there is provided, for the novel uses as defined herein, a pharmaceutical composition comprising an aqueous solution containing the lactate salt (particularly the L-lactate) or citrate salt or mixtures thereof of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (such as) in a concentration of greater than 1 mg/ml, typically greater than 5 mg/ml of the liquid carrier (e.g. water or buffered systems), more typically greater than 15 mg/ml, more typically greater than 20 mg/ml and preferably greater than 25 mg/ml.

In a preferred embodiment, the pharmaceutical composition comprises an aqueous solution containing the L-lactate salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in a concentration of greater than 1 mg/ml, typically greater than 5 mg/ml of the liquid carrier (e.g. water), more typically greater than 15 mg/ml, typically greater than 20 mg/ml and preferably greater than 25 mg/ml.

In another aspect, the invention provides, for the novel uses as defined herein, an aqueous solution of the lactate salt (particularly the L-lactate) or citrate salt or mixtures thereof of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea,
wherein the aqueous solution has a pH of 2 to 6, for example 2 to 5, and more particularly 4 to 6 such as 4 to 5.

In the aqueous solutions defined above, the salt may be any of the salts described herein but, in one preferred embodiment is the L-lactate salt. In one preferred embodiment, the salt is a mixture of L-lactate and citrate salts.

The invention also provides, for the novel uses as defined herein, an aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureain protonated form together with one or more counter ions and optionally one or more further counter ions. In one embodiment one of the counter ions is selected from lactate and citrate. In another embodiment one of the counter ions is from the formulation buffer as described herein such as citrate. In a further embodiment there may be one or more further counter ions such as a chloride ion (e.g. from saline).

The invention therefore provides, for the novel uses as defined herein, an aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureain protonated form together with one or more counter ions selected from L-lactate and citrate, and optionally one or more further counter ions such as a chloride ion.

In the situation where there is more than one counter ions the aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureain protonated form will potentially contain a mixture of counter ions for example a mixture of L-lactate and citrate counter ions and optionally one or more further counter ions such as a chloride ion.

The invention therefore provides, for the novel uses as defined herein, an aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureain protonated form together with one or more counter ions selected from L-lactate and citrate and optionally one or more further counter ions such as a chloride ion, and a mixture thereof.

The invention also provides, for the novel uses as defined herein, an aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureain protonated form together with one or more counter ions and optionally one or more IV excipients for dilution to achieve isotonic formulation. In one embodiment one of the counter ions is selected from L-lactate and citrate. In another embodiment one of the counter ions is from the formulation buffer as described herein such as citrate. In a further embodiment there may be one or more IV excipients as detailed in the United States Pharmacopeia and the National Formulary such as a hexose sugar e.g. dextrose (D-glucose). The invention therefore
provides an aqueous solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-
benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form together with one or more
counter ions selected from L-lactate and citrate, and optionally one or more IV excipients such
as dextrose. In the situation where there is more than one counter ions the aqueous solution of
1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in
protonated form will potentially contain a mixture of counter ions for example a mixture of
lactate and citrate counter ions and optionally one or more further IV excipients such as a
dextrose. The invention therefore provides an aqueous solution of 1-cyclopropyl-3-[3-(5-
morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form
together with one or more counter ions selected from L-lactate and citrate and optionally one or
more further IV excipients such as a dextrose, and a mixture thereof.

The aqueous solutions can be formed inter alia by dissolving a lactate salt in a solution of
citrate ions (e.g. a citrate buffer) or by dissolving a citrate salt in a solution of lactate ions. The
lactate and citrate ions may be present in the solution in a lactate:citrate ratio of from 10:1 or
less, for example 10:1 to 1:10, more preferably less than 8:1, or less than 7:1, or less than 6:1,
or less than 5:1 or less than 4:1 or less than 3:1 or less than 2:1 or less than 1:1, more
particularly from 1:1 to 1:10. In one embodiment, the lactate and citrate ions are present in the
solution in a lactate:citrate ratio of from 1:1 to 1:10, for example 1:1 to 1:8, or 1:1 to 1:7 or 1:1
to 1:6 or 1:1 to 1:5, e.g. approximately 1:4:4.

The aqueous solutions of the salts may be buffered or unbuffered but in one embodiment are
buffered.

In another aspect, there is provided, for the novel uses of the invention as defined herein, a
pharmaceutical composition comprising a lyophilised formulation containing the lactate salt or
citrate salt or mixtures thereof of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-
benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea, wherein the formulation has a pH of 2 to 6, for
example 2 to 5, and more particularly 4 to 6 such as 4 to 5.

In one preferred embodiment the lyophilised formulation defined above, the salt is the L-
lactate.

The invention also provides, for the novel uses of the invention as defined herein, a lyophilised
formulation of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-
pyrazol-4-yl]-urea in protonated form together with one or more counter ions. In one
embodiment one of the counter ions is L-lactate. In another embodiment one of the counter
ions is from the formulation buffer as described herein such as citrate.
The invention therefore provides, for the novel uses of the invention as defined herein, a lyophilised formulation of L-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form together with one or more counter ions selected from L-lactate and citrate. In the situation where there is more than one counter ions the aqueous solution of L-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form will potentially contain a mixture of counter ions for example a mixture of L-lactate and citrate counter ions.

The invention therefore provides, for the novel uses of the invention as defined herein, a lyophilised formulation of L-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea in protonated form together with one or more counter ions selected from lactate, citrate and a mixture thereof.

In one preferred embodiment the lyophilised formulation defined above, the salt is a L-lactate and the buffer salt is citrate.

In one embodiment, the lactate and citrate ions are present in the lyophilised formulation in a lactate: citrate ratio of from 10:1 or less, for example 10:1 to 1:10, more preferably less than 8:1, or less than 7:1, or less than 6:1, or less than 5:1 or less than 4:1 or less than 3:1 or less than 2:1 or less than 1:1, more particularly from 1:1 to 1:10, for example 1:1 to 1:8, or 1:1 to 1:7 or 1:1 to 1:6 or 1:1 to 1:5, e.g. approximately 1:4.4.

The lyophilised formulation of the salts may be buffered or unbuffered but in one embodiment are buffered.

In the context of the salt formed with lactic acid, a preferred buffer is a buffer formed from citric acid and corrected with NaOH or HCl to the correct pH, for example at a solution pH of approximately 4.5. At this pH and in the citrate buffer, the free base has a solubility of about 80 mg/ml respectively.

The lyophilised formulation is then reconstituted into a sterile aqueous solution containing an IV excipient such as saline or dextrose, preferably dextrose.

Crystal Structures of L-Cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl) -lH-pyrazol-4-yll-urea  and Salts thereof

As described above, the lactate or citrate salts of L-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea can be amorphous or substantially crystalline.

In one particular embodiment, the lactate or citrate salts are substantially crystalline, the term "substantially crystalline" having the meaning defined above. In particular the lactate salt of L-
cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea is substantially crystalline.

The crystals described herein and the crystal structures and their employment for the novel uses of the invention as defined herein form further aspects of the invention.

Where the lactate salt (particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea is substantially crystalline, one single crystalline form may predominate, although other crystalline forms may be present in minor and preferably negligible amounts.

The crystalline forms of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea contain less than or equal to about 5% by weight other crystalline forms of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea, in particular containing less than or equal to about 1% by weight of other crystalline forms.

In a preferred embodiment, the invention provides a substantially crystalline salt (e.g. a lactate salt (particularly the L-lactate) as defined herein) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea containing a single crystalline form of the salt and no more than 5% by weight of any other crystalline forms of the salt.

Preferably, the single crystalline form is accompanied by less than 4%, or less than 3%, or less than 2% of other crystalline forms, and in particular contains less than or equal to about 1% by weight of other crystalline forms. More preferably, the single crystalline form is accompanied by less than 0.9%, or less than 0.8%, or less than 0.7%, or less than 0.6%, or less than 0.5%, or less than 0.4%, or less than 0.3%, or less than 0.2%, or less than 0.1%, or less than 0.05%, or less than 0.01%, by weight of other crystalline forms, for example 0% by weight of other crystalline forms.

The crystals and their crystal structures can be characterised using a number of techniques including single crystal X-ray crystallography, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and infra red spectroscopy, e.g. Fourier Transform infra-red spectroscopy (FTIR). The behaviour of the crystals under conditions of varying humidity can be analysed by gravimetric vapour sorption studies and also by XRPD.

Determination of the crystal structure of a compound can be performed by X-ray crystallography which can be carried out according to the conventional methods such as those described herein and in Fundamentals of Crystallography, C. Giacovazzo, H. L. Monaco, D.

The crystal structure of the lactate salt and the dihydrate free base of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea has been determined by X-ray crystallography - see Examples 69 and 71 of WO 2006/070195.

Tables 2 and 4 of Examples 69 and 71 of WO 2006/070195 (at pages 203 and 207) give coordinate data for crystals of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea in Crystallographic Information File (CIF) Format (see Hall, Allen and Brown, Acta Cryst. (1991). A47, 655-685; http://www.iucr.ac.uk/iucr-top/cif/home.html). Alternative file formats such as a PDB file format (e.g. format consistent with that of the EBI Macromolecular Structure Database (Hinxton, UK)) may be used or preferred by others of skill in the art. However it will be apparent that the use of a different file format to present or manipulate the coordinates of the Tables is within the scope of the present invention. The numbers in brackets in the Tables represents the deviation (s.u., standard uncertainty). The crystal structure of the lactate salt is illustrated in Figures 4 and 5 of WO 2006/070195.

In one embodiment the invention provides, for the novel uses of the invention as defined herein, a lactate salt (particularly the L-lactate) of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea which is crystalline and has a crystal structure as defined by the coordinates in Table 4 of WO 2006/070195 (at page 207).

In another embodiment the invention provides, for the novel uses of the invention as defined herein, a lactate salt (particularly the L-lactate) of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea which is crystalline and has a crystal structure as set out in Figures 4 and 5 of WO 2006/070195.

In another embodiment the invention provides, for the novel uses of the invention as defined herein, a lactate salt (particularly the L-lactate) of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea which is crystalline and has a crystal structure that belongs belong to an orthorhombic space group P2₁2₁2₁ (# 19) and has crystal lattice parameters at 97(2) K α=9.94(10), 6=15.03(10), c=16.18(10) Å, α=β=γ=90°.

In another embodiment the invention provides, for the novel uses of the invention as defined herein, a lactate salt (particularly the L-lactate) of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-
H-benzoimidazol-2-yl)-H-pyrazol-4-yl]urea which is crystalline and has crystal lattice parameters at room temperature $\alpha=10.08(10)$, $6=15.22(10)$, $c=16.22(10)$ Å, $\alpha=\beta=\gamma=90^\circ$.

Accordingly, in another embodiment, the invention provides, for the novel uses of the invention as defined herein, a lactate salt (particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-H-benzoimidazol-2-yl)-H-pyrazol-4-yl]urea which is crystalline and:

(a) has a crystal structure as set out in Figures 4 and 5 of WO 2006/070195; and/or
(b) has a crystal structure as defined by the coordinates in Table 4 of WO 2006/070195; and/or
(c) has crystal lattice parameters at $97(2) K \ a=9.94(10)$, $6=15.03(10)$, $c=16.18(10)$ Å, $\alpha=\beta=\gamma=90^\circ$; and/or
(d) has crystal lattice parameters at room temperature $\ a=10.08(10)$, $6=15.22(10)$, $c=16.22(10)$ Å, $\alpha=\beta=\gamma=90^\circ$; and/or
(e) has a crystal structure that belongs to an orthorhombic space group P2;2;2; ( # 19).

The substantially crystalline salts preferably are substantially free of residual organic solvent used, e.g. to recrystallise or otherwise purify the salt, or other solvent such as water.

In one embodiment the crystals of the lactate salt (particularly the L-lactate) of the compounds of Formula (I) and (V), in particular lactate salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-H-benzoimidazol-2-yl)-H-pyrazol-4-yl]-urea are crystals which contain less than 10% by weight of residual solvent (e.g. water or an organic solvent), for example less than 5% residual solvent.

In one embodiment, the crystalline salts (e.g. the lactate salts -particularly the L-lactate) are anhydrous, the term "anhydrous" having the meaning defined above.

In another embodiment the crystalline lactate salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-H-benzoimidazol-2-yl)-H-pyrazol-4-yl]-urea contains residual organic solvent e.g. ethanol in the range of about 0 to 5% by weight for example about 2% ethanol.

Alternatively, the crystalline structure of a compound can be analysed by the solid state technique of X-ray Powder Diffraction (XRPD). XRPD can be carried out according to the conventional methods such as those described herein (see Examples 70 and 72 of WO 2006/070195) and in Introduction to X-ray Powder Diffraction, Ron Jenkins and Robert L. Snyder (John Wiley & Sons, New York, 1996). The presence of defined peaks (as opposed to random background noise) in an XRPD diffractogram indicates that the compound has a degree of crystallinity.
A compound’s X-ray powder pattern is characterised by the diffraction angle (2θ) and/or interplanar spacing (d) parameters of an X-ray diffraction spectrum or pattern. These are related by Bragg’s equation, nλ=2d Sin θ, (where n=1; λ=wavelength of the radiation or cathode used; d=interplanar spacing; and θ=diffraction angle). Herein, interplanar spacings, diffraction angle and overall pattern are important for identification of crystal in the X-ray powder diffraction, due to the characteristics of the data. The relative intensity should not be strictly interpreted since it may be varied depending on the direction of crystal growth, particle sizes and measurement conditions. In addition, the diffraction angles usually mean ones which coincide in the range of 2θ±0.2°. The peaks mean main peaks and include peaks not larger than medium at diffraction angles other than those stated above.

Both the lactate salt and free base forms of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea have been characterised by XRPD. In each case, the powder X-ray diffraction patterns are expressed in terms of the diffraction angle (2θ), interplanar spacing (d) and/or relative intensities. Tables 3, 5 and 6 in Examples 70 and 72 of WO 2006/070195 show the interplanar spacing (d) values of the X-ray diffraction spectrum that correspond to the diffraction angle values of the free base, lactate salt and dihydrate free base forms of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea.

Therefore 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl- lH-benzoimidazol-2-yl)- lH-pyrazol-4-yl]-urea has X-ray powder diffraction patterns essentially as shown in Figure 3, 6, 7 or 8 and/or Tables 3, 5 or 6 of WO 2006/070195.

The invention therefore provides, for the novel uses of the invention as defined herein, crystals of salts (e.g. lactate - particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea having an X-ray powder diffraction patterns which are substantially as in Figure 3, 6, 7 or 8 of WO 2006/070195. Preferably the compound of the present invention is a compound which exhibits peaks at the same diffraction angles as those of the X-ray powder diffraction pattern shown in Figure 3, 6, 7 or 8 and/or Table 3 and/or Table 5 and/or Table 6 of WO 2006/070195 and optionally has same the relative intensity.

The invention further provides, for the novel uses of the invention as defined herein, a crystal of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea lactic acid salt (particularly the L-lactate) which has an X-ray powder diffraction pattern essentially as shown in Figure 6 of WO 2006/070195. Accordingly, in another embodiment, the invention provides, for the novel uses of the invention as defined herein, a substantially
crystalline lactate salt (particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea which exhibits peaks at the same diffraction angles as those of the X-ray powder diffraction pattern shown in Figure 6 of WO 2006/070195. Preferably the peaks have the same relative intensity as the peaks in Figure 6 of WO 2006/070195. Therefore the invention provides, for the novel uses of the invention as defined herein, a substantially crystalline lactic acid salt (particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea having an X-ray powder diffraction pattern substantially as shown in Figure 6 of WO 2006/070195.

The X-ray powder diffraction pattern of the lactate salt may be characterised by the presence of peaks at the diffraction angles (2θ) and interplanar spacings (d), and preferably the intensities shown in Table 5 in Example 72 of WO 2006/070195.

Therefore the invention provides, for the novel uses of the invention as defined herein, a crystal of cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea lactate (particularly the L-lactate), which shows an X-ray powder diffraction pattern having characteristic peaks at a diffraction angle (2θ±1.0 degree such as ±0.2 degree, in particular ±0.1 degree) of Table 5 of Example 72 of WO 2006/070195.

The invention also provides, for the novel uses of the invention as defined herein, crystals of cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea lactate salt (particularly the L-lactate) having an X-ray powder diffraction pattern showing major peaks of diffraction angles 2θ of 17.50, 18.30, 19.30, 19.60, and 21.85 ±1.0 degree such as ±0.2 degree, in particular ±0.1 degree.

Therefore in one embodiment the invention provides, for the novel uses of the invention as defined herein, a crystalline form of cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea lactate salt (particularly the L-lactate) characterized by peaks in the X-ray diffraction pattern at 12.40, 15.20, 15.60, 17.50, 18.30, 18.50, 19.30, 19.60, 21.85, and 27.30±1.0 degrees two-theta.

The crystal of cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea lactate salt (particularly the L-lactate) is also characterised in that the characteristic X-ray powder diffraction pattern is represented by the spacings between lattice planes, d (A) of Table 5 of Example 72 of WO 2006/070195.

In a further embodiment the invention provides, for the novel uses of the invention as defined herein, a crystal of cyclopropyl-3-[3-(6-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-
pyrazol-4-yl]-urea lactate salt (particularly the L-lactate), which possess an X-ray powder
diffraction pattern whose characteristic peaks appear as the lattice spacing (d) of the powder X-
ray diffraction at 5.06, 4.85, 4.60, 4.53, and 4.07, more particularly lattice spacing (d) of the
powder X-ray diffraction at 7.13, 5.83, 5.68, 5.06, 4.85, 4.79, 4.60, 4.53, 4.07, and 3.26
angstrom.

Therefore, in another embodiment, the invention provides, for the novel uses of the invention as
defined herein, a substantially crystalline L-lactate salt (particularly the L-lactate) of 1-
cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-IH-pyrazol-4-yl]-urea
having an X-ray powder diffraction pattern characterised by the presence of major peaks at the
diffraction angles (2Θ) of 17.50, 18.30, 19.30, 19.60, and 21.85 degrees, more particularly
12.40, 15.20, 15.60, 17.50, 18.30, 18.50, 19.30, 19.60, 21.85, and 27.30 degrees, and
interplanar spacings (d) of 5.06, 4.85, 4.60, 4.53, and 4.07, more particularly 7.13, 5.83, 5.68,
5.06, 4.85, 4.79, 4.60, 4.53, 4.07, and 3.26 angstrom.

In a further embodiment, the invention provides, for the novel uses of the invention as defined
herein, a substantially crystalline L-lactate salt of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-
1H-benzoimidazol-2-yl)-IH-pyrazol-4-yl]-urea having an X-ray powder diffraction pattern
characterised by the presence of peaks at the diffraction angles (2Θ and interplanar spacings
(d), and preferably the intensities shown in Table 5 of Example 72 of WO 2006/070195.

The crystalline salts of the invention can also be characterised by differential scanning
 calorimetry (DSC).

The lactate salt has been analysed by DSC and exhibits onset at 190 °C and a peak at 194-197
°C.

Accordingly, in another aspect, the invention provides, for the novel uses of the invention as
defined herein, a lactate salt (particularly the L-lactate) of which is anhydrous and exhibits
onset at 190 °C and/or an endothermic peak at 194-197 °C when subjected to DSC.

The term "onset" as used herein in connection with DSC refers to the start of an endothermic
peak in the DSC scan, where the peak is the point of maximum heat output.

Therefore a further aspect of the invention concerns the novel uses of the lactate salt
(particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-
2-yl)-IH-pyrazol-4-yl]-urea which exhibits peaks at the same diffraction angles as those of the
X-ray powder diffraction pattern shown in Figure 6, 7 or 8 of WO 2006/070195 and further
exhibits onset at 190 °C and/or an endothermic peak accompanying decomposition in the vicinity of a peak at 194-197 °C according to thermal analysis (DSC).

The behaviour of the salts of the invention in conditions of high humidity can be analysed by standard gravimetric vapour sorption (GVS) methods, for example as described in Section E of Example 68 of WO 2006/070195.

The lactate salt can exist in a stable anhydrous crystalline form in conditions of high relative humidity does not undergo changes in crystal structure under such conditions.

The salts of the invention can be further characterised by infra-red spectroscopy, e.g. FTIR.

The infra-red spectrum of the lactate salt (KBr disc method) contains characteristic peaks at 3229, 2972 and 1660 cm⁻¹.

Accordingly, in a further embodiment, the invention provides, for the novel uses of the invention as defined herein, a (preferably substantially crystalline) lactic acid salt (particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea that exhibits an infra-red spectrum, when analysed using the KBr disc method, that contains characteristic peaks at 3229, 2972 and 1660 cm⁻¹.

As will be evident from the foregoing paragraphs, the lactate salt (particularly the L-lactate) of the invention can be characterised by a number of different physicochemical parameters.

Accordingly, in a preferred embodiment, the invention provides a L-lactate salt (particularly the L-lactate) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea which is crystalline and is characterised by any one or more (in any combination) or all of the following parameters, namely that the salt:

(a) has a crystal structure as set out in Figures 4 and 5 of WO 2006/070195; and/or
(b) has a crystal structure as defined by the coordinates in Table 4 in Example 71 of WO 2006/070195 herein; and/or
(c) has crystal lattice parameters at 97(2) K α=9.94(10), β=15.03(10), c=16.18(10) Å, α=β=γ = 90°; and/or
(d) has crystal lattice parameters at room temperature a=\(0.08(1\,0)\), b=\(5.22(1\,0)\), c=\(6.22(10)\) Å, α=β=γ = 90°; and/or
(e) has a crystal structure that belongs belong to an orthorhombic space group P2\(_1\)2\(_1\)2\(_1\) (# 19); and/or
(f) has an X-ray powder diffraction pattern characterised by the presence of major peaks at the diffraction angles (2Θ) of 17.50, 18.30, 19.30, 19.60, and 21.85 degrees, more particularly 12.40, 15.20, 15.60, 17.50, 18.30, 18.50, 19.30, 19.60, 21.85, and
27.30 degrees, and/or interplanar spacings \( d \) of 5.06, 4.85, 4.60, 4.53, and 4.07, more particularly 7.13, 5.83, 5.68, 5.06, 4.85, 4.79, 4.60, 4.53, 4.07, and 3.26 angstrom; and/or

(g) exhibits peaks at the same diffraction angles as those of the X-ray powder diffraction pattern shown in Figure 6 or Table 5 of Example 72 of WO 2006/070195 and optionally wherein the peaks have the same relative intensity as the peaks in Figure 6; or Table 5 of Example 72 of WO 2006/070195 and/or

(h) has an X-ray powder diffraction pattern substantially as shown in Figure 6 of WO 2006/070195; and/or

(i) is anhydrous and exhibits onset at 190 °C and/or an endothermic peak at 194.197 °C when subjected to DSC; and/or

(j) exhibits an infra-red spectrum, when analysed using the KBr disc method, that contains characteristic peaks at 3229, 2972 and 1660 cm\(^{-1}\).

Crystal Structures of l-Cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-

lH-pyrazol-4-yll-urea free base

The free base of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea can also be amorphous or substantially crystalline. In one particular embodiment, the free base is substantially crystalline, the term "substantially crystalline" having the meaning defined above. In one embodiment, the free base of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea exists in a dihydrate crystalline form.

The novel uses of crystals described herein and the crystal structures form further aspects of the invention.

The crystal structure of the free base dihydrate of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea has been determined by X-ray crystallography.

In one embodiment, the invention provides, for the novel uses of the invention as defined herein, the dihydrate free base of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea which is crystalline and (i) has a crystal structure as defined by the coordinates in Table 2 of WO 2006/070195; and/or (ii) wherein the crystals belong to a monoclinic space group \( P2_1/n \) (\# 14) with crystal lattice parameters \( a=6.66(10), b=15.18(10), c=17.71(10) \) \( \text{Å} \), \( \beta=98.53(2) ^\circ \), \( \alpha=\gamma=90^\circ \).

The free base forms of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea have been characterised by XRPD. Therefore free base forms of l-
cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea
have X-ray powder diffraction patterns essentially as shown in Figures 3, 6, 7 or 8 and/or
Tables 3, 5 or 6 in Examples 70 and 72 of WO 2006/070195.

Accordingly, in one embodiment, the invention provides, for the novel uses of the invention as defined herein, crystals of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base exhibiting X-ray powder diffraction patterns containing peaks at the same diffraction angles as those of the X-ray powder diffraction pattern shown in Figure 3, 6, 7 or 8 and/or Table 3 and/or Table 5 and/or Table 6 of WO 2006/070195 and wherein the peaks optionally have the same relative intensity.

The invention also provides, for the novel uses of the invention as defined herein, a crystal of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base, which shows an X-ray powder diffraction pattern having characteristic peaks at a diffraction angle (2θ±1.0 degree such as ±0.2 degree, in particular ±0.1 degree) of Table 2 of Example 69 of WO 2006/070195.

In a further embodiment the invention, for the novel uses of the invention as defined herein, provides a crystal of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea free base, which possess an X-ray powder diffraction pattern whose characteristic peaks appear as the lattice spacing (d) of Table 3 of Example 69 of WO 2006/070195.

The free base of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea exhibits peaks at the same diffraction angles as those of the X-ray powder diffraction pattern shown in Figure 3 and/or Table 3 of WO 2006/070195 and further exhibits an exothermic peak accompanying decomposition in the vicinity of 193°C according to thermal analysis (DSC).

**Biological Activity**

Based on the data provided herein it is envisaged that the compound of formula (I), or salts, solvates or tautomers thereof, would be useful:

a) in the prophylaxis or treatment of a disease state or condition mediated by a kinase, or a mutated form thereof, which is:

- a member of the AXL family, such as AxI, Mer and Sky, in particular Mer.
- a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, i, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ)
- a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS)
- a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2
- a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1
- a Salt-inducible kinase (SIK)
- a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4
- a member of the p21 activated kinase (PAK) family in particular PAK5
- a member of the Brain specific kinase family, Brain specific kinases 1 and 2
- a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2; or

b) as an antibacterial agent; or

c) as a neuroprotective agent, as an immunosuppressive agent or as anti-osteolytic agent;

d) in the prophylaxis or treatment of a disease selected from the following:

- pain;
- coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF), hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease, lung injury;
- disease state or condition results in excessive bone formation, Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients;
- proliferative vitreoretinopathy, liver fibrosis, renal failure, irritable bowel syndrome (IBS), oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy;
cerebral ischemia, Coffin-Lowry syndrome, Borna disease, spinocerebellar ataxia type 14 (SCA14), schizophrenia, transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, pancreatitis and metal (e.g. lead) poisoning;

- pancreatic adenocarcinoma, gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases;
- adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts; and
- allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

The compound of Formula (I) and the lactate or citrate salts of compound of the formula (I) are inhibitors of kinases selected from:

- AXL family, such as Axl, Mer and Sky, in particular Mer.
- Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2
- DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1
- Salt-inducible kinase (SIK)
- CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-1R or FMS)
- 90kDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4
- a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ)
- p21 activated kinase (PAK) family in particular PAK5
- Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2; and
- Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2.

In particular, the compound of Formula (I) and the lactate or citrate salts of compound of the formula (I) are inhibitors of kinases selected from AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase
family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2).

In particular, the compound of Formula (I) and the lactate or citrate salts of compound of the formula (I) are inhibitors of kinases selected from Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4), PKC- PKC e.g. PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.

In one embodiment, the compound of Formula (I) and the lactate or citrate salts of compound of the formula (I) are inhibitors of kinases selected from PKC e.g. PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 and FMS.

In one embodiment, the compound of Formula (I) and the lactate or citrate salts of compound of the formula (I) are inhibitors of kinases selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 and PAK5.

As a consequence of their activity in modulating or inhibiting these kinases, they will be useful in providing a means of arresting, or recovering control of a wide range of cellular pathways involved in non-oncological and oncological diseases, such as cancer. It is therefore anticipated that, in addition to the novel uses defined herein, the compound will prove useful in treating or preventing a range of diseases.

The compound of the invention will be useful in treating conditions such as cancer which are mediated by the kinases described herein or mutated forms thereof.

One sub-group of disease states and conditions where the compound of formula I or the lactate or citrate salts thereof will be useful consists of pain, heart conditions and bone disorders.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermis, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall
bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or rhabdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma. In addition hematopoietic tumours of lymphoid lineage can include small cell lymphocytic lymphoma.

The cancers may be cancers which are sensitive to inhibition of kinases, including mutated forms of the kinases, outlined herein.

In one embodiment the cancer is a leukaemia or lymphoma, in particular leukemia.

In another embodiment, the cancer is leukaemia or lymphoma including chronic lymphocytic leukaemia, mantle cell lymphoma, B-cell lymphoma (such as diffuse large B cell lymphoma), acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukaemia.

In a further embodiment, the cancer is leukaemia including chronic lymphocytic leukaemia, acute lymphocytic leukemia, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukaemia.

Whether or not a particular cancer is one which is sensitive to inhibition by a kinase outlined herein may be determined by means of a cell growth assay as set out in the examples below or by a method as set out in the section headed "Methods of Diagnosis".

The kinases are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore inhibitors of the kinases could also be useful in the treatment of the following diseases other than cancer; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis,
psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular
diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative
disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease,
amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar
degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated
myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-
induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia
and aplastic anemia; degenerative diseases of the musculoskeletal system, for example,
osteoarthritis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis,
and cancer pain.

One group of cancers includes adenocarcinomas in particular pancreatic adenocarcinomas and
gastric adenocarcinomas.

Another sub-set of cancers includes invasive and/or metastatic breast cancer.

The compound is also anticipated for use in the treatment of metastasis from ovarian cancer,
uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and
hairy cell leukemia, in particular bone metastases.

The compounds of Formula (I) and the lactate (particularly the L-lactate) or citrate salts of the
compound of the formula (I), are inhibitors of Mer activity. Mer is overexpressed in a range of
cancers and as such, they will be useful in providing a means of preventing the growth or
inducing apoptosis of neoplasias. It is therefore anticipated that the compound will prove
useful in treating or preventing proliferative disorders such as cancers in particular gastric
adenocarcinoma. In particular tumours with overexpression, upregulation or activating mutants
of Mer may be particularly sensitive to the inhibitors. For example, Mer inhibitors may be
useful in the treatment of adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating
lymphoblasts.

The compounds of Formula (I) and the lactate (particularly the L-lactate) or citrate salts of the
compound of the formula (I), are inhibitors of Mskl or Msk2 activity. MSK1 and MSK2 are
activated by either extracellular signal-regulated kinase (ERK) or p38 mitogen-activated
protein kinases in response to stress or mitogenic extracellular stimuli. As such inhibitors of
MSK family have a role as neuroprotectors. Inhibitors of MSK1 or 2 kinases may be useful in
the treatment and/or prophylaxis of, or protection from, disorders associated with neuronal
degeneration resulting from ischemic events, including cerebral ischemia after cardiac arrest,
stroke and multi-infarct dementia, lung ischemia-reperfusion and reducing lung reperfusion.
injury severity and also after cerebral ischemic events such as those resulting from head injury, surgery and/or during childbirth. For example, the compounds may be used as neuroprotective agents to prevent or reduce the damage to tissue following an injury. Thus where a patient is suffering from injury, the compounds of the invention may be administered to provide a neuroprotective effect to prevent or reduce the extent of damage to the appropriate issue. The invention therefore provides the use of a compound of the formula (I) for the manufacture of a medicament for use as a neuroprotective agent.

Msks are also involved in inflammation and and such may be useful in the treatment and/prophylaxis of inflammatory conditions such as irritable bowel syndrome (IBS). The invention therefore provides the use of a compound of the formula (I) for the manufacture of a medicament for treatment and/prophylaxis of irritable bowel syndrome (IBS).

The compounds of Formula (I) and the lactate (particularly the L-lactate) or citrate salts of the compound of the formula (I), are inhibitors of DRAK activity. DRAK is involved in a range of bone related disorders and is strongly expressed in bone marrow tissues. The invention therefore provides the use of a compound of the formula (I) for the manufacture of a medicament for treatment and/prophylaxis of conditions resulting in excessive bone formation.

The compounds of Formula (I) and the lactate (particularly the L-lactate) or citrate salts of the compound of the formula (I), are inhibitors of FMS activity. FMS plays a role in mammary gland development and are important in osteolytic processes. FMS inhibitors may be useful in the treatment of invasive and metastatic breast cancer, osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents for example in the treatment of arthritis. FMS inhibitors may be useful in methods of treating autoimmune diseases; and diseases with an inflammatory component; treating metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; and treating pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain; as well as osteoporosis, Paget's disease, and other diseases in which bone resorption mediates morbidity including rheumatoid arthritis, and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone. C-Fms has also been linked to diseases such as atherosclerosis, fibrosis and proliferative vitreoretinopathy.

The invention therefore provides the use of a compound of the formula (I), salts or crystalline forms thereof as defined herein, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition mediated by a FMS; and wherein the disease state or condition is selected from autoimmune diseases; and diseases with an inflammatory component; treating metastasis from ovarian cancer, uterine cancer, breast cancer, prostate
cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia; and treating pain,
including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory,
and neurogenic pain; as well as osteoporosis, Paget's disease, and other diseases in which bone
resorption mediates morbidity including rheumatoid arthritis, and other forms of inflammatory
arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma; tumor metastasis to
bone; treatment of invasive and metastatic breast cancer; osteolytic disease associated with
bone metastasis and other bone diseases in patients and as anti-osteolytic agents;
atherosclerosis, fibrosis and proliferative vitreoretinopathy.

In particular the compound of formula (I) may be useful in the treatment of metastasis from
ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer,
stomach cancer, hairy cell leukemia; treatment of invasive and metastatic breast cancer; and
treating pain, including skeletal pain caused by tumor metastasis or osteoarthritis, or visceral,
inflammatory, and neurogenic pain; as well as Paget's disease, and other diseases in which bone
resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor
metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients and as anti-osteolytic agents and proliferative vitreoretinopathy.

The compounds of Formula (I) and the lactate (particularly the L-lactate) or citrate salts of the
compound of the formula (I), are inhibitors of RSK activity including RSK1, RSK2, RSK3 and
RSK4 (in particular RSK2, 3, and 4). RSK has also been suggested as a potential therapeutic
target for liver fibrosis as it has a contributory role in the development of the disease. In
addition, inappropriate RSK activity has been implicated in the etiology of a number of other
diseases including cardiomyopathy, infection, and metal poisoning. There is evidence to show
that the pathway is involved upon exposure to lead. Further, elevated activity of MAPK, the
immediate upstream RSK activator, has also been shown in various neural and heart
pathologies, inflammation, and Borna disease and so an RSK inhibitor may be useful in the
treatment of these disorders. RSK2 is also important in normal development and has been
associated with Coffin-Lowry syndrome.

Therefore in a further aspect is the use of a compound of the formula (I), salts or crystalline
forms thereof as defined herein, for the manufacture of a medicament for the treatment or
prophylaxis of liver fibrosis, cardiomyopathy, Coffin-Lowry syndrome, Borna disease and lead
poisoning.

The compounds of Formula (I) and the lactate (particularly the L-lactate) or citrate salts of the
compound of the formula (I), are inhibitors of PKC activity, in particular PKC-mu and PKC-
gamma. The PKC family is involved in multiple cell signaling pathways and the control of
many cellular processes, and therefore compounds acting on this family are useful in the
treatment of a range of conditions.

PKC-µ plays a role in heart diseases and inhibitors of PCK-µ can therefore be used in the
treatment of heart disease and its manifestations, including coronary artery disease,
cardiomyopathy (e.g. dilated cardiomyopathy), myocardial infarction, myocardial contraction,
congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as
congestive heart failure (CHF).

The invention therefore provides the use of a compound of the formula (I), salts or crystalline
forms thereof as defined herein, for the manufacture of a medicament for the treatment or
prophylaxis of coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF).

An inhibitor of PKC may also provide a method of preventing pathologic heart failure by
identifying a patient at risk of developing pathologic heart failure; and administering (via
intravenous, oral, transdermal, sustained release, delayed release, controlled release,
suppository, sublingual administration, or direct injection into cardiac tissue) to the patient
compound (I). The patient at risk may exhibit one or more of a list of risk factors comprising
long standing uncontrolled hypertension, uncorrected valvular disease, chronic angina, or
recent myocardial infarction, or a patient at risk maybe identified by measuring an indicative
parameters such as right ventricular ejection fraction, left ventricular ejection fraction,
ventricular wall thickness, heart weight/body weight ratio, right or left ventricular weight body
weight ratio, or cardiac weight normalization measurement. The patient at risk may also have a
congenital, familiar, or genetic predisposition to heart disease, heart failure or cardiac
hypertrophy. Heart failure or symptoms thereof may comprise ischemia, cardiomyopathy,
aortic stenosis, or other heart muscle diseases.

The invention also provides the use of a compound of the formula (I), salts or crystalline forms
thereof as defined herein, for the manufacture of a medicament for the treatment or prophylaxis
of diseases such as hypertension including chronic hypoxic pulmonary hypertension (PHTN)
disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis,
interstitial lung disease and lung injury.

Inhibitors of PKCµ may be useful in the treatment of pancreatic adenocarcinoma and PKCµ-
mediated cell resistance. The invention therefore provides the use of a compound of the
formula (I), salts or crystalline forms thereof as defined herein, for the manufacture of a
medicament for the treatment or prophylaxis of pancreatic adenocarcinoma and PKCµ-
mediated cell resistance.
PKCγ mutations resulting in increased kinase activity have been found in neurodegenerative disorders such as spinocerebellar ataxia type 14 (SCA14). The invention therefore provides the use of a compound of the formula (I), salts or crystalline forms thereof as defined herein, for the manufacture of a medicament for the treatment or prophylaxis of spinocerebellar ataxia type 14 (SCA14).

PKC-gamma has also been found to have a role in pain. Therefore invention therefore provides the use of the compound of formula I, salts or crystalline forms thereof as defined herein, for the treatment of pain.

A further aspect of the invention is the use of compounds of formula (I) and inhibitors thereof in the treatment and/or prophylaxis of allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

Members of the PKB family including PKCβ are also involved in other disease areas.

Inhibition of PKCβ can delay or even reverse diabetic retinopathy, nephropathy and neuropathy. Thus PKCβ inhibitors are currently in clinical trials to treat diabetic induced vascular abnormalities. Therefore a further aspect of the invention is the compound of formula (I) for use in the treatment of diabetic retinopathy, nephropathy and neuropathy.

The compound of formula I is also an inhibitor of PAK5. Inhibitors of PAK5 may have a role in the treatment of organ transplantation, cardiomyopathies, renal failure, oxidative stress-related neurodegenerative disorders. Inhibitors of PAK5 are also useful for the treatment of diabetic nephro- and neuropathy, and inhibition of dendritic spine formation and neurite outgrowth in primary neurons and neuroblastoma cells through the activation of Rac/Cdc42-PAK signaling pathways. Therefore a further aspect of the invention is the compound of formula (I) for use in the treatment of organ transplantation, cardiomyopathies, renal failure, oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy.

The compounds are also expected to be useful in the treatment of transplant rejection and are expected to be immunosuppressive agents. The compounds of this invention are therefore useful in the treatment of resistance to transplantation, in transplant rejection, in graft vs. host disease, and pancreatitis. In the treatment of resistance to transplantation, a compound of this invention may be used either prophylactically or in response to an adverse reaction by the human subject to a transplanted organ or tissue. When used prophylactically, a compound of this invention is administered to the patient or to the tissue or organ to be transplanted in advance of the transplantation operation. Prophylactic treatment may also include
administration of the medication after the transplantation operation but before any signs of adverse reaction to transplantation are observed. When administered in response to an adverse reaction, a compound of this invention is administered directly to the patient in order to treat resistance to transplantation after outward signs of the resistance have been manifested.

Therefore a further aspect of the invention is the compound of formula (I) for use in the treatment of organ transplantation, resistance to transplantation, in transplant rejection, in graft vs. host disease, and pancreatitis.

The compound of formula I is also an inhibitor of BrSK1 and 2, in particular 2. BrSK2 is primarily expressin the brain and as such its modulation will have an effect in a range of brain diseases and disorders, including psychotic and neurological conditions. Inhibitors of BrSK may have a role in the treatment of schizophrenia and cerebral ischemia.

Crohn's disease (also known as granulomatous colitis and regional enteritis) is an autoimmune disease causing inflammation of the GI tract. Several risk factors for Crohn's disease have been identified in recent genome-wide association studies some of which are kinases. A further aspect of the invention therefore provides a compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of Crohn's disease.

In a further embodiment the lactate or citrate salts of compound of formula (I) are used to treat the conditions or diseases described herein.

The activity of the compound of formula I and/or the lactate or citrate salts of compound of the invention as inhibitors of the kinases described herein can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC_{50} value.

### Bone Disorders

The compound of formula I has activity against a number of kinases implicated bone disorders.

Paget's Disease, also known as osteitis deformans, can start in any bone in the body. It is rare before the age of 60. The disease involves the thickening of the bones but instead of becoming tougher and stronger the bones, paradoxically, become softer and tend to deform easily. If Paget's Disease affects the bone of the spine, nerves are often compressed producing pain.

In one aspect of the invention the compound is provided for use in the treatment of bone disorders including Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients.
The invention also provides compounds of formula I for use as antosteolytic agents.

The invention therefore further provides the use of a compound of the formula (I), salts or crystalline forms thereof as defined herein, for the manufacture of a medicament for the treatment or prophylaxis of hypercalcemia, osteoarthritis, or symptomatic treatment of bone metastasis.

Heart Conditions

The kinases which the compound of formula I has activity against are implicated in a range of cardiac conditions.

The invention therefore provides the compound of formula I for use in the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy (e.g. dilated cardiomyopathy), myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

Cardiomyopathy, which literally means "heart muscle disease", is the deterioration of the function of the myocardium for any reason. Cardiomyopathy is a disease in which the heart muscle becomes inflamed and does not function correctly. There may be multiple causes including viral infections. Patients suffering from cardiomyopathy are often at risk of arrhythmia or sudden cardiac death or both. There are three main types of cardiomyopathy: dilated, hypertrophic and restrictive. Intrinsic cardiomyopathy has a number of causes including drug and alcohol toxicity, certain viral or bacterial infections (including Hepatitis C), and various genetic and idiopathic (i.e., unknown) causes.

Dilated cardiomyopathy (DCM), the most common form, and is one of the leading indications for heart transplantation. In DCM the heart (especially the left ventricle) is enlarged and the pumping function is diminished. Approximately 40% of cases are familial, but the genetics are poorly understood compared with HCM. In some cases it manifests as peripartum cardiomyopathy, and in other cases it may be associated with alcoholism.

Hypertrophic cardiomyopathy (HCM or HOCM), is a genetic disorder caused by various mutations in genes encoding sarcomeric proteins. In HCM the heart muscle is thickened, which can obstruct blood flow and prevent the heart from functioning properly.

Restrictive cardiomyopathy (RCM) is an uncommon cardiomyopathy. The walls of the ventricles are stiff, but may not be thickened, and resist the normal filling of the heart with blood.
There are a range of other cardiac conditions under the term cardiomyopathy include: Coronary artery disease; Congenital heart disease; Ischemic (or ischaemic) cardiomyopathy; Hypertensive cardiomyopathy; Valvular cardiomyopathy; Inflammatory cardiomyopathy; Cardiomyopathy secondary to a systemic metabolic disease and Alcoholic cardiomyopathy.

The activity of the compounds in treating a range of heart conditions is considered to arise from their activity as inhibitors of PKC\textsubscript{mu}, RSK and/or PAK5. Such activity can be measured using the assay set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC\textsubscript{50} value. Preferred compounds for use in the present invention are compounds having an IC\textsubscript{50} value of less than 1 micromolar, more preferably less than 0.1 micromolar.

Pain

The range of pain sensations experienced and multiple mechanisms involved make a precise definition of pain difficult, therefore in the present invention the term "pain" is used in the broadest sense to describe a spectrum of conditions including nociceptive pain, arising from tissue damage or inflammation, pain related to noxious stimuli, acute pain, chronic pain, and neuropathic pain.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or palliative treatment of pain, in particular anti-nociceptive and anti-allodynic treatment of pain.

Examples of types of pain for which the compounds of the present invention will be useful in treating include nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia (e.g. mechanical allodynia), post operative pain, pain due to hypersensivity (e.g. due to alcohol or drug withdrawal), headache, inflammatory pain (rheumatic, dental, dysmenorrhoea or infection), neurological pain, neurogenic pain, skeletal pain (caused by tumor metastasis or osteoarthritis), musculoskeletal pain, cancer related pain or vascular pain.

In one embodiment, the pain may be other than cancer pain.

In another embodiment, the pain may be cancer pain. For example, the cancer pain may be cancer pain resulting from structural damage, bone metastasis, periosteal irritation, and nerve entrapment which is the most common complication of both benign and metastatic bone disease, and presents a significant problem in both hospital and community practice (Coleman,
1997, Cancer 80; 1588-1594). In another embodiment the cancer related pain is pain associated with cancer therapy, e.g. postchemotherapy syndromes, chronic postsurgical pain syndromes, post radiation syndromes or bone cancer pain.

One subgroup of types of pain includes nociception, somatic pain, visceral pain, acute pain, chronic pain, hyperalgesia, allodynia, post operative pain, pain due to hypersensivity, headache, inflammatory pain (rheumatic, dental, dysmenorrhoea or infection), neurological pain, musculoskeletal pain or vascular pain.

In another subgroup the pain includes skeletal pain (e.g. caused by tumor metastasis or osteoarthritis), visceral, inflammatory, and neurogenic pain

A further aspect of the invention provides the compounds of formula (I) for use in the treatment and/or prophylaxis of allodynia.

A further aspect of the invention provides the compounds of formula (I) for use in the treatment and/or prophylaxis of hyperalgesia.

In particular it provides compounds of formula (I) for use in the treatment and/or prophylaxis of allodynia (e.g. mechanical allodynia or EtOH or opiate withdrawal-associated allodynia) and hyperalgesia (e.g. thermal hyperalgesia and hyperalgesia during alcohol or opiate withdrawal (also known as alcohol or opiate withdrawal-associated hyperalgesia).

The pain may be pain associated with a disease or pathological condition in a mammal.

Therefore in one embodiment of the invention, the compound of formula I is used for the direct treatment of pain in diseases and medical conditions.

The invention provides the use of the compound of formula I, salts or crystalline forms thereof as defined herein, for the treatment of pain including lessening or reducing pain, management of pain and attenuation of nociception. Pain management includes both a lessening of pain and/or induction of analgesia. The compound is contemplated for treatment of acute pain or chronic pain, as well as for prophylactic treatment of anticipated pain (e.g. palliative treatment).

The compound can be administered for use in modulating pain, typically for use in lessening pain, preventing future pain, and/or inhibiting heightened sensitivity to noxious stimuli.

Acute pain is that generally short lived with a specific origin e.g. soft tissue damage/trauma (including post surgical pain), inflammation or infection, usually with no persistent psychological reaction. Acute pain can be modulated by analgesics or treatment of the underlying condition e.g. antibiotics to treat infection.
Chronic pain is a more complex condition involving persistent pain over long periods with, sometimes with no apparent cause and with no apparent biological purpose. Chronic pain can often have psychological consequences. Common causes of chronic pain include low-back pain, headache, pain associated with cancer, arthritis pain and fibromyalgia or myofascial pain.

Neuropathic pain is distinct from "normal" or nociceptive pain, usually results from neurological dysfunction and has a complex and variable etiology. It is often characterised by hyperalgesia (lowered pain threshold and enhanced perception) and allodynia (innocuous thermal or mechanical stimuli causing a perception of pain). Neuropathic pain often fails to respond to the same drugs as nociceptive conditions and is therefore more difficult to treat.

Neuropathic pain can arise whenever nerves are damaged by trauma or amputation, disease (herpes zoster, diabetes, cancer), or chemical injury (e.g. as a side effect of drug treatment with nucleotide anti-HIV or some antineoplastic drugs). Examples would include monoradiculopathies, trigeminal neuralgia, post herpetic neuralgia, complex regional pain syndromes and peripheral neuropathies.

The treatment of pain using the compound of formula I includes the treatment of nociception in particular preventing or protecting against nociception (causing the clinical symptoms not to develop); inhibiting nociception (arresting or suppressing the development of clinical symptoms); and/or relieving nociception (causing the regression of clinical symptoms).

Peripheral neuropathy is a neurodegenerative condition affecting peripheral nerves usually manifesting as one or a combination of motor, sensory, sensorimotor, or autonomic dysfunction. Peripheral neuropathies can result from disease e.g. diabetes (diabetic neuropathy), alcoholism, acquired immunodeficiency syndrome (AIDS), drug therapies e.g. treatment with cytostatics or genetic predisposition (e.g. Metachromatic leukodystrophy). Peripheral neuropathies are often accompanied by pain conditions.

In addition, the compound of formula (I) can be used inter alia in the treatment of pain conditions such as acute and chronic pain (as well as, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, trauma, musculo-skeletal injury or disease, visceral diseases) and migraine headache. Additionally the painful conditions can be neuropathic; examples of such conditions are post-herpetic neuralgia, diabetic neuropathy, drug-induced neuropathy, HIV-mediated neuropathy, sympathetic reflex dystrophy or causalgia, fibromyalgia, myofacial pain, entrapment neuropathy, phantom limb pain and trigeminal neuralgia. Neuropathic conditions include central pain related to stroke, multiple sclerosis, spinal cord injury, arachnoiditis, neoplasms, syringomyelia, Parkinson's disease and epilepsy.
Another sub-group of pain conditions includes all of the pain conditions listed in the preceding paragraph other than cancer pain, i.e. pain associated with cancer.

The present invention is particularly applicable to the palliative treatment of pain, i.e. the direct relief of pain in addition to the relief of pain as the result of amelioration of the underlying disease or medical condition, which is the cause of the pain. Thus, advantageously the invention provides methods and uses for the direct analgesic or acute treatment of pain.

The potential activity of the compounds in treating pain conditions may be tested using a variety of well known techniques. Examples of such techniques include observations of spontaneous pain (e.g. heat (Hargreaves test and hot plate test), cold (application of acetone), paw pressure test (Randal Siletoe test) or mechanical (von Frey hairs) stimuli or rat tail clip test) or similar/equivalent assays, in test species exposed to the test compound in comparison to appropriate controls.

These models could be further modified to improve sensitivity or to test inflammatory pain behaviour by injection of an inflammatory agent (formalin, carageenan, capsaicin, complete Freud's adjuvant, or incomplete Freud's adjuvant) given intra-plantar or intra-articular prior to testing. Activity of the compounds in neuropathic pain conditions could be evaluated using the "Chung" model of peripheral neuropathy (Kim SH, Chung JM., Pain 1992; 50: 355-363). In vivo electro-physiological single cell recordings or nerve fibre recordings could be employed to measure spontaneous and evoked firing rates. Immunohistochemical evidence e.g. staining for substance P, cGRP, galanin, or other relevant substances might also be used.

Lessening or reducing pain refers to a process by which the level of pain a subject perceives is reduced relative to the level of pain the same or a similar subject perceived (or would have perceived) in the absence of or prior to the administration of a therapeutic agent. Pain levels can be calibrated on a subjective scale, or by measuring the subject's response to the pain by, for example, release of stress related factors or the activity of pain-transducing nerves in the peripheral nervous system or the central nervous system. Pain levels can also be calibrated by measuring the amount of an analgesic required for the subject to report that no pain is present or for a subject to stop exhibiting symptoms of pain).

The activity of the compounds in treating pain is considered to arise from their activity as inhibitors of PKC-gamma and/or FMS, in particular PKC-gamma. Such activity can be measured using the assay set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC₅₀ value. Preferred compounds for use in
the present invention are compounds having an IC₅₀ value of less than 1 micromolar, more preferably less than 0.1 micromolar.

**Mutated Kinases**

Protein kinases play widespread essential roles in transducing extracellular signals that regulate cell proliferation, differentiation, and survival, and consequently, might contribute to tumorigenesis through a variety of mechanisms. Excessive or inappropriate signaling via these kinases can be achieved through structural changes that relieve the requirement for activation by ligands or other upstream signals or by virtue of being overexpressed, inappropriately stabilised or mutationally activated.

Mutations can arise naturally in a population and be translated through the germline which might have little impact on the physiological function of the kinase but might change the sensitivity of the mutated kinase to one or more inhibitors. Such germline mutations can be more frequent in certain racial and cultural groups. Mutations arising in tumours as a consequence of disease or drug treatment (somatic mutations) are non-heritable.

Chromosome translocations that produce fusions between tyrosine kinases and other cellular proteins can also result in dysregulated kinase activity owing to either subcellularly mislocalized kinase activity, inappropriate kinase expression, loss of a regulatory domain or de-regulated kinase activity due to conformational changes. Mutations that directly impact kinase catalytic domains can affect the interaction with protein substrates, potentially resulting in an altered profile of downstream signaling. Thus, kinase mutations can result in qualitative as well as quantitative changes in signaling, and so there might be multiple mechanisms by which activating kinase mutations contribute to oncogenesis. Mutations can also activate kinases by effective stabilization of a specific state of the enzyme e.g. an intermediate state of the enzyme. The kinase can also be stabilised by post translational modification.

In addition, for certain drugs acquired drug resistance will substantially limit the clinical benefit of kinase inhibitors as single agent therapies. Acquired resistance to drugs is often associated with primary or secondary mutations within the kinase domain that impair drug binding while retaining oncogenic kinase activity. Acquired drug resistant kinase mutations that arise in patient populations treated with kinase inhibitors can occur, in part, in the regions of the protein that bind to or interact with the particular inhibitor used in therapy. Such mutations reduce the capacity of the inhibitor to bind to and inhibit the kinase in question. This can occur at any of the amino acid residues which interact with the inhibitor or are important for supporting the
binding of said inhibitor to the target. Another inhibitor that binds to a target kinase without
requiring the interaction with the mutated amino acid residue will likely be unaffected by the
mutation and will remain an effective inhibitor of the enzyme (Carter et al, PNAS, 2005, 102,
31, 11011-110116). Other potential resistance mechanisms include amplification of the kinase
gene, activation of additional kinases, and reduced bioavailability of the drug.

One common site at which drug resistant mutations occur is the so-called gate keeper residue.
This particular residue forms a key site of interaction for several kinase inhibitors and their
respective targets. For example, imatinib (Gleevec) binds in part to threonine 315 the gate
keeper residue in the abl kinase domain. T315I mutations are one of the major forms of drug
resistance arising in imatinib treated CML patients and may also be seen in patients with acute
lymphoblastic leukemia.

Thus the term "mutated kinases" or "mutated form of a kinase" includes mutations to the kinase
that occur (i) as mutations transmitted through the germline or (ii) those occurring locally and
are non-heritable (somatic mutations). In both cases the mutations could be due to genetic or
chromosomal aberration. Somatic mutations can often arise as a point mutation or deletion due
to treatment with clinical compounds.

In one embodiment it may be preferred that the treatment is related to or directed at a mutated
form of a kinase, such as discussed herein. Diagnosis of tumours with such mutations or driven
by mutated kinases could be performed using techniques known to a person skilled in the art
and as described herein such as RTPCR and FISH. Compound I might be particularly effective
in cases where the targeted kinase has undergone mutational activation. In particular the
mutated kinase is selected from PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5.

In one embodiment, the compound is used to treat a disease characterized by excessive activity
of a kinase described herein (in particular RSK). The term "excessive kinase activity", as used
herein, refers to an increase in activity of the kinase in a cell with a disease or disorder, relative
to the amount of such activity in an otherwise identical normal cell. In another embodiment,
the present invention encompasses a method for treating a disease characterized by excessive
kinase activity, comprising the step of administering to a subject in need thereof, a
pharmaceutical composition comprising an effective amount of compound I. In one
embodiment the excessive activity is due to a mutation.

**Antibacterial Activity**
Antibacterial activity against various human and animal pathogens is important as a means of treating or preventing conditions caused by, or contributed to, by Gram-positive or Gram-negative bacteria. Antibiotic compounds with activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compound of the present invention is regarded as effective against both Gram-positive and Gram-negative pathogens in particular Gram-negative.

The lactate or citrate salts of the compound of the formula (I) have activity against Gram-positive and Gram-negative bacteria. In one aspect the invention provides the use of the compound of the formula (I) as defined herein as an antibacterial agent.

The compound of the formula (I) as defined herein may be used in animal medicine (for example in the treatment of mammals such as humans), or in the treatment of plants (e.g. in agriculture and horticulture), or as general antibacterial agents, for example as preservatives and disinfectants.

In one embodiment, the invention provides a compound of the formula (I) as defined herein for use in the prophylaxis or treatment of a bacterial infection in a mammal such as a human.

Also provided is the use of a compound of the formula (I) thereof as defined herein for the manufacture of a medicament for use in the prophylaxis or treatment of a bacterial infection in a mammal such as a human.

In one embodiment, a person or animal being treated according to the methods herein is infected with Gram-positive bacterium such as a Staphylococcus bacterium in particular S. aureus, including against drug resistant strains thereof.

For example, the compounds of the invention can be administered to humans or animals to inhibit the growth of bacteria, such as Staphylococcus, including MRSA.

In another embodiment, a person or animal being treated according to the methods herein is infected with a Gram-negative bacterium such as a Pseudomonas bacterium, in particular Pseudomonas aeruginosa, including against drug resistant strains thereof.

Compounds with anti-bacterial activity can be used in the treatment of a range of conditions caused by bacteria. The compounds of the invention can also be administered for the treatment or prophylaxis of systemic bacterial infections. The compounds of the invention may be administered to human patients suffering from, or at risk of infection by topical bacterial infections.
Bacterial infections that can be treated or prevented include infections caused by Gram-positive bacteria, such as *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Mycobacteria* spp. and *Listeria* spp., and Gram-negative bacteria, such as *Escherichia* spp., *Salmonella* spp., *Pseudomonas* spp., *Helicobacter* spp., *Legionella* spp., *Moraxella* spp., *Neisseria* spp., *Hemophilus* spp., *Klebsiella* spp., *Actinobacteria* spp., *Proteus*, *Shigella* and *Enterobacter* spp. These bacterial genera include species such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus diogenes*, *Streptococcus pneumoniae*, *Streptococcus mutans*, *Streptococcus gordonii*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Helicobacter pylori*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Haemophilus ducreyi*, *Enterobactericeae pneumococci*, *Enterobacter faecalis*, *Pseudomonas aeruginosa*, *Pseudomonas pseudomallei*, *Proteus mirabilis* and *Shigella dysenteriae*.

Gram-positive bacteria are involved in a range of diseases, for example *C. botulinum* causes botulism, *C. difficile* causes pseudomembranous colitis, *C perfringens* causes food poisoning, gas gangrene and enterotoxemia ("overeating disease" or "pulpy kidney disease" in sheep and goats), *C. tetani* is the causative organism of tetanus, *B. anthracis* causes anthrax and *Listeria* are responsible for listeriosis. Streptococcal infections include strep throat, impetigo, cellulitis, erysipelas, tonsillitis, and scarlet fever, and certain Streptococcus species are responsible for many cases of meningitis, bacterial pneumonia, endocarditis, and necrotizing fasciitis (the 'flesh-eating' bacterial infections). Important clinical infections caused by *Enterococcus* include urinary tract infections, bacteremia, bacterial endocarditis, diverticulitis, and meningitis.

*Mycobacteria* cause a number of serious diseases in mammals, including tuberculosis and leprosy.

Respiratory tract infections can be caused by certain Gram-negative strains including *Haemophilus influenzae* and *Moraxella catarrhalis*. Respiratory tract-associated infections include bronchitis e.g. tracheobronchitis, sinusitis, laryngitis and otitis media, and pneumonia in particular, bronchopneumonia, as well as exacerbations of existing chronic obstructive pulmonary disease (COPD). Other *Moraxella* species are involved in eye infection in mammals such as *M. lacunata* in blepharoconjunctivitis and *M. bovis* is involved in bovine eye infections, resulting in a progressive, non-self-limiting keratitis, ulceration and - ultimately - rupture of the cornea.
In the Neisseria genus, N. gonorrhoeae (also called the gonococcus) causes gonorrhoea and N. meningitidis (also called the meningococcus) is one of the most common causes of bacterial meningitis and the causative agent of meningococcal septicaemia. Salmonella causes typhoid fever, paratyphoid fever, and foodborne illness, and while many Escherichia are harmless commensals, some species are human pathogens and the cause of urinary tract infections and gastrointestinal diseases ranging from simple diarrhoea to dysentery-like conditions. E. coli is responsible for the vast majority of Escherichia-related pathogenesis, other members of the genus have also been implicated in human disease. Klebsiella organisms can lead to a wide range of disease states, notably pneumonia, urinary tract infections, septicemia, Ankylosing spondylitis, and soft tissue infections. H. pylori is strongly associated with peptic ulcers, chronic gastritis, duodenitis, and stomach cancer. L. pneumophila causes legionellosis (Legionnaires' disease), a potentially fatal form of pneumonia which can affect anybody, but which principally affects those who are susceptible because of age, illness, immunosuppression, smoking etc. The Haemophilus genus includes commensal organisms along with some significant pathogenic strains such as H. influenzae a cause of bacteremia, sepsis and bacterial meningitis and can cause ear (otitis media) and eye (conjunctivitis) infections, cellulitis, osteomyelitis, epiglottitis, joint infections, lower respiratory tract infections, sinusitis, and is associated with pneumonia. H. ducreyi is the causative agent of chancroid. Enterobacteriaceae family cause opportunistic infections in immunocompromised (usually hospitalized) hosts with urinary and respiratory tract are the most common sites of infection such as in venous catheter insertions, and/or surgical procedures. Proteus genus includes pathogens responsible for many human urinary tract infections and Shigella is the causative agent of human shigellosis and dysentery.


Further conditions caused by, or contributed to by bacteria include community acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital acquired lung infections or bone and joint infections, and other bacterial infections, for example, mastitis, catheter infection, foreign body, prosthesis infections or peptic ulcer disease.
Therefore these compounds are useful in the treatment of community acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital acquired lung infections, bone and joint infections, and other bacterial infections, for example, mastitis, catheter infection, foreign body, prosthesis infections or peptic ulcer disease.

5 *S. aureus* is implicated in skin infections, such as pimples, impetigo, boils, cellulitis, folliculitis, furuncles, carbuncles, endocarditis, osteomyelitis, septic arthritis, pneumonia and meningitis, toxic shock syndrome (TSS), food poisoning, and scalded skin syndrome (Staphylococcal scalded skin syndrome or SSSS). It is a major cause of nosocomial infections, causing infection of surgical wounds and sites of indwelling medical devices (e.g. prosthetic joints), which may lead to sepsis for example septicemia.

The compound of the invention are useful in the treatment of skin infections (in particular pimples, impetigo, boils, cellulitis, folliculitis, furuncles, carbuncles), endocarditis, osteomyelitis, septic arthritis, pneumonia, meningitis, toxic shock syndrome (TSS), food poisoning and scalded skin syndrome (Staphylococcal scalded skin syndrome or SSSS). The compound of the invention is useful in the treatment of nosocomial infections for example sepsis and septicemia.

In one embodiment the skin infection is a complicated skin and soft tissue infection (eSSTI). In one embodiment the skin infection is a diabetic foot infection.

*P. aeruginosa* infects the pulmonary tract, urinary tract, external ear, burns, wounds, causes blood infections and is the most frequent colonizer of medical devices (e.g. catheters).

*Pseudomonas* can cause community acquired pneumonias, as well as ventilator-associated pneumonias, is responsible for a considerable proportion of intensive care infections and is also a common cause of post-operative infection in radial keratotomy surgery patients. Cystic fibrosis patients are predisposed to *P. aeruginosa* infection of the lungs. *P. aeruginosa* may also be a common cause of "hot-tub rash" (dermatitis).

The compound of the invention are useful in the treatment of infections the pulmonary tract, urinary tract, external ear, burns, wounds, blood; intensive care infections; infection of the lungs in cystic fibrosis patients; post-operative infection in radial keratotomy surgery patients; pneumonias such as community acquired pneumonias and ventilator-associated pneumonias; and dermatitis.

Antibacterial agents can be used against infections of the type hereinbefore defined, or opportunistic infections that commonly occur in debilitated and immunosuppressed patients such as patients with leukemias and lymphomas, people who are receiving immunosuppressive
therapy, and patients with predisposing conditions such as diabetes mellitus or AIDS, as well as for non-immunosuppressed patients.

One embodiment of the invention provides the compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition caused by a Gram-negative bacteria such as *H. pylori*; and wherein the disease state or condition is stomach cancer.

The compound of the invention can also be useful for treatment of bacterial infections in, and diseases resulting from bacteria, in plants and animals. In particular, the compound of the invention can also be useful for treatment of *M. bovis* infections in cattle, mastitis in dairy cows, bumblefoot in chickens and soft rot. Therefore the compound of the invention is useful in treatment of vegetal and animal infections. In another aspect, the invention provides an antibacterial composition for agricultural (including horticultural) use, comprising a compound of the formula (I) as defined herein together with an agriculturally acceptable diluent or carrier.

The invention further provides a method of treating an animal (including a mammal such as a human), plant or seed having a bacterial infection, which comprises treating said animal, plant or seed, or the locus of said plant or seed, with an effective amount of a compound of the formula (I) as defined herein.

The invention also provides a method of treating a bacterial infection in a plant or seed which comprises treating the plant or seed with an antibacterially effective amount of an antibacterial composition containing a compound of the formula (I) as defined herein.

In one embodiment the disease state or condition is an infection.

**Testing of Antibacterial Activity**

The antibacterial spectrum and potency of a particular compound may be determined in a range of standard test systems. Assays described in the art can be used to screen for agents which may be useful for inhibiting at least Gram-negative and Gram-positive bacteria. The screening assays can be used to identify anti-bacterial agents which may have therapeutic value in the treatment of human, mammal and plant bacterial infections.

The antibacterial properties of the compounds of the invention may be demonstrated and assessed using in vivo conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal with an appropriate bacterial infection using standard techniques. The *in vivo* evaluation of the compound can be carried out at a series of dose levels
by intraperitoneal or intravenous injection or by oral administration, to mice that have been
inoculated with a bacterium. The activity of the compounds can be assessed by monitoring the
growth of the bacterial infection in groups of treated and untreated mice. The activity may be
measured in terms of the dose level at which the compound provides 50% protection against the
lethal effect of the infection (PD_{50}).

The efficacy of the antimicrobial activity may be demonstrated by the Preservative Efficacy
Test (PET) described in European Pharmacopeia 5th Edition, Chpt 5.1.3. 'Efficacy Of
Antimicrobial Preservation'. The Preservative Efficacy Test (PET) gives an indication of the
antimicrobial activity of a preparation. The Preservative Efficacy Test investigates the
antimicrobial efficacy of a preparation against two bacterial strains, one Gram-negative and one
Gram-positive, and two fungal strains. During development of a pharmaceutical preparation, it
may be demonstrated that the antimicrobial activity of the preparation as such or, if necessary,
with the addition of a suitable preservative or preservatives provides adequate protection from
adverse effects that may arise from microbial contamination or proliferation during storage and
use of the preparation. The preparation tested herein comprised the compound of formula I in
lactate salt form in citrate buffer, therefore the PET described herein in Example 17 and
Example 18 can be used to determine if the pharmaceutical preparation itself has antimicrobial
activity.

The test consists of challenging the preparation with a prescribed inoculum of suitable micro-
organisms, storing the inoculated preparation at a prescripted temperature, withdrawing samples
from the container at specified intervals of time a and counting the organisms in the samples so
removed. The antimicrobial activity of the preparation is investigated over the period of
validity to ensure that such activity has not been impaired by storage. The preservative
properties of the preparation are considered adequate if, in the conditions of the test, there was
a significant fall or no increase, as appropriate, in the number of micro-organisms at the
conditions tested. The criteria of acceptance for preservative efficacy in terms of decrease in
the number of micro-organisms with time, vary for different types of preparations according to
the degree of protection intended. In addition the results can be used to demonstrate that the
compound has antibacterial activity.

In addition the antibacterial properties can be tested using standard in-vitro test systems. The in
vitro Minimum Inhibitory Concentration (MIC: El/fl) has been an indicator of in vitro
antibacterial activity widely used in the art. The MIC of test compounds can be determined by
a standard agar dilution method, (Chemotherapy, 1981, 29 (1), 76), or for example as laid out
below in the Example 19. MIC can also be determined using the microtitre broth dilution
method (National Committee for Clinical Laboratory Standards (1997), Methods for dilution

By way of example, in vitro evaluation of the antibacterial activity of the compounds can be performed by determining the minimum inhibitory concentration (M.I.C.) which is the concentration of the test compounds, in a suitable medium, at which growth of the particular microorganism fails to occur. In practice, a series of agar plates, each having the test compound incorporated at a particular concentration is inoculated with a standard culture and each plate is then incubated for an appropriate period at 37 °C. The plates are then examined for the presence or absence of growth of the bacteria and the appropriate M.I.C. value is noted.

Alternatively the antibacterial activity of a compound can be tested by Minimum Bactericidal Dilution and a protocol outlining an example of this assay can be found in Example 21. In addition the bioactivity of these compounds can be tested by Kirby-Bauer diffusion assay against methicillin resistant S. aureus (MRSA). The activity of the compound against samples from isolated from skin can be determined using the Residual Skin Test, for example using a protocol as described in Example 22.

The activity of the compounds in treating bacterial infections is considered to arise from their activity as inhibitors of Gram-positive (e.g. S. aureus) and Gram-negative (e.g. P. aeruginosa) bacterium as demonstrated in the PET. Such activity can be measured using the assay set forth in the examples below.

Drug Resistant Bacteria

As described above resistance of Gram-negative and Gram-positive bacteria to certain drugs can be inherent to the organism or acquired due to mutation or transfer of genes from other microorganisms. Resistance to antibiotics can arise due to a number of different mechanisms including blocking the antibiotic's accumulation (e.g. efflux pumps), modification of the antibiotic (e.g. beta-lactamases) or changes in the antibacterial target itself (e.g. ribosomal modification (erm) strains).

Thus the term "drug resistant bacteria" or "drug resistant strains thereof" includes bacteria that are resistant to drugs (i) due to inherent or (ii) acquired resistance to the drug.

In one embodiment it may be preferred that the treatment is related to or directed at a drug resistant strain of a bacteria, such as discussed herein. Diagnosis of drug resistant bacterial
infections can be performed using techniques known to a person skilled in the art and as described herein. In particular the drug resistant strain of bacteria is MRSA.

The compound could therefore be useful in the treatment of the following infections: nosocomial pneumonia caused by *S. aureus* (methicillin- susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains (MDRSP) where MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillins, second-generation cephalosporins, macrolides, tetracyclines, and tnmethopnm /sulfamethoxazole); complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *S. aureus* (methicillin- susceptible and -resistant strains), *Streptococcus pyogenes, or Streptococcus agalactiae*; uncomplicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*; vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia; and community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multidrug-resistant strains MDRSP), also in cases with concurrent bacteremia, or caused by *S. aureus* (methicillin- susceptible strains only).

The compound of the invention are useful in the treatment of conditions such as nosocomial pneumonia, community acquired pneumonia, caused by methicillin-resistant *S. aureus* (MRSA) , including concurrent bacteremia, penicillin resistance and sensitive streptococcus pneumoniae, diabetic foot infections and skin and skin structure infections, and all other infections caused by bacteria sensitive to the compounds described in the invention. The compounds of the present invention may be effective against a number of human or animal pathogens, clinical isolates, including vancomycin-resistant organisms and methicillin- resistant organisms.

In one embodiment the compound of the invention is anti-MRSA.

Advantages of 1-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-vH-urea (The Compound of formula (I))

The compound of the formula (I) has a number of advantages over prior art compounds. For example, the compound of formula (I) is potent in its activities against different kinases including kinases implicated in cancer development and maintenance such as Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCμ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2 kinases (see Table A). Many of the kinases targeted by the compound lie in oncogenic signalling pathways and have the potential to contribute in a positive way to the anti-tumour action of the compound (Rsk, Mer, PKC). In addition the
potency against a number of kinases could be of potential interest in the treatment of pain, heart conditions (e.g. CHF), and bone disorders.

Table A: Inhibition of kinases in vitro by Compound I

<table>
<thead>
<tr>
<th>Protein</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mer</td>
<td>1-10</td>
</tr>
<tr>
<td>Rsk2</td>
<td>1-10</td>
</tr>
<tr>
<td>Rsk3</td>
<td>1-10</td>
</tr>
<tr>
<td>DRAK1</td>
<td>10-30</td>
</tr>
<tr>
<td>PKCᵦ</td>
<td>10-30</td>
</tr>
<tr>
<td>Rsk4</td>
<td>10-30</td>
</tr>
<tr>
<td>BrSK2</td>
<td>30-100</td>
</tr>
<tr>
<td>Fms</td>
<td>30-100</td>
</tr>
<tr>
<td>Msk2</td>
<td>30-100</td>
</tr>
<tr>
<td>PAK5</td>
<td>30-100</td>
</tr>
<tr>
<td>PKCᵧ</td>
<td>30-100</td>
</tr>
<tr>
<td>Rsk1</td>
<td>30-100</td>
</tr>
<tr>
<td>SIK</td>
<td>30-100</td>
</tr>
<tr>
<td>TLK2</td>
<td>30-100</td>
</tr>
</tbody>
</table>

In addition further kinases targeted by the compound could be of interest in particular in preventing or inhibiting further members of the PKC family (PKCα, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ) Mskl, and BrSKl. (Table B).

Table B: Inhibition of further kinases in vitro by Compound I

<table>
<thead>
<tr>
<th>Protein</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrSK1</td>
<td>100 – 300</td>
</tr>
<tr>
<td>Mskl, PKCα, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ, PKCᵦ</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

The compound of formula (I) is also advantageous over prior art compounds in that it has different susceptibilities to P450 enzymes (Table A).

Table C: Inhibition of expressed cytochrome P450 isoforms in vitro.

<table>
<thead>
<tr>
<th>P450 isoform</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In addition, compounds of the invention are also advantageous over prior art compounds in that they exhibit improvements with regard to drug metabolism and pharmacokinetic properties. In particular the compounds of the invention have reduced plasma protein binding. The binding of the compound to plasma proteins was comparably moderate across all species tested, ranging from 61% in rat to 82% in mouse plasma. This could confer the advantage of having more free drug available in the systemic circulation to reach the appropriate site of action to exert its therapeutic effect. Increased free fraction to exert pharmacological action in tumours potentially leads to improved efficacy which thereby allows reduced dosages to be administered.

The compound of formula (I) has a reduced toxicity and therefore a greater therapeutic window. Furthermore, salt forms of the compound of formula (I) demonstrate improved solubility in aqueous solution and better physicochemical properties, e.g. a lower logD.

**Methods for the Preparation of the Compound of the Formula (I) and Processes for**

Preparation 1-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea

The compound of the formula (I) can be prepared in accordance with synthetic methods well known to the skilled person.

These are as described in WO 2005/002552 and WO 2006/070195, the contents of which are incorporated herein by reference. In particular, the contents of WO 2005/002552 which relate to the relevant processes at pages 88 to 96 are hereby incorporated herein by reference. In particular, the contents of WO 2006/070195 which relate to the relevant processes at pages 90 to 101 are hereby incorporated herein by reference.

In particular, processes for the preparation of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea are as described in WO 2006/070195, the contents of which are incorporated herein by reference. In particular, the contents of WO 2006/070195...
which relate to the relevant processes at pages 102 to 109 are hereby incorporated herein by
reference.

The invention contemplates methods for preparing the compound of the invention for use in the
treatments described herein which comprises the provision of 4-amino-1H-pyrazole-3-
carboxylic acid (2-amino-4-morpholin-4-ylmethyl-phenyl)-amide or 4-amino-1H-pyrazole-3-
carboxylic acid (2-amino-5-morpholin-4-ylmethyl-phenyl)-amide and protected forms thereof
as chemical intermediates. One particular preferred chemical intermediate of formula
((XXVII) of WO 2006/070195 is [3-(2-amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-1H-
pyrazol-4-yl]-carbamic acid tert-butyl ester. One particularly preferred chemical intermediate
of Formula (XXVIII) of WO 2006/070195 is [3-(2-amino-5-morpholin-4-ylmethylphenyl-
carbamoyl)-1H-pyrazol-4-yl]-carbamic acid tert-butyl ester.

The compound of formula ((XXVIIa) of WO 2006/070195 in the process for preparing 3-(5-
morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine or a salt thereof or
process for preparing 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-
1H-pyrazol-4-yl]-urea or a salt thereof above, can be prepared by a process which comprises:

(i) reaction of a compound of the formula (XXIX), where PG is an amine-protecting group
which is removable with acid, APG;

(ii) with a compound of the formula (XXXI) in an organic solvent in the presence of a coupling
agent such as EDC and HOBt.

Optionally the processes described herein have the further step of recrystallising the salt to give
a crystalline form, e.g. a crystalline form as defined herein.

Methods of Purification

Methods of purification of Compound (I) are as described in WO 2006/070195, the contents of
which are incorporated herein by reference. In particular, the contents of WO 2006/070195
which relate to purification at pages 109 to 110 are hereby incorporated herein by reference.

Recrystallisation

Techniques for recrystallisation of Compound (I) are as described in WO 2006/070195, the
contents of which are incorporated herein by reference. In particular, the contents of WO
2006/070195 which relate to recrystallisation at pages 110 to 111 are hereby incorporated
herein by reference.
Therefore, in a further embodiment the lactate salt of the compound prepared herein is optionally recrystallised to give a crystalline form, e.g. a crystalline form as defined herein.

**Pharmaceutical Formulations**

While it is possible for a compound (e.g. a compound of the formula (I) or 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or all salts thereof such as the lactate or citrate salt) to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents; for example agents that reduce or alleviate some of the side effects associated with chemotherapy. Particular examples of such agents include anti-emetic agents and agents that prevent or decrease the duration of chemotherapy-associated neutropenia and prevent complications that arise from reduced levels of red blood cells or white blood cells, for example erythropoietin (EPO), granulocyte macrophage-colony stimulating factor (GM-CSF), and granulocyte-colony stimulating factor (G-CSF).

Thus, the present invention further provides, for the novel uses of the invention as defined herein, pharmaceutical compositions, as defined above, and pharmaceutical compositions made by a method comprising admixing a compound of the formula (I) or (I’) or 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or all salts thereof such as the lactate or citrate salt, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Accordingly, in a further aspect, the invention provides, for the novel uses of the invention as defined herein, the lactate or citrate salt or mixtures thereof of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea as defined herein in the form of pharmaceutical compositions.
The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump.

The skilled person will have the expertise to select the appropriate amounts of ingredients for use in the formulations. For example tablets and capsules typically contain 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) Pigments. Slow release tablets would in addition contain 0-99% (w/w) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

One particular pharmaceutical composition is a form suitable for administration via topical routes. In one embodiment the compound is provided as an antibacterial composition adapted for direct application to skin (for example human skin). One of skill in the art will appreciate that the activity of the present compositions can be affected through the selection of excipients to provide varying degree of skin penetration or to control release. Activity of the present formulations can be increased by occlusion of the skin after application with a suitable bandage or wrap. One of skill in the art will also recognize that persistent action can be increased by use of controlled release technologies which delay release of active over time. As a topical treatment, an effective amount of a compound of Formula I is admixed in a pharmaceutically acceptable gel or cream vehicle that can be applied to the patient's skin at the area of treatment. Preparation of such creams and gels is well known in the art and can include penetration enhancers.

The invention further encompasses methods for inhibiting the growth of bacteria by contacting the bacteria with an effective amount of the compound of the invention in vitro or in vivo, or by applying the compound to a substrate (surface) likely to come in contact with the bacteria, such as a work surface, table, surgical instrument, implant or other device to be placed in or on the body (i.e., foreign object to be inserted into a subject, such as a stent, catheter, access port,
intravenous delivery tube (Hickman), heart valve, dental implant, electro-mechanical device, prosthetic device, glucose sensor, or stabilizing device such as orthopedic nails and pins), eating or cooking utensil, etc. The subject invention also concerns substrates which have a compound of the invention attached or applied thereto.

The formulations contemplated herein can also be coated or otherwise incorporated into medical devices such as wipes, sponges, bandages, surgical drapes, hospital gowns, surgical gowns. Formulations can be developed that are suitable for in disinfecting medical devices. Such formulations could be in the form of a liquid which could be used for spraying onto surfaces, soaking of devices, pumping through devices or incorporated into wipes for decontaminating a surface.

Pharmaceutical formulations 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. Examples of these are described in R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230. In addition, they may contain co-solvents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, inter alia, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended recipient. The formulations 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.

A drug molecule that is ionizable can be solubilized to the desired concentration by pH adjustment if the drug's pKa is sufficiently away from the formulation pH value. The acceptable range is pH 2-12 for intravenous and intramuscular administration, but subcutaneously the range is pH 2.7-9.0. The solution pH is controlled by either the salt form of the drug, strong acids/bases such as hydrochloric acid or sodium hydroxide, or by solutions of buffers which include but are not limited to buffering solutions formed from glycine, citrate, acetate, maleate, succinate, histidine, phosphate, tris(hydroxymethyl)aminomethane (TRIS), or carbonate.

The combination of an aqueous solution and a water-soluble organic solvent/surfactant (i.e., a cosolvent) is often used in injectable formulations. The water-soluble organic solvents and
surfactants used in injectable formulations include but are not limited to propylene glycol, ethanol, polyethylene glycol 300, polyethylene glycol 400, glycerin, dimethylacetamide (DMA), N-methyl-2-pyrrolidone (NMP; Pharmasolve), dimethylsulphoxide (DMSO), Solutol HS 15, Cremophor EL, Cremophor RH 60, and polysorbate 80. Such formulations can usually be, but are not always, diluted prior to injection.

Propylene glycol, PEG 300, ethanol, Cremophor EL, Cremophor RH 60, and polysorbate 80 are the entirely organic water-miscible solvents and surfactants used in commercially available injectable formulations and can be used in combinations with each other. The resulting organic formulations are usually diluted at least 2-fold prior to IV bolus or IV infusion.

Alternatively increased water solubility can be achieved through molecular complexation with cyclodextrins

Liposomes are closed spherical vesicles composed of outer lipid bilayer membranes and an inner aqueous core and with an overall diameter of <100 µm. Depending on the level of hydrophobicity, moderately hydrophobic drugs can be solubilized by liposomes if the drug becomes encapsulated or intercalated within the liposome. Hydrophobic drugs can also be solubilized by liposomes if the drug molecule becomes an integral part of the lipid bilayer membrane, and in this case, the hydrophobic drug is dissolved in the lipid portion of the lipid bilayer. A typical liposome formulation contains water with phospholipid at 5-20 mg/ml, an isotonicifier, a pH 5-8 buffer, and optionally cholesterol.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

The pharmaceutical formulation can be prepared by lyophilising a compound of the formula (I) or 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or all salts thereof such as the lactate or citrate salt thereof as defined herein. Lyophilisation refers to the procedure of freeze-drying a composition. Freeze-drying and lyophilisation are therefore used herein as synonyms. A typical process is to solubilise the compound and the resulting formulation is clarified, sterile filtered and aseptically transferred to containers appropriate for lyophilisation (e.g. vials). In the case of vials, they are partially stoppered with lyo-stoppers. The formulation can be cooled to freezing and subjected to lyophilisation under standard conditions and then hermetically capped forming a stable, dry lyophile formulation. The composition will typically have a low residual water content, e.g.
less than 5% e.g. less than 1% by weight based on weight of the lyophile.

The lyophilisation formulation may contain other excipients for example, thickening agents, dispersing agents, buffers, antioxidants, preservatives, and tonicity adjusters. Typical buffers include phosphate, acetate, citrate and glycine. Examples of antioxidants include ascorbic acid, sodium bisulphite, sodium metabisulphite, monothioglycerol, thiourea, butylated hydroxytoluene, butylated hydroxyl anisole, and ethylenediaminetetraacetic acid salts. Preservatives may include benzoic acid and its salts, sorbic acid and its salts, alkyl esters of para-hydroxybenzoic acid, phenol, chlorobutanol, benzyl alcohol, thimerosal, benzalkonium chloride and cetylpyridinium chloride. The buffers mentioned previously, as well as dextrose and sodium chloride, can be used for tonicity adjustment if necessary.

Bulking agents are generally used in lyophilisation technology for facilitating the process and/or providing bulk and/or mechanical integrity to the lyophilized cake. Bulking agent means a freely water soluble, solid particulate diluent that when co-lyophilised with the compound or salt thereof, provides a physically stable lyophilized cake, a more optimal freeze-drying process and rapid and complete reconstitution. The bulking agent may also be utilised to make the solution isotonic.

The water-soluble bulking agent can be any of the pharmaceutically acceptable inert solid materials typically used for lyophilisation. Such bulking agents include, for example, sugars such as glucose, maltose, sucrose, and lactose; polyalcohols such as sorbitol or mannitol; amino acids such as glycine; polymers such as polyvinylpyrrolidone; and polysaccharides such as dextran.

The ratio of the weight of the bulking agent to the weight of active compound is typically within the range from about 1 to about 5, for example of about 1 to about 3, e.g. in the range of about 1 to 2.

Alternatively they can be provided in a solution form which may be concentrated and sealed in a suitable vial. Sterilisation of dosage forms may be via filtration or by autoclaving of the vials and their contents at appropriate stages of the formulation process. The supplied formulation may require further dilution or preparation before delivery for example dilution into suitable sterile infusion packs.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.
Pharmaceutical compositions of the present invention for parenteral injection can also comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

If a compound not stable in aqueous media or has low solubility in aqueous media it can be formulated as a concentrate in organic solvents. The concentrate can then be diluted to a lower concentration in an aqueous system, and can be sufficiently stable for the short period of time during dosing. Therefore in another aspect, there is provided a pharmaceutical composition comprising a non aqueous solution composed entirely of one or more organic solvents, which can be dosed as is or more commonly diluted with a suitable IV excipient (saline, dextrose; buffered or not buffered) before administration (Solubilizing excipients in oral and injectable formulations, Pharmaceutical Research, 21(2), 2004, p201-230). Examples of solvents and surfactants are propylene glycol, PEG300, PEG400, ethanol, dimethylacetamide (DMA), N-methyl-2-pyrrolidone (NMP, Pharmasolve), Glycerin, Cremophor EL, Cremophor RH 60 and polysorbate. Particular non aqueous solutions are composed of 70-80% propylene glycol, and 20-30% ethanol. One particular non aqueous solution is composed of 70% propylene glycol, and 30% ethanol. Another is 80% propylene glycol and 20% ethanol. Normally these solvents are used in combination and usually diluted at least 2-fold before IV bolus or IV infusion. The typical amounts for bolus IV formulations are -50% for Glycerin, propylene glycol, PEG300, PEG400, and -20% for ethanol. The typical amounts for IV infusion formulations are -15% for Glycerin, 3% for DMA, and -10% for propylene glycol, PEG300, PEG400 and ethanol.
In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion. For intravenous administration, the solution can be dosed as is, or can be injected into an infusion bag (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

In another preferred embodiment, the pharmaceutical composition is in a form suitable for subcutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing a compound of the formula (I) or l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or all salts thereof such as the lactate or citrate salt can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg: lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (e.g.; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit™ type polymer) can be designed to release
the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragees, tablets or capsules.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragee cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.
Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

Alternatively, the antibacterial compounds can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

The a compound of the formula (I) or 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea or all salts thereof such as the lactate or citrate salt will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, or 1 nanogram to 2 milligrams of active ingredient. Within this range, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.
The compound and pharmaceutically acceptable compositions thereof, can be administered to the person or animal via any suitable route. The compound of the invention can also be formulated for livestock and the use thereof is contemplated by the present invention.

In addition to the therapeutic uses described above, anti-bacterial agents can be used, for example, as preservatives in foodstuff, feed supplement for promoting weight gain in livestock, or in disinfectant formulations for treatment of non-living matter, e.g., for decontaminating hospital equipment and rooms. Side by side comparison of inhibition of a bacterium infecting mammals versus insects or parasites, such as the Drosophila, will permit identification of the human/mammalian and insect bacteria that the compound can discriminate between.

Accordingly, the present invention expressly contemplates the use and formulation of the compounds of the invention in insecticides, such as for use in management of insects like the fruit fly.

In yet another embodiment, the antibacterial activity can be used for treatment of bacteria that infect plants. Thus, the present invention specifically contemplates formulations of the compound for agricultural applications, such as in the form of a defoliant or the like.

For agricultural and horticultural purposes the compounds of the invention may be used in the form of a composition formulated as appropriate to the particular use and intended purpose. Thus the compounds may be applied in the form of dusting powders, or granules, seed dressings, aqueous solutions, dispersions or emulsions, dips, sprays, aerosols or smokes. Compositions may also be supplied in the form of dispersible powders, granules or grains, or concentrates for dilution prior to use. Such compositions may contain such conventional carriers, diluents or adjuvants as are known and acceptable in agriculture and horticulture and they can be manufactured in accordance with conventional procedures. The compositions may also incorporate other active ingredients, for example, compounds having herbicidal or insecticidal activity or a further fungicide. The compounds and compositions can be applied in a number of ways, for example they can be applied directly to the plant foliage, stems, branches, seeds or roots or to the soil or other growing medium, and they may be used not only to eradicate disease, but also prophylactically to protect the plants or seeds from attack. By way of example, the compositions may contain from 0.01 to 1 wt.% of the active ingredient. For field use, likely application rates of the active ingredient may be from 50 to 5000 g/hectare.

The invention also contemplates the use of the compound of the formula (I) as defined herein in the control of wood decaying bacteria and in the treatment of soil where plants grow, paddy fields for seedlings, or water for perfusion. Also contemplated by the invention is the use of the
compound of the formula (I) as defined herein to protect stored grain and other non-plant loci from bacterial infestation.

**Methods of Treatment**

A compound of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or a salt thereof such as the lactate or citrate salt as defined herein will be useful as an antibacterial agent and in the prophylaxis or treatment of a range of disease states or conditions as defined herein, for example diseases or conditions for caused by Gram-positive and Gram-negative bacteria or mediated by a member of the AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. Msk2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, e.g. RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) kinases.

The compound of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

Patients that can be treated include humans and other mammals (such as primates (monkey, chimpanzee, ape, etc.) dog, cat, cow, pig, horse, etc.), or bird, reptile, etc.

The compound of formula (I) may be used to treat pain or bacterial conditions in patients. Prior to treatment, a diagnosis of pain or the bacterial condition will be carried out by someone skilled in the art. This could include obtaining history and characteristics of the pain or infection, physical examination of the patient and any appropriate diagnostic tests. Once the type of pain or infection has been determined, a compound of formula (I) may be administered in an amount effective to treat the pain or infection.

As stated above, the terms "treatment" and "treat" in the context of pain or bacterial conditions include both prophylactic and palliative treatment. Thus, the compound of formula (I) may be used in a prophylactic sense to prevent the onset of pain or infection or to prevent pain or
infection from worsening, or they may be used to reduce or eliminate pain or infection in a
patient suffering from pain or infection.

The compound of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-
benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt
will typically be administered in amounts that are therapeutically or prophylactically useful and
which generally are non-toxic. However, in certain situations (for example in the case of life
threatening diseases or in the case of extreme pain or infection, or pain or infections associated
with a terminal condition), the benefits of administering a compound of the formula (I) may
outweigh the disadvantages of any toxic effects or side effects, in which case it may be
considered desirable to administer compounds in amounts that are associated with a degree of
toxicity.

The compound of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-
benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt
may be administered over a prolonged term to maintain beneficial therapeutic effects or may be
administered for a short period only. Alternatively they may be administered in a pulsatile or
continuous manner. An ordinarily skilled clinician can readily assess the patient to determine
optimal dosage, dosage form, and dosage schedule for the patient. A typical daily dose of the
compound can be in the range from 100 picograms to 100 milligrams per kilogram of body
weight, more typically 5 nanograms to 25 milligrams per kilogram of bodyweight, and more
usually 10 nanograms to 15 milligrams per kilogram (e.g. 10 nanograms to 10 milligrams, and
more typically 1 microgram per kilogram to 20 milligrams per kilogram, such as 1 micrograms
to 10 milligrams) per kilogram of bodyweight although higher or lower doses may be
administered where required. The compound can be administered on a daily basis or on a
repeat basis every 2, or 3, or 4, or 5, or 6, or 7, or 10 or 14, or 21, or 28 days for example.

Ultimately, however, the quantity of compound administered and the type of composition used
will be commensurate with the nature of the disease or physiological condition being treated
and will be at the discretion of the physician.

An example of a daily dose of the compound comprises administering a compound of the
formula (I) as defined herein, for example the lactate salt of compound I at a starting dosage of
1 mg/m²/day - 100 mg/m²/day, in particular 1 mg/m²/day - 10 mg/m²/day more particularly 3-
6mg/m²/day (equivalent to 2.5-5 mg free base/m²/day) or at an efficacious dose of the lactate
salt of compound I of 2.5 mg/m²/day - 1.5 g/m²/day, in particular 25 mg/m²/day - 600
mg/m²/day, more particularly 200-500 mg/m²/day such as 250 mg/m²/day or 45-200mg/m²/day
such as 45-150mg/m²/day or 56-185 mg /m²/day (equivalent to 45-150 mg free base /m²/day)
although higher or lower doses may be administered where required. Ultimately, the quantity
of compound administered and the type of composition used will be commensurate with the
to the nature of the disease or physiological condition being treated and will be at the discretion of the
physician.

In one particular dosing schedule, a patient will be given a continuous IV infusion of the
compound or a salt thereof, for example the compound of formula (I), for periods of 2 hour to
120 hour, for example 2 to 96 hour in particular for 24 to 72 hour and the treatment repeated at a
desired interval such as every one to three weeks.

More particularly, a patient may be given a continuous IV infusion of the compound or a salt
thereof for periods of 24 hour daily for 5 days and the treatment repeated every week, or for
periods of 24 hour and the treatment repeated every week, or for periods of 48 hour and the
treatment repeated every two weeks or for periods of 72 hour and the treatment repeated every
three weeks.

In another particular dosing schedule, a patient is given an infusion of the compound as an IV
bolus over 2 hour once a day for a week every 1, 2, or 3 weeks or over 2 hour once every 1, 2,
or 3 weeks.

Higher doses such as 1.5 g/m²/day could be administered using a dosing regimen with frequent
off-treatment periods such as 24 to 48 hour continuous IV fusion every one to two weeks.

Lower dosages such could be administered using a dosing regimens with more sustained dosing
(but still cyclical on/off) such as 48 to 72 hour continuous IV fusion every two to three weeks.

In particular, compounds of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl)-IH-
benzoimidazol-2-yl]-IH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt
in particular the lactate salt could be administered to a patient at 250 mg/m²/day for 72 hours by
continuous IV infusion every 3 weeks.

In another embodiment, compounds of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-
ylmethyl-IH-benzoimidazol-2-yl)-IH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate
or citrate salt in particular the lactate salt could be administered to a patient over a five day
treatment cycle.

For human antibacterial use, the compound of the formula (I) as defined herein can be
administered alone or in admixture with a pharmaceutical carrier selected in accordance with
the intended route of administration and standard pharmaceutical practice. For oral and
parenteral administration to human patients, the daily dosage level of the antibacterial
compounds of the invention can be from 0.01 to 10 mg/kg (in divided doses), depending on inter alia the potency of the compounds when administered by either the oral or parenteral route. Tablets or capsules of the compounds may contain, for example, from 5 mg to 0.5 g of active compound for administration singly or two or more at a time as appropriate. The physician in any event will determine the actual dosage (effective amount) which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient.

Ultimately, however, the quantity of compound administered, the dosing regimen chosen and the type of composition used will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) (l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt as defined herein can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents or therapies that may be administered or used together (whether concurrently or at different time intervals) with the compounds of the invention include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders, microtubule inhibitors (tubulin targeting agents), particular examples being cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes, mitomycin C and radiotherapy. In one embodiment the compounds of the formula (I) (l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt may be combined with a DNA targeting agents such as topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders particularly cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine mitomycin C and radiotherapy.

Other examples of therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) (l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt as defined herein include monoclonal antibodies and signal transduction inhibitors.

For the case of kinase inhibitors combined with other therapies, the two or more treatments may be given in individually varying dose schedules and via different routes. Thus, for example, the salt forms of compound I (e.g. the lactate or citrate salts and mixtures thereof)
may be administered as solutions by the parenteral route whilst another therapeutic agent may be administered orally.

Where the compound of the formula (I) (l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt is administered in combination therapy with one, two, three, four or more other therapeutic agents (preferably one or two, more preferably one), the compounds can be administered simultaneously (either in the same or different pharmaceutical formulation) or sequentially. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The compounds of the formula (I) (l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) (l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt and one, two, three, four or more other therapeutic agents can be, for example, formulated together in a dosage form containing two, three, four or more therapeutic agents. In an alternative, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

A person skilled in the art would know through his or her common general knowledge the dosing regimes and combination therapies to use.

**Methods of Diagnosis of Condition mediated by Kinases**

Prior to administration of the compound of formula (I) i.e. l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea and its salts and crystalline forms thereof, such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is a disease state or condition mediated by a kinase, or mutated form thereof, which is selected from:

- a member of the AXL family, such as Axl, Mer and Sky, in particular Mer.
- a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2
- a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1
- a Salt-inducible kinase (SIK)
- a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS)
- a member of the 9OkDa ribosomal S6 kinase family such as RSK1-4, in particular RSK2, RSK3, RSK4
- a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, λ, and μ), in particular PKC-mu (PKCμ) or PKC-gamma (PKCγ)
- a member of the p21 activated kinase (PAK) family in particular PAK5
- a member of the Brain specific kinase family, Brain specific kinases 1 and 2 (BRSK1/2), in particular BrSK2, or
- a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2

and is a disease state or condition which would be susceptible to treatment with a compound of the formula (I) and salts, solvates or tautomers thereof.

In a particular embodiment, prior to administration of a compound of the formula (I), (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 9OkDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) or a mutated form thereof as defined herein, and in particular Mer, MSK2, DRAK1, SIK, FMS, RSK1-4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKCμ), PKC-gamma (PKCγ), PAK5, BrSK2 and TLK2 kinases.

A biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality (e.g. contains a mutated form of a kinase as described above) or abnormal protein expression which leads to over-activation of a kinase or to
sensitisation of a pathway to normal kinase activity. Alternatively or in addition, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by upregulation of a particular kinase and thus may be particularly sensitive to an inhibitor of that kinase. The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations.

In the case of the kinases defined herein, a biological sample taken from a patient may be analysed to determine whether a condition or disease that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to up-regulation of the levels or activity of the kinase or to sensitisation of a pathway to normal kinase activity, or to upregulation of the kinase signalling pathways such as kinase ligand levels or kinase ligand activity or to upregulation of a biochemical pathway downstream of kinase activation.

Examples of such abnormalities that result in activation or sensitisation of the kinase signal include loss of, or inhibition of apoptotic pathways, up-regulation of the receptors or ligands, or presence of mutant variants of the receptors or ligands.

Conditions driven by mutants or up-regulation of kinases, in particular over-expression of kinases, or gain-of-function mutants of kinases, may be particularly sensitive to an inhibitor of that kinase. Point mutations engendering gain-of-function have been identified in a number of conditions. In addition, genetic aberrations of the kinase such as chromosomal translocations or point mutations resulting in ectopically expressed or deregulated, constitutively active, kinases have been identified.

Alternatively, a biological sample taken from a patient may be analysed for loss of a negative regulator or suppressor of a particular kinase (AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) or a mutated form thereof as defined herein, and in particular PKC-mu, BrSK2 or FMS kinases). In the present context, the term "loss" embraces the deletion of a gene encoding the regulator or suppressor, the truncation of the gene (for example by mutation), the truncation
of the transcribed product of the gene, or the inactivation of the transcribed product (e.g. by point mutation) or sequestration by another gene product.

Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of over-expression, up-regulation or activation of a kinase. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify mutations of a particular kinase. The term marker also includes markers which are characteristic of up regulation of the activity of a kinase, including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins. The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations.

The diagnostic tests are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, buccal spear, biopsy or urine.

Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of over-expression, up-regulation or activation of the kinases described herein (AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSKI -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) including any of the isoforms thereof. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify mutations of the kinases described herein. The term marker also includes markers which are characteristic of up regulation of the kinases including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins.

More specifically, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSKI -4, in particular RSK2, RSK3, RSK4), PKC family (e.g.}
PKC-mu (PKCµ) or PKC-gamma (PKCγ), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) or a mutated form thereof as defined herein, and in particular PKC-mu, BrSK2 or FMS kinases. Tumours with upregulation of the kinases described herein may be particularly sensitive to compound I. Tumours may preferentially be screened for upregulation of the kinases described herein prior to treatment. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of the kinases described.

Identification of an individual carrying a mutation in a kinase such as AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2), and in particular PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5 kinases may mean that the patient would be particularly suitable for treatment with an inhibitor of the kinase in question. Tumours may preferentially be screened for presence of a kinase mutant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody or by using the RT-PCR and FISH techniques described above.

In addition, mutant forms of, for example a kinase such as AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK), CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1 -4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCµ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2), and in particular PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5 kinases, can be identified by direct sequencing of, for example, tumour biopsies using PCR and methods to sequence PCR products directly as hereinbefore described. The skilled person will recognize that all such well-known techniques for detection of the over expression, activation or mutations of the aforementioned proteins could be applicable in the present case.

Conditions (including tumours) with activating mutants of the kinases described herein (AXL family (e.g. Mer), Mitogen- and stress-activated kinase family (e.g. MSK2), DAP kinase-related apoptosis-inducing protein kinase family (e.g. DRAK1), Salt-inducible kinase (SIK),
CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS), 90kDa ribosomal S6 kinase family (in particular RSK1-4, in particular RSK2, RSK3, RSK4), PKC family (e.g. PKC-mu (PKCμ) or PKC-gamma (PKCγ)), p21 activated kinase (PAK) family (e.g. PAK5), Brain specific kinase family (e.g. BrSK2) and Tousled-like kinase (TLK) family (e.g. TLK2) including any of the isoforms thereof, may be particularly sensitive to compound (I) and therefore may be screened for activating mutants prior to treatment with Compound (I).

Methods of identification and analysis of mutations and up-regulation of proteins are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridization such as fluorescence in situ hybridization (FISH).

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc., or Innis, M.A. et-al., eds. PCR Protocols: a guide to methods and applications, 1990, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook et al., 2001, 3rd Ed, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference.

An example of an in-situ hybridisation technique for assessing mRNA expression would be fluorescence in-situ hybridisation (FISH) (see Angerer, 1987 Meth. Enzymol., 152: 649).

Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labeled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtiter plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques can be used for detection of upregulation or mutants of any of the kinases described herein, or loss of control of the pathways which they are involved in.

Therefore, all of these techniques could also be used to identify patients or tumours particularly suitable for treatment with the compound of the invention.

In one embodiment of the invention, prior to administration of a compound of the formula (I), (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against Mer, MSK2, DRAK1, SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKC\(\mu\)), PKC-gamma (PKC\(\gamma\)), PAK5, BrSK2 and/or TLK2. These techniques may also be used for screening for diseases or conditions caused by the up-regulation or mutants of Mer, MSK2, DRAK1 , SIK, FMS, RSK1 -4 (in particular RSK2, RSK3, RSK4, PKC-mu (PKC\(\mu\)), PKC-gamma (PKC\(\gamma\)), PAK5, BrSK2 and TLK2 kinases.

In another embodiment of the invention, prior to administration of a compound of the formula (I) (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against PKC e.g. PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 or FMS kinases. These techniques may also be used for screening for diseases or conditions caused by the up-regulation or mutants of PKC e.g. PKC gamma or PKC-mu, RSK e.g. RSK2, PAK5, BrSK2 or FMS kinases. These techniques may also be used for screening for diseases or conditions caused by the overexpression of TLK2, Mer, MSK e.g. Msk2, RSK e.g. RSK2, or PAK5 kinases. Abnormal
levels of proteins can be measured using standard enzyme assays, for example, those assays described herein. Activation or overexpression could also be detected in a tissue sample, for example a tumour tissue, by measuring the tyrosine kinase activity with an assay such as that available from Chemicon International. The tyrosine kinase of interest would be immunoprecipitated from the sample lysate and its activity measured.

Alternative methods for the measurement of the over expression or activation of kinases including the isoforms thereof, include the measurement of microvessel density. This can for example be measured using methods described by Orre and Rogers (Int. J. Cancer 1999 84(2) 101-8). Assay methods also include the use of markers.

Mutations have been observed for a number of the kinases described herein including PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5. The methods described herein could be used to identify patients harbouring these mutations. These techniques may also be used for screening for diseases or conditions caused by the up-regulation or mutants of PKC e.g. PKC gamma, FMS, RSK e.g. RSK2 or PAK5 kinases.

Complex chromosomal aberrations can be present in the conditions described herein. Specific alterations in complex karyotypes are difficult to define by conventional cytogenetics alone. A more comprehensive view of the recurrent aberrations can be obtained when spectral karyotyping (SKY) and fluorescence in situ hybridization (FISH) with selected probes on bone marrow samples are used (Cancer Genet. Cytogenet. 2006,165(1), 51-63, Trost D et al). A detailed analysis of specific breakpoints and deletions can reveal recurrent involvement of specific chromosomal bands harboring known tumor suppressor genes or oncogenes. Correlation with clinical parameters may reveal the prognostic significance of these genetic subgroups.

Genetic instability is a common feature of many diseases. Thus a number of techniques known to the skilled person could be used to determine whether a condition was associated with chromosomal aberrations. Therefore an aspect of the invention is a method of detecting whether a patient is suffering from a disease, in particular cancer, exhibiting chromosomal aberrations and treating them with a compound of the invention.

In another embodiment, prior to administration of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or a salt thereof, such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against PKC-mu, BrSK2 or FMS kinases.
For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to over-activation of the kinase or to sensitisation of a pathway to normal kinase activity. Examples of such abnormalities that result in activation or sensitisation of the kinase signal include up-regulation or presence of mutants. Tumours with mutants of or up-regulation, in particular over-expression, may be particularly sensitive to kinase inhibitors. Alternatively or in addition, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by upregulation of kinase described herein and thus may be particularly sensitive to compound (I). The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations.

The diagnostic tests are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, or urine.

The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody.

**Methods of Diagnosis of Bacterial Infection**

Prior to administration of the compound of formula (I) i.e. 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea and its salts and crystalline forms thereof, such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is a disease state or condition mediated by a Gram-negative or Gram-positive bacterium and is a disease state or condition which would be susceptible to treatment with a compound of the formula (I) and salts, solvates or tautomers thereof.

In a particular embodiment, prior to administration of a compound of the formula (I), (1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea) or all salts thereof such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with an antibacterial compound.

A biological sample taken from a patient may be analysed to determine whether a condition or disease, such as infection, that the patient is or may be suffering from is one which is caused by Gram-negative bacteria, Gram-positive bacteria, or a drug resistant strain thereof. The patient
may be subjected to a diagnostic test to detect the species of bacterium. The term diagnosis includes screening. The diagnostic tests are typically conducted on a biological sample selected from infection site samples, tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, buccal swabs, biopsy or urine. The skilled person will recognize that all such well-known techniques for detection of the Gram-negative, Gram-positive and drug resistant strains of bacteria could be applicable in the present case.

Thus, the patient may be subjected to a diagnostic test to detect a disease or condition caused by a bacterium, in particular a Gram-negative or Gram-positive bacterium including any drug resistant strain thereof. More specifically, the patient may be subjected to a diagnostic test to disease or condition caused by \textit{S. aureus} or \textit{P. aeruginosa}. In addition, the patient may be subjected to a diagnostic test to detect a disease or condition caused by a drug resistant strain of the bacterium.

Identification of an individual carrying a bacterium such as \textit{S. aureus} or \textit{P. aeruginosa} may mean that the patient would be particularly suitable for treatment with the compound of formula (I). Methods of identification and analysis of bacteria are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as MIC.

In one embodiment of the invention, prior to administration of a compound of the formula (I), \( \text{I-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea} \) or all salts thereof such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having antibacterial activity, in particular activity against Gram-positive bacteria such as \textit{S. aureus} and Gram-negative bacteria such as \textit{P. aeruginosa}.

In another embodiment of the invention, prior to administration of a compound of the formula (I) \( \text{I-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea} \) or all salts thereof such as the lactate or citrate salt, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against \textit{S. aureus} and/or \textit{P. aeruginosa}. These techniques may also be used for screening for diseases or conditions caused by \textit{S. aureus} and/or \textit{P. aeruginosa}.

\textbf{EXAMPLES}
The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the following abbreviations are used.

- **AcOH**: acetic acid
- **BOC**: tert-butyloxycarbonyl
- **CDI**: 1,1-carbonyldiimidazole
- **DMAW90**: Solvent mixture: DCM: MeOH, AcOH, H₂O (90:18:3:2)
- **DMAW120**: Solvent mixture: DCM: MeOH, AcOH, H₂O (120:18:3:2)
- **DMAW240**: Solvent mixture: DCM: MeOH, AcOH, H₂O (240:20:3:2)
- **DCM**: dichloromethane
- **DMF**: dimethylformamide
- **DMSO**: dimethyl sulphoxide
- **EDC**: 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide
- **Et₃N**: triethylamine
- **EtOAc**: ethyl acetate
- **Et₂O**: diethyl ether
- **HOAt**: 1-hydroxyazabenzotriazole
- **HOBt**: 1-hydroxybenzotriazole
- **MeCN**: acetonitrile
- **MeOH**: methanol
- **SiO₂**: silica
- **TBTU**: N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
- **THF**: tetrahydrofuran

**Analytical LC-MS System and Method Description**

In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using the systems and operating conditions set out in WO 2006/070195 at pages 137 to 144.

**Mass Directed Purification LC-MS System**

Preparative LC-MS is a standard and effective method used for the purification of small organic molecules such as the compounds described herein. The methods for the liquid chromatography (LC) and mass spectrometry (MS) can be varied to provide better separation of the crude materials and improved detection of the samples by MS. Optimisation of the
preparative gradient LC method will involve varying columns, volatile eluents and modifiers, and gradients. Methods are well known in the art for optimising preparative LC-MS methods and then using them to purify compounds. Such methods are described in Rosentretreter U, Huber U.; Optimal fraction collecting in preparative LC/MS; J Comb Chem.; 2004; 6(2), 159-64 and Leister W, Strauss K, Wisnoski D, Zhao Z, Lindsley C., Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries; J Comb Chem.; 2003; 5(3); 322-9.

One such system for purifying compounds via preparative LC-MS is described in WO 2006/070195 at pages 140-144 although a person skilled in the art will appreciate that alternative systems and methods to those described could be used. In particular, normal phase preparative LC based methods might be used in place of the reverse phase methods described here. Most preparative LC-MS systems utilise reverse phase LC and volatile acidic modifiers, since the approach is very effective for the purification of small molecules and because the eluents are compatible with positive ion electrospray mass spectrometry. Employing other chromatographic solutions e.g. normal phase LC, alternatively buffered mobile phase, basic modifiers etc as outlined in the analytical methods described above could alternatively be used to purify the compounds.

From the information provided someone skilled in the art could purify the compounds described herein by preparative LC-MS.

The starting materials for each of the Examples are commercially available unless otherwise specified.

EXAMPLE 1

IA. Synthesis of (3,4-Dinitro-phenyl)-morpholin-4-yl-methanone

![Chemical structure]

A mixture of 3,4-dinitrobenzoic acid (10.0 g) and thionyl chloride (30 ml) was heated at reflux for 2 hours, cooled to ambient temperature and excess thionyl chloride removed through azeotrope with toluene. The residue was taken up in THF (100 ml) and morpholine (4.1 ml) and Et₃N (7.2 ml) added concurrently to the mixture at 0°C. The mixture was stirred for 3 hours, water (100 ml) added and then extracted with EtOAc. The organic portion was washed with brine, dried (MgSO₄) and reduced in vacuo. Recrystallisation of the residue from MeOH
gave (3,4-dinitro-phenyl)-morpholin-4-yl-methanone (8.23 g) as a yellow solid. (\(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.3 (d, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 3.7-3.5 (m, 8H)).

### IB. Synthesis of (3,4-Diamino-phenyl)-morpholin-4-yl-methanone

A mixture of (3,4-dinitro-phenyl)-morpholin-4-yl-methanone (1.0 g) and 10% Pd/C (150 mg) in MeOH (30 ml) was shaken under a hydrogen atmosphere at ambient temperature for 10 hours, then filtered through a plug of Celite and reduced \textit{in vacuo} to give (3,4-diamino-phenyl)-morpholin-4-yl-methanone (900 mg). (\(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 6.6 (s, 1H), 6.5 (s, 2H), 4.8 (s, 1.5H), 4.6 (s, 1.5H), 4.1 (s, 1H), 3.6 (m, 4H), 3.4 (m, 4H)).

### IC. Synthesis of 4-Morpholin-4-ylmethyl-benzene-1,2-diamine

To a mixture of (3,4-dinitro-phenyl)-morpholin-4-yl-methanone (2.84 g) in dry THF (50 ml) was added NaBH\(_4\) (954 mg) followed drop-wise by BF\(_3\)\_Et\(_2\)O (3.2 ml). The mixture was stirred at ambient temperature for 3 hours and then quenched through addition of MeOH. The mixture was reduced \textit{in vacuo}, partitioned between EtOAc and water and the organic portion washed with brine, dried (MgSO\(_4\)) and reduced \textit{in vacuo}. The residue was purified \textit{via} flash column chromatography eluting with EtOAc to give 4-(3,4-dinitro-benzyl)-morpholine (1.08 g).

A mixture of 4-(3,4-dinitro-benzyl)-morpholine (550 mg) and 10% Pd/C (75 mg) in MeOH (10 ml) was shaken under a hydrogen atmosphere at ambient temperature for 4 hours, then filtered through a plug of Celite and reduced \textit{in vacuo} to give 4-morpholin-4-ylmethyl-benzene-1,2-diamine (483 mg) as the major component of a mixture.

### ID. Synthesis of 5-morpholin-4-ylmethyl-2-(4-nitro-1H-ripyrazol-3-yl)-1H-benzimidazole
A mixture of 4-morpholin-4-ylmethyl-benzene-1,2-diamine (2.30 g, 11.1 mmol), 4-nitro-lH-pyrazole-3-carboxylic acid (1.57 g, 10.0 mmol), EDC (2.13 g, 11.1 mmol) and HOBt (1.50 g, 11.1 mmol) in dry DMF (25 ml) was stirred at ambient temperature for 24 hours. The mixture was reduced in vacuo and the crude residue dissolved in AcOH (40 ml) and heated at reflux for 3 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography eluting with 0-20% MeOH in EtOAc to give 5-morpholin-4-ylmethyl-2-(4-nitro-lH-pyrazol-3-yl) lH-benzimidazole as a yellow solid. (1.0 g, 61%). (LC/MS: R<sub>t</sub> 1.83, [M + H]<sup>+</sup> 329).

IE. Synthesis of 3-(5-morpholin-4-ylmethyl-lH-benzimidazol-2-yl)-lH-pyrazol-4-ylamine

Palladium on carbon (10%, 0.08 g) was added to solution of 5-morpholin-4-ylmethyl-2-4-nitro-lH-pyrazol-3-yl) lH-benzimidazole (0.82 g, 2.5 mmol) in DMF (30 ml) under an atmosphere of nitrogen. The mixture was shaken under a hydrogen atmosphere for 4 hours then filtered through Celite, washing with MeOH. The filtrate was concentrated in vacuo to give 3-(5-morpholin-4-ylmethyl-lH-benzimidazol-2-yl)-lH-pyrazol-4-ylamine as a brown solid (530 mg, 71%). (LC/MS: R<sub>t</sub> 1.94, [M + H]<sup>+</sup> 299).

IF. Synthesis of l-Cyclopropyl-S-P-fS-mo phol^v-methyl-lH-benzoimidazol^v-yiH-pyrazol-4-v1]-urea

Based on example 24 of WO 2006/070195, a mixture of 3-(5-morpholin-4-ylmethyl-lH-benzimidazol-2-yl)-lH-pyrazol-4-ylamine (Example IE.), (100 mg, 0.33 mmol), and CDI (217 mg, 1.34 mmol) in THF (2 ml) was subjected to microwave irradiation (150° C, 150 W) for 15 minutes. Cyclopropylamine was then added and the reaction mixture irradiated again under identical conditions for a further 15 minutes. After cooling, the heterogeneous mixture was filtered, the filtrate was concentrated and the residue purified by column chromatography (LC/MS Acidic : R<sub>t</sub> 1.59 [M + H]<sup>+</sup> 382.24).
Free Base and Salts of l-Cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-
1H-pyrazol-4-yll -urea

This was carried out as described in Example 62 of WO 2006/070195 at pages 175 to 176 (the content of which is incorporated herein by reference).

EXAMPLE 3

Determination of the Solubilities of the Free Base and Salts of l-Cyclopropyl-3-r3-(5-
morpholin-4-ylmethyl- lH-benzoimidazol-2-yl)- 1H-pyrazol-4-yll -urea

This was carried out as described in Example 63 of WO 2006/070195 at pages 176 to 178 (the content of which is incorporated herein by reference).

From data gathered to date, it is apparent that the compounds of the invention, and in particular the free base and salts of l-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-
yl)-lH-pyrazol-4-yll]-urea (in particular the L-lactate), will have a number of advantages over prior art compounds. In particular, such advantages include one or more of the following:

• Improved solubility in aqueous solution;
• Better physicochemical properties in particular lower logD;
• Differences in susceptibility to P450 enzymes;
• Improvement in drug metabolism and pharmacokinetic properties;
• Improved stability, e.g. improved shelf life and/or improved thermal stability;
• Reduced dosage requirements;
• Improved potency versus therapeutic targets and in particular Aurora A and B;
• Improved cell activity in proliferation and clonogenic assays;
• Improved anti-cancer activity; and
• Improved therapeutic index.

In particular the L-lactic acid salt form of the compound had good stability at elevated temperatures, adequate aqueous solubility in acidic buffer systems and it was non-hygroscopic with no apparent polymorph or hydrate formation.

EXAMPLE 4

Preparation of l-Cyclopropyl-3-r3-(5-Morpholin-4-ylmethyl-lH-Benzoimidazol-2-yl)-1H-
Pyrazol-4-yll-Urea lactate salt

This was carried out as described in Example 64 of WO 2006/070195 at page 178 (the content of which is incorporated herein by reference).
EXAMPLE 5

Synthesis of the L-lactate salt of 1-cyclopropyl-3-r3-(5-morhorin-4-ylmethyl-lH-benzoimidazol-2-yiy 1H-pyrazol-4-yl -urea

This was carried out as described in Example 65 of WO 2006/070195 at pages 178 to 185 (the content of which is incorporated herein by reference) which is further outlined here.

Stage 1: Synthesis of (3,4-dinitro-phenyl)-morpholin-4-yl-methanone

A solution of 3,4-dinitrobenzoic acid (10 g, 47 mmol, 1 eq.) and DMF (0.1 mL) in THF (100 mL) was treated with thionyl chloride (4.5 mL, 62 mmol, 1.3 eq.) then heated to reflux for 2.5 h. The mixture was cooled in ice then triethylamine (10 mL, 71 mmol, 1.1 eq.) was added over 20 min, keeping internal temperature <5 °C. Morpholine (6.2 mL, 71 mmol, 1.5 eq) was added to the resulting thick yellow suspension over 15 min, keeping internal temperature <10 °C. The ice-bath was removed and the mixture allowed to warm to r.t. After 15 min, a further portion of morpholine (1 mL, 11 mmol, 0.24 eq.) was added and the mixture stirred overnight. The mixture was diluted with water (250 mL) and cooled in ice. A beige solid was filtered off under suction, washed with a further portion of cold water (25 mL) and dried in vacuo to afford the title compound (12.7 g, 96%).

Stage 2: Synthesis of 4-(3,4-dinitro-benzyl)-morpholine

Sodium borohydride (3.36 g, 89 mmol, 2.1 eq.) was ground, placed in a nitrogen-flushed flask and suspended in THF (120 mL). After cooling to ~0 °C, boron trifluoride etherate (11.3 mL, 89 mmol, 2.1 eq.) was added via syringe. This reaction is mildly exothermic and some hydrogen evolution was noted. 4-(3,4-Dinitrobenzoyl)morpholine (11.91 g, 42 mmol, 1.0 eq.) was added as a solid in one portion, the vessel being rinsed with an additional portion of THF (20 mL). The ice-bath was removed and the suspension stirred at r.t. for 3 h before cooling again in ice. Methanol (100 mL) was added cautiously (hydrogen evolution) then the mixture was brought to reflux for 1 h. The mixture was concentrated in vacuo then the residue was partitioned between ethyl acetate (100 mL) and 1:1 saturated sodium bicarbonate solution/water (100 mL). The organic phase was separated, washed with water (50 mL) then brine (100 mL) and dried (MgSO₄). The initial bicarbonate wash was extracted a second time with ethyl acetate
(50 mL), this extract then being washed with the same aqueous washes used for the first extract before drying (MgSO₄), combination and concentration to afford 10.97 g of crude material. Recrystallisation from methanol (45 mL, 10 mL wash) gave the title compound (9.34 g, 83%).

**Stage 3:** Synthesis of 4-morphlm-4-ylmethyl-benzene-1,2-diamine

4-(3,4-Dinitrobenzyl)morpholine (21 g, 101 mmol) was suspended in ethanol (0.9 L) and the vessel purged with nitrogen. 10% Palladium on charcoal (1.05 g) was suspended in ethanol (25 mL) and added to the substrate. The mixture was cooled in ice then the atmosphere exchanged for hydrogen. The mixture was allowed to warm to 15-20 °C and hydrogenation continued at ambient pressure for 2 days. The vessel was purged with nitrogen then the mixture was filtered through Celite, rinsing with ethanol (0.3 L) in portions. Concentration afforded the title compound (15.8 g, 97%).

**Stage 4:** Synthesis of 4-nitro-lH-pyrazole-3-carboxylic acid methyl ester

A 20L reaction vessel equipped with a digital thermometer and stirrer was charged with 4-nitro-lH-pyrazole-3-carboxylic acid (1.117Kg, 7.1 lmol, lwt) and methanol (8.950L, 8vol). The reaction mixture was stirred under nitrogen, cooled to 0 to 5°C, thionyl chloride (0.581L, 8.0mol, 0.52vol) added over 180 minutes and the resultant mixture allowed to warm to and stir at 18 to 22°C overnight after which time ¹H NMR analysis (d₆-DMSO) indicated reaction completion. The reaction mixture was concentrated under reduced pressure at 40 to 45°C, the residue treated with toluene and re-concentrated (3x 2.250L, 3x 2vol) under reduced pressure at 40 to 45°C to give 4-nitro-lH-pyrazole-3-carboxylic acid methyl ester as an off-white solid (1.210Kg, 99.5%th).

**Stage 5:** Synthesis of 4-amino-lH-pyrazole-3-carboxylic acid methyl ester

A 20L reaction vessel equipped with a digital thermometer and stirrer was charged with palladium on carbon (10% wet paste, 0.170Kg, 0.14wt) under nitrogen. In a separate vessel, a
slurry of 4-nitro-1H-pyrazole-3-carboxylic acid methyl ester (1.210Kg, 7.07mol, lwt) in ethanol (12.1OL, 10vol) was warmed to 30 to 35°C to effect dissolution and the solution added to the catalyst under nitrogen. Following a nitrogen-hydrogen purge sequence an atmosphere of hydrogen was introduced and the reaction mixture maintained at 28 to 30°C until reaction completion (5 to 10 hours) was noted by 1H NMR analysis (d6-DMSO). Following a purge cycle, the reaction mixture under nitrogen was filtered and the liquors concentrated under reduced pressure to give 4-amino-1H-pyrazole-3-carboxylic acid methyl ester (0.987Kg, 98.9%th).

**Stage 6: Synthesis of 4-tert-butoxycarbonylamino-1H-pyrazole-3-carboxylic acid**

![Chemical Structure](image)

To a mixture of 4-amino-1H-pyrazole-3-carboxylic acid methyl ester (50.0 g, 355 mmol) in dioxane (500 mL) was added 2M aqueous NaOH solution (213 mL, 426 mmol), the mixture heated to 50°C and stirred for 5 h. To this mixture was then added (BOC)_2O (81.4 g, 373 mmol), using a dioxane rinse (100 mL) and the mixture heated at 50°C for a further 5 h, then stirred at ambient for 14 h. The dioxane was removed in vacuo and water (1 L) added. The mixture was taken to pH ~2 using cone, aqueous HCl solution and the solid formed collected by filtration and dried on the filter. The solid was dried further through azeotrope with toluene (x3) and in the vacuum oven to give 4-tert-butoxycarbonylamino-1H-pyrazole-3-carboxylic acid (70.0 g, 87%) as a violet solid.

**Stage 7: Synthesis of 3-(2-amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-1H-pyrazol-4-yl-carbamic acid tert-butyl ester**

![Chemical Structure](image)

A mixture of 4-tert-butoxycarbonylamino-1H-pyrazole-3-carboxylic acid (10.0 g, 44.1 mmol), 4-morpholin-4-ylmethyl-benzene-1,2-diamine (10.0 g, 48.5 mmol), EDC (10.14 g, 52.9 mmol) and HOBt (7.15 g, 52.9 mmol) in DMF (150 mL) was stirred at ambient temperature for 20 h and then the majority of the solvent removed in vacuo. The residue was partitioned between EtOAc (150 mL) and saturated aqueous NaHC θ 3 (150 mL), the layers separated and the organic portion washed with brine, dried over MgSθ 4 and reduced in vacuo to give [3-(2-amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-1H-pyrazol-4-yl]-carbamic acid tert-butyl
ester (17.6 g, 96%) as a brown solid. LC/MS analysis indicates product contains -15% of the di-amide. This shows at approx. 5% level in ¹H NMR. Di-amide is cleaved in subsequent step.

Stage 8: Synthesis of 3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-ylamine

A mixture of [3-(2-amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-lH-pyrazol-4-yl]-carbamic acid tert-butyl ester (12.0 g, 28.8 mmol) and 2M aqueous HCl solution (50 mL) was heated at 85 °C for 14 h, then allowed to cool to ambient temperature. Solid Na₂CO₃ was carefully added until mixture was pH ~ 8.5 and solution was saturated. A dark coloured gummy liquid was formed. The mixture was allowed to settle and the solvent decanted. To the remaining residue was added EtOH (60 mL), the mixture heated at reflux for 1 h and then hot filtered, washing with EtOH (2 x 20 mL), to remove inorganic residues. The filtrate was reduced in vacuo to give a glassy solid which was then stirred in Et₂O (60 mL) for 1 h and the resultant purple coloured powder collected by filtration and dried in vacuo to give 3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-ylamine (6.8 g, 80%, -90% purity).

Stage 9: Synthesis of 7-morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaza-cyclopentaralfluoren-5-one

To a mixture of 3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-ylamine (3.2 g, 10.7 mmol) in anhydrous THF (50 mL) stirring at ambient temperature was added 1,1'-carbonyldiimidazole (1.78 g, 11 mmol). The mixture was heated at reflux for 14 h and then cooled to ambient. The solid formed was collected by filtration, washed with THF (20 mL) and dried in vacuo to give 7-morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaza-cyclopenta[a]fluoren-5-one (2.34 g, 67%) as a pink solid.

Stage 10: Synthesis of 1-cyclopropyl-3-r-3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-vH-urea.
To a mixture of 7-morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaza-cyclopenta[a]-fluoren-5-one (10.7 g, 32.9 mmol) in NMP (65 mL) was added cyclopropylamine (6.9 mL, 99 mmol). The mixture was heated at 100 °C for 5 h. LC/MS analysis indicated -75% conversion to product, therefore a further portion of cyclopropylamine (2.3 mL, 33 mmol) was added, the mixture heated at 100 °C for 4 h and then cooled to ambient. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL). The organic portion was washed with sat. aq. NH₄Cl (2 x 50 mL) and brine (50 mL) and then the aqueous portions re-extracted with EtOAc (3 x 100 mL). The combined organic portions were dried over MgSO₄ and reduced in vacuo to give 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea as an orange glassy solid (9.10 g).

**Stage 11: Synthesis of 1-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea, L-lactate salt**

To a solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea (9.10 g, 24 mmol) in EtOAc-iPrOH (1:1, 90 mL) was added L-lactic acid (2.25 g, 25 mmol). The mixture was stirred at ambient temperature for 24 h then reduced in vacuo. The residue was given consecutive slurries using toluene (100 mL) and Et₂O (100 mL) and the resultant solid collected and dried (8.04 g).

This solid was purified by recrystallisation from boiling iPrOH (200 mL) to give after drying 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea, L-lactate salt (5.7 g) as a beige solid.

**EXAMPLE 6A**
Stage 1: Preparation of (3,4-dinitrophenyl)-morpholin-4-yl-methanone

\[ \text{C}_6\text{H}_5\text{N}_2\text{O}_4 \quad \text{FW: 212.12} \]

\[ \xrightarrow{1. \text{SOCl}_2} \]

\[ \text{C}_7\text{H}_8\text{N}_2\text{O}_4 \quad \text{FW: 281.22} \]

3,4-Dinitrobenzoic acid (1.000Kg, 4.71mol, 1.0wt), tetrahydrofuran (10.00L, 10.0vol), and dimethylformamide (0.010L, 0.01vol) were charged to a flask under nitrogen. Thionyl chloride (0.450L, 6.16mol, 0.45vol) was added at 20 to 30°C and the reaction mixture was heated to 65 to 70°C. Reaction completion was determined by \(^1\)H NMR analysis (d\(_6\)-DMSO), typically in 3 hours. The reaction mixture was cooled to Oto 5°C and triethylamine (1.25L, 8.97mol, 1.25vol) was added at Oto 10°C. Morpholine (0.62L, 7.07mol, 0.62vol) was charged to the reaction mixture at 0 to 10°C and the slurry was stirred for 30 minutes at 0 to 10°C. Reaction completion was determined by \(^1\)H NMR analysis (Ck-DMSO). The reaction mixture was warmed to 15 to 20°C and water (4.00L, 4.0vol) was added. This mixture was then charged to a 40L flange flask containing water (21.00L, 21.0vol) at 15 to 25°C to precipitate the product. The flask contents were cooled to and aged at 0 to 5°C for 1 hour and the solids were collected by filtration. The filter-cake was washed with water (4x 5.00L, 4x 5.0vol) and the pH of the final wash was found to be pH 7. The wet filter-cake was analysed by \(^1\)H NMR for the presence of triethylamine hydrochloride. The filter-cake was dried at 40 to 45°C under vacuum until the water content by KF <0.2%w/w, to yield (3,4-dinitrophenyl)-morpholin-4-yl-methanone (1.286Kg, 97.0%, KF 0.069%w/w) as a yellow solid.

Stage 2: Preparation of 4-(3,4-dinitro-benzyl)-morpholine

\[ \text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_5 \quad \text{FW: 281.22} \]

(3,4-Dinitrophenyl)-morpholin-4-yl-methanone (0.750Kg, 2.67mol, 1.0wt) and tetrahydrofuran (7.50L, 10.0vol) were charged to a flask under nitrogen and cooled to 0 to 5°C. Boron trifluoride etherate (0.713L, 5.63mol, 0.95vol) was added at 0 to 5°C and the suspension was stirred at this temperature for 15 to 30 minutes. Sodium borohydride (0.212Kg, 5.60mol, 0.282wt) was added in 6 equal portions over 90 to 120 minutes. (A delayed exotherm was noted 10 to 15 minutes after addition of the first portion. Once this had started and the reaction mixture had been re-cooled, further portions were added at 10 to 15 minute intervals, allowing the reaction to cool...
between additions). The reaction mixture was stirred at 0 to 5°C for 30 minutes. Reaction completion was determined by $^1$H NMR analysis ($d_6$-DMSO). Methanol (6.30L, 8.4vol) was added dropwise at 0 to 10°C to quench the reaction mixture (rapid gas evolution, some foaming). The quenched reaction mixture was stirred at 0 to 10°C for 25 to 35 minutes then warmed to and stirred at 20 to 30°C (exotherm, gas/ether evolution on dissolution of solid) until gas evolution had slowed. The mixture was heated to and stirred at 65 to 70°C for 1 hour. The mixture was cooled to 30 to 40°C and concentrated under vacuum at 40 to 45°C to give crude 4-(3,4-dinitro-benzyl)-morpholine (0.702Kg, 98.4%) as a yellow/orange solid.

4-(3,4-Dinitro-benzyl)-morpholine (2.815kg, 10.53mol, 1.0wt) and methanol (12.00L, 4.3vol) were charged to a flask under nitrogen and heated to 65 to 70°C. The temperature was maintained until complete dissolution. The mixture was then cooled to and aged at 0 to 5°C for 1 hour. The solids were isolated by filtration. The filter-cake was washed with methanol (2x 1.50L, 2x 0.5vol) and dried under vacuum at 35 to 45°C to give 4-(3,4-dinitro-benzyl)-morpholine (2.353Kg, 83.5% based on input Stage 2, 82.5% overall yield based on total input Stage 1 material,) as a yellow solid.

Stage 3: Preparation of 4-morpholin-4-yl-methyl-benzene-1,2-diamine

4-(3,4-Dinitro-benzyl)-morpholine (0.800Kg, 2.99mol, 1.0wt), and ethanol (11.20L, 14.0vol) were charged to a suitable flask and stirred at 15 to 25°C and a vacuum / nitrogen purge cycle was performed three times. 10% Palladium on carbon (10%Pd/C, 50%wt paste, 0.040Kg, 0.05wt wet weight) was slurried in ethanol (0.80L, 1.0vol) and added to the reaction. The mixture was cooled to 10 to 20°C and a vacuum / nitrogen purge cycle was performed three times. A vacuum / hydrogen purge cycle was performed three times and the reaction was stirred under a hydrogen atmosphere at 10 to 20°C. Reaction completion was determined by $^1$H NMR analysis ($d_6$-DMSO), typically 14 to 20 hours. A vacuum / nitrogen purge cycle was performed three times and the reaction mixture was filtered through glass microfibre paper under nitrogen. The filter-cake was washed with ethanol (3x 0.80L, 3x 1.0vol) and the combined filtrate and washes were concentrated to dryness under vacuum at 35 to 45°C to give 4-morpholin-4-yl-methyl-benzene-1,2-diamine (0.61 IKg 98.6%) as a brown solid.
Stage 4: Preparation of 4-nitro-lH-pyrazole-3-carboxylic acid methyl ester

4-Nitro-lH-pyrazole-3-carboxylic acid (1.00kg, 6.37mol, 1.0wt) and methanol (8.00L, 8.0vol) were charged to a flange flask equipped with a mechanical stirrer, condenser and thermometer. The suspension was cooled to O to 5°C under nitrogen and thionyl chloride (0.52L, 7.12mol, 0.52vol) was added at this temperature. The mixture was warmed to 15 to 25°C over 16 to 24 hours. Reaction completion was determined by 1H NMR analysis (d6-DMSO). The mixture was concentrated under vacuum at 35 to 45°C. Toluene (2.00L, 2.0vol) was charged to the residue and removed under vacuum at 35 to 45°C. The azeotrope was repeated twice using toluene (2.00L, 2.0vol) to give 4-nitro-lH-pyrazole-3-carboxylic acid methyl ester (1.071Kg, 98.3%) as an off white solid.

Stage 5: Preparation of 4-amino-lH-pyrazole-3-carboxylic acid methyl ester.

A suspension of 4-nitro-lH-pyrazole-3-carboxylic acid methyl ester (1.084Kg, 6.33mol, 1.0wt) and ethanol (10.84L, 10.0vol) was heated to and maintained at 30 to 35°C until complete dissolution occurred. 10% Palladium on carbon (10% Pd/C wet paste, 0.152Kg, 0.14wt) was charged to a separate flask under nitrogen and a vacuum / nitrogen purge cycle was performed three times. The solution of 4-nitro-lH-pyrazole-3-carboxylic acid methyl ester in ethanol was charged to the catalyst and a vacuum / nitrogen purge cycle was performed three times. A vacuum / hydrogen purge cycle was performed three times and the reaction was placed under an atmosphere of hydrogen. The reaction mixture was stirred at 28 to 30°C until deemed complete by 1H NMR analysis (d6-DMSO). The mixture was filtered under nitrogen and concentrated under vacuum at 35 to 45°C to give 4-amino-lH-pyrazole-3-carboxylic acid methyl ester (0.883Kg, 98.9%) as a purple solid.
Stage 6: Preparation of 4-tert-butoxycarbonylamino-1H-pyrazole-3-carboxylic acid

![Chemical structure](image)

4-Amino-1H-pyrazole-3-carboxylic acid methyl ester (1.024Kg, 7.16mol, 1.0wt) and dioxane (10.24L, 10.0vol) were charged to a flange flask equipped with a mechanical stirrer, condenser and thermometer. 2M aq. Sodium hydroxide solution (4.36L, 8.72mol, 4.26vol) was charged at 15 to 25°C and the mixture was heated to 45 to 55°C. The temperature was maintained at 45 to 55°C until reaction completion, as determined by ¹H NMR analysis (d₆-DMSO). Di-tert-butyl dicarbonate (Boc anhydride, 1.667Kg, 7.64mol, 1.628wt) was added at 45 to 55°C and the mixture was stirred for 55 to 65 minutes. ¹H NMR IPC analysis (d₆-DMSO) indicated the presence of 9% unreacted intermediate. Additional di-tert-butyl dicarbonate (Boc anhydride, 0.141Kg, 0.64mol, 0.14wt) was added at 55°C and the mixture was stirred for 55 to 65 minutes. Reaction completion was determined by ¹H NMR analysis (d₆-DMSO). The dioxane was removed under vacuum at 35 to 45°C and water (17.60L, 20.0vol) was added to the residue. The pH was adjusted to pH 2 with 2M aq. hydrochloric acid (4.30L, 4.20vol) and the mixture was filtered. The filter-cake was slurried with water (10.00L, 9.7vol) for 20 to 30 minutes and the mixture was filtered. The filter-cake was washed with heptanes (4.10L, 4.0vol) and pulled dry on the pad for 16 to 20 hours. The solid was azeodried with toluene (5x 4.00L, 5x 4.6vol) then dried under vacuum at 35 to 45°C to give 4-tert-butoxycarbonylamino-1H-pyrazole-3-carboxylic acid (1.389Kg, 85.4%) as a purple solid.

Stage 7: Preparation of r3-(2-amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-1H-pyrazol-4-vH-carbamic acid tert-butyl ester

![Chemical structure](image)
4-fert-Butoxycarbonylamino-lH-pyrazole-3-carboxylic acid (0.750Kg, 3.30 mol, 1.Owt), 4-morpholin-4yl-methyl-benzene-l,2-diamine (0.752Kg, 3.63mol, 1.Owt) and N,N-dimethylformamide (11.25L, 15.0vol) were charged under nitrogen to a flange flask equipped with a mechanical stirrer and thermometer. 1-Hydroxybenzotriazole (HOBT, 0.540Kg, 3.96mol, 1.0vol) was added at 15 to 25°C. N-(3-Dimethylaninopropyl)-N'-ethylcarbodiimide (EDC, 0.759Kg, 3.96mol, 1.Owt) was added at 15 to 25°C and the mixture was stirred at this temperature for 16 to 24 hours. Reaction completion was determined by 1H NMR analysis. The reaction mixture was concentrated under vacuum at 35 to 45°C. The residue was partitioned between ethyl acetate (7.50L, 10.Ovol) and sat. aq. sodium hydrogen carbonate solution (8.03L, 10.7vol) and the layers were separated. The organic phase was washed with brine (3.75L, 5.0vol), dried over magnesium sulfate (1.00Kg, 1.33wt) and filtered. The filter-cake was washed with ethyl acetate (1.50L, 2.0vol). The combined filtrate and wash were concentrated under vacuum at 35 to 45°C to give [3-(2-amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-lH-pyrazol-4-yl]-carbamic acid tert-butyl ester (1.217Kg, 88.6%) as a dark brown solid.

Stage 8: Preparation of 3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-ylamine

[3-(2-Amino-4-morpholin-4-ylmethyl-phenylcarbamoyl)-lH-pyrazol-4-yl]-carbamic acid tert-butyl ester (1.350Kg, 3.24 mol, 1.Owt) and ethanol (6.75L, 5.0vol) were charged to a flange flask equipped with a mechanical stirrer, condenser and thermometer. Cone. aq. hydrochloric acid (1.10L, 13.2 mol, 0.80vol) was added at 15 to 30°C under nitrogen and the contents were then heated to 70 to 80°C and maintained at this temperature for 16 to 24 hours. A second portion of hydrochloric acid (0.1 IL, 1.32 mol, 0.08vol) was added at 70 to 80°C and the reaction was heated for a further 4 hours. Reaction completion was determined by HPLC analysis. The reaction mixture was cooled to 10 to 20°C and potassium carbonate (1.355Kg, 9.08mol, 1.Owt) was charged portionwise at this temperature. The suspension was stirred until gas evolution ceased and was then filtered. The filter-cake was washed with ethanol (1.35L, 1.Ovol) and the filtrates retained. The filter-cake was slurried with ethanol (4.00L, 3.0vol) at 15 to 25°C for 20 to 40 minutes and the mixture was filtered. The filter-cake was washed with ethanol (1.35L, 1.Ovol) and the total combined filtrates were concentrated under vacuum at 35
Stage 9: Preparation of 7-morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaza-cyclopentar[a]fluoren-5-one

As a mixture of two regioisomers

3-(5-Morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

(0.993 Kg, 3.33 mol, 1.0 wt) and tetrahydrofuran (14.0 L, 15.0 vol) were charged to a flange flask equipped with a mechanical stirrer, condenser and thermometer. The contents were stirred under nitrogen at 15 to 25°C and 1,1'-carbonyldiimidazole (0.596 Kg, 3.67 mol, 0.60 wt) was added. The contents were then heated to 60 to 70°C and stirred at this temperature for 16 to 24 hours. Reaction completion was determined by TLC analysis. The mixture was cooled to 15 to 20°C and filtered. The filter-cake was washed with tetrahydrofuran (4.00 L, 4.0 vol) and pulled dry for 15 to 30 minutes. The solid was dried under vacuum at 35 to 45°C to yield 7-morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaza-cyclopenta[a]fluoren-5-one (0.810 Kg, 75.0% th, 92.19% by HPLC area) as a purple solid.
Stage 10: Preparation of 1-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl -urea

\[
\text{C}_{15}H_{19}N_{5}O_{2}\quad \text{FW} 323.38
\]

As a mixture of two regioisomers

7-Morpholin-4-ylmethyl-2,4-dihydro-1, 2,4,5a, 10-pentaaza-cyclopenta[a]fluoren-5-one (0.797Kg, 2.46mol, 1.0wt) and 1-methyl-2-pyrrolidinone (2.40L, 3.0vol) were charged to a flange flask equipped with a mechanical stirrer, condenser and thermometer. Cyclopropylamine (0.279Kg, 4.88mol, 0.351wt) was added at 15 to 30°C under nitrogen. The contents were heated to 95 to 105°C and stirred at this temperature for 16 to 24 hours. Reaction completion was determined by 1H NMR analysis. The reaction mixture was cooled to 10 to 20°C and ethyl acetate (8.00L, 10.Ovol) and sat. aq. sodium chloride (2.50L, 3.0vol) were charged, the mixture was stirred for 2 to 5 minutes and the layers separated. The organic phase was stirred with sat. aq. sodium chloride (5.00L, 6.Ovol) for 25 to 35 minutes, the mixture filtered and the filter-cake washed with ethyl acetate (0.40L, 0.5vol). The filter-cake was retained and the filtrates were transferred to a separating funnel and the layers separated. The procedure was repeated a further 3 times and the retained solids were combined with the organic phase and the mixture concentrated to dryness under vacuum at 35 to 45°C. The concentrate was dissolved in propan-2-ol (8.00L, 10.Ovol) at 45 to 55°C and activated carbon (0.080Kg, 0.1 wt) was charged. The mixture was stirred at 45 to 55°C for 30 to 40 minutes and then hot filtered at 45 to 55°C. The filter-cake was washed with propan-2-ol (0.40L, 0.5vol). Activated carbon (0.080L, 0.1 wt) was charged to the combined filtrates and wash and the mixture stirred at 45 to 55°C for 30 to 40 minutes. The mixture was hot filtered at 45 to 55°C and the filter-cake washed with propan-2-ol (0.40L, 0.5vol). The filtrates and wash were concentrated under vacuum at 35 to 45°C. Ethyl acetate (8.00, 10.Ovol) and water (2.20L, 3.0vol) were charged to the concentrate at 25 to 35°C and the mixture stirred for 1 to 2 minutes. The layers were separated and the organic phase was concentrated under vacuum at 35 to 45°C. Ethyl acetate (4.00L, 5.0vol) was charged to the residue and concentrated under vacuum at 35 to 45°C. Ethyl acetate (4.00L, 5.0vol) was charged to the residue and the mixture was stirred for 2 to 20 hours at 15 to 25°C. The mixture was cooled to and aged at 0 to 5°C for 90 to 120 minutes and then filtered. The filter-cake was washed with ethyl acetate (0.80L, 1.Ovol) and pulled dry for 15 to 30 minutes. The solid was dried under vacuum at 35 to 45°C to yield 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-
benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (0.533Kg, 56.8%, 93.20% by HPLC area) as a brown solid.

Several batches of Stage 9 product were processed in this way and the details of the quantities of starting material and product for each batch are set out in Table IA.

Table IA- Yields from urea formation step - Stage 10

<table>
<thead>
<tr>
<th>Batch</th>
<th>Input (g) of 7-Morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaazacyclopenta[a]fluoren-5-one</th>
<th>Input (g) of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea</th>
<th>Chemical purity by HPLC area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>680</td>
<td>442</td>
<td>91.80</td>
</tr>
<tr>
<td>2</td>
<td>882</td>
<td>487</td>
<td>91.21</td>
</tr>
<tr>
<td>3</td>
<td>879</td>
<td>445</td>
<td>91.66</td>
</tr>
<tr>
<td>4</td>
<td>797</td>
<td>533</td>
<td>93.20</td>
</tr>
</tbody>
</table>

Stage 11: Preparation of 1-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-vi$i$yi) H-pyrazol-4-yl]-urea L-lactic acid salt

1-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (1.859Kg, 4.872mol, 1.0wt), propan-2-ol (9.00L, 5.0vol) and ethyl acetate (8.00L, 4.5vol) were charged to a flange flask equipped with a mechanical stirrer and thermometer. The contents were stirred under nitrogen and L-lactic acid (0.504Kg, 5.59mol, 0.269wt) was added at 15 to 25°C followed by a line rinse of ethyl acetate (0.90L, 0.5vol). The mixture was stirred at 15 to 25°C for 120 to 140 minutes. The solid was isolated by filtration, the filter-cake washed with ethyl acetate (2x 2.00L, 2x 1.Ovol) and pulled dry for 20 to 40 minutes. The filter-cake was dissolved in ethanol (33.00L, 17.7vol) at 75 to 85°C, cooled to 65 to 70°C and the solution clarified through glass microfibre paper. The filtrates were cooled to and aged at 15 to 25°C for 2 to 3 hours. The crystallised solid was isolated by filtration, the filter-cake washed with ethanol (2x 1.00L, 2x 0.5vol) and pulled dry for at least 30 minutes. The solid was dried under
vacuum at 35 to 45°C to yield 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea L-lactic acid salt (1.386Kg, 58.7%th, 99.47% by HPLC area,) as a dark pink uniform solid.

$^1$H NMR data (400 MHz, CD$_3$OD) $\delta$ 8.08 (s, 1H, pyrazole-CH), 7.66 (s, 1H, aryl-CH), 7.60 (d, $J = 8.0$ Hz, 1H, aryl-CH), 7.29 (d, $J = 8.5$ Hz, 1H, aryl-CH), 4.15 (q, $J = 7.0$ Hz, 1H, lactate-CH), 3.96 (s, 2H, benzyl-CH$_2$), 3.79 - 3.77 (m, 4H, morpholino-(CH$_2$)$_2$), 2.82 - 2.80 (m, 4H, morpholino-(CH$_2$)$_2$), 2.74 - 2.68 (m, 1H, lactyl-CH), 1.98 (br s, 2H, cyclopropyl-CH$_2$), 0.98 (br s, 2H, cyclopropyl-CH$_2$).

The infra-red spectrum of the lactate salt (KBr disc method) included characteristic peaks at 3229, 2972 and 1660 cm$^{-1}$.

Without wishing to be bound by any theory, it is believed that the infra red peaks can be assigned to structural components of the salt as follow:

**Peak:**

<table>
<thead>
<tr>
<th>Peak</th>
<th>Due to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3229 cm$^{-1}$</td>
<td>N-H</td>
</tr>
<tr>
<td>2972 cm$^{-1}$</td>
<td>aliphatic C-H</td>
</tr>
<tr>
<td>1660 cm$^{-1}$</td>
<td>urea C=O</td>
</tr>
</tbody>
</table>

**EXAMPLE 6B**

Stage 1: Preparation of 1-cyclopropyl-3-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea

As a mixture of two regioisomers

7-Morpholin-4-ylmethyl-2,4-dihydro-l, 2,4,5a, 10-pentaaza-cyclopenta[a]fluoren-5-one (1.Owt, prepared as outlined above in Example 66A) and a solvent such as n-butanol, butyronitrile, glycol or toluene (3.0vol) can be charged to a flange flask equipped with a mechanical stirrer, condenser and thermometer. Cyclopropylamine (0.351wt) can be added at temperature such as 15 to 30 °C under an inert atmosphere e.g. nitrogen. The contents can be heated to 40 to 105 °C, in particular 40-80 °C and stirred at this temperature for 16 to 24 hours. Reaction
completion can be determined by $^1$H NMR analysis. The reaction mixture can then be cooled to 10 to 20°C. The product can then be isolated by organic-aqueous extraction method as outlined above in Example 66A, or an alternative method of isolation may be employed such as the addition of an anti-solvent, for example n-heptanes, to the reaction mixture. This could allow the reaction product to precipitate with subsequent isolation by filtration. The solid can then be dried under vacuum at 35 to 45°C to yield 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea. At this stage the solid can be purified by recrystallisation from an appropriate solvent, preferably a Class 2 or 3 solvent\(^1\). In addition, alternative methods of purification aside from recrystallisation may be employed for purification of the product such as flash column chromatography or filtration through a plug of silica gel or reverse-phase silica gel.

**Stage 2: Preparation of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea L-lactic acid salt**

![](attachment:image.png)

1-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (1.Owt), in a Class 2 or Class 3 solvent, in particular a Class 3 solvent such as aqueous ethanol (5.0-10.0 vol), can be charged to a flange flask equipped with a mechanical stirrer and thermometer. The contents are stirred under an inert atmosphere e.g. nitrogen and L-lactic acid (0.269wt) can be added at 15 to 25°C followed by a line rinse of the appropriate solvent such as aqueous ethanol (0.5vol). The mixture can be stirred at 15 to 25°C for 120 to 140 minutes. The solid may be isolated by filtration or by use of addition of anti-solvent such as n-butanol to bring the salt out of solution and then isolated by filtration. The filter-cake can be washed with the appropriate solvent (2x 1.Ovol) and pulled dry for 20 to 40 minutes. The filter-cake can then be dissolved in a Class 2 or Class 3 solvent, or mixture thereof, in particular a Class 3 solvent (-3-60 vol) at 40 to 150°C, cooled to 40 to 70°C and the solution clarified through glass microfibre paper. The filtrates can be cooled to and aged at 15 to 25°C for 2 to 3 hours.

\(^1\) Class 3 and Class 2 solvents are as outlined Q3C - *Tables and List* in Guidance for Industry Q3C Impurities: Residual Solvents (Nov 2003, CDER, CBER, FDA, ICH) and as further outlined in Impurities: Guideline for Residual Solvents (1997, ICH).
The crystallised solid can be isolated by filtration, the filter-cake washed with the appropriate solvent (2x 0.5-2 vol) and pulled dry for at least 30 minutes. The solid can then be dried under vacuum at 35 to 45°C to yield 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-IH-pyrazol-4-yl]-urea L-lactic acid salt. In addition, alternative methods of purification aside from recrystallisation may be employed for purification of the product such as flash column chromatography or filtration through a plug of silica gel or reverse-phase silica gel.

**EXAMPLE 6C**

Further to the above examples, the preparation of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-IH-pyrazol-4-yl]-urea L-lactic acid salt can be completed using the revised procedures outlined below.

**Stage 1: Preparation of 1-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-IH-pyrazol-4-vH-urea**

7-Morpholin-4-ylmethyl-2,4-dihydro-1,2,4,5a,10-pentaaza-cyclopenta[a]fluoren-5-one (1.0wt, prepared as outlined above in Example 66A) and 1-methyl-2-pyrrolidinone (3.0vol) are charged to a suitably sized flange flask equipped with a mechanical stirrer, condenser and thermometer. Cyclopropylamine (0.35 lwt) is added at 15 to 30°C under nitrogen. The contents are then heated to 95 to 105°C and stirred at this temperature until the reaction is judged complete by H NMR analysis. Once complete, the reaction mixture is cooled to 16 to 25°C and added slowly (approximately 2 to 3 hours) to stirred ca. 13% w/w sodium chloride solution (11.5vol) whilst maintaining the mixture at 16 to 25°C. A precipitate is formed. The transfer of the reaction mixture is completed with a 1-methyl-2-pyrrolidinone (0.5vol) rinse at 16 to 25°C. The precipitated solid is collected by filtration, washed with water (0.5vol) and pulled dry on the filter until deemed suitable for handling. The solid is suspended in ethyl acetate (5.0vol) and water (6.0vol) and stirred at 16 to 25°C for 60 to 70 minutes. The solid is collected by filtration, sequentially washed with ethyl acetate (1.0vol) and mixed heptanes (2x 2.0vol) and dried on the filter until deemed suitable for handling. The solid is suspended in ethyl acetate
(4.0vol) and stirred at 15 to 25°C for at least 60 minutes. The solid is collected by filtration, washed with ethyl acetate (1.0vol) and pulled dry on the filter to yield crude 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (60 to 80%w/w) as a dark brown/red solid.

Crude 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (1.0wt) is dissolved in propan-2-ol (15vol) at 45 to 55°C and activated carbon (DARCO KB) (0.2wt) is charged. The mixture is stirred at 45 to 55°C for 60 to 70 minutes and then hot filtered at 45 to 55°C. The filter-cake is washed with propan-2-ol (2.5vol). Activated carbon (DARCO KB) (0.2wt) is charged to the combined filtrate and wash and the mixture stirred at 45 to 55°C for 60 to 70 minutes. The mixture is hot filtered at 45 to 55°C and the filter-cake is washed with propan-2-ol (2.5vol). The combined filtrate and wash are concentrated under vacuum at 35 to 45°C to yield the desired product, 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureaL-lactic acid salt as a brown foam in 65 to 100%w/w yield.

Stage 2: Preparation of 1-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-vH-urea L-lactic acid salt

Using material generated from the alternative procedure in Example 66C Stage 1 (above), the salt formation procedure can be performed as in Example 66A Stage 11 (above), to give 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ureaL-lactic acid salt as an off-white solid.

EXAMPLE 7
Synthesis of Crystalline Free Base And Crystalline Salt Forms Of 1-Cyclopropyl-3-r3-(5-Morpholin-4-ylmethyl-1H-Benzimidazol-2-yl)-1H-Pyrazol-4-ylL-Urea

This was carried out as described in Example 67 of WO 2006/070195 at pages 196 to 197 (the content of which is incorporated herein by reference).

EXAMPLE 8
Characterisation of 1-Cyclopropyl-S-P -(5-Morpholin-4-ylmethyl-1H-Benzimidazol-2-yl)-1H-Pyrazol-4-vH-Urea Free Base and Salts

This was carried out as described in Example 68 of WO 2006/070195 at pages 197 to 201 and as further described in Example 68 of WO 2007/077435 (the content of both which is incorporated herein by reference).

EXAMPLE 9
Determination of the crystal structure of l-Cyclopropyl-3-r3-(5-Morphol-4-ylmethyl-lH-Benzoimidazol-2-yl)-lH-Pyrazol-4-yll-Urea dihydrate free base by X-ray diffraction

This was carried out as described in Example 69 of WO 2006/070195 at pages 201 to 204 (the content of which is incorporated herein by reference).

5 EXAMPLE 10

Determination of the XRPD pattern of l-cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-lH-Benzoimidazol-2-yl)-lH-pyrazol-4-yll-urea free base

This was carried out as described in Example 70 of WO 2006/070195 at pages 204 to 205 (the content of which is incorporated herein by reference).

10 EXAMPLE 11

Determination of the crystal structure of l-Cyclopropyl-3-r3-(5-Morpholin-4-ylmethyl-lH-Benzoimidazol-2-yl)-lH-Pyrazol-4-yll-Urea lactate salt

This was carried out as described in Example 71 of WO 2006/070195 at pages 205 to 209 (the content of which is incorporated herein by reference).

15 EXAMPLE 12

1-Cyclopropyl-3-[3-(5-Morpholin-4-ylmethyl- lH-Benzimidazol-2-yl)- lH-Pyrazol-4-yll -Urea salt stability at 40°C 75% RH

This was carried out as described in Example 72 of WO 2006/070195 at pages 209 to 211 (the content of which is incorporated herein by reference).

20 BIOLOGICAL ACTIVITY

EXAMPLE 13

Kinase Inhibitory Activity Assays

The inhibitory activity against these enzymes was assayed at Millipore (previously Upstate Discovery Ltd), Dundee using their radiometric Kinase Profiler™ system. Enzymes were prepared at 10x final concentration in enzyme buffer (as described in table below). Enzymes were then incubated in assay buffer with various substrates and 35P-ATP (-500 cpm/pmole) as described in the table.

The reaction was initiated by the addition of Mg/ATP. The reaction was allowed to proceed for 40 minutes at room temperature before being stopped with 5 µl of a 3% phosphoric acid solution. Ten µl of the reaction mix was transferred to either a filtermatA or P30 filtermat and
washed three times in 75 mM phosphoric acid and once in methanol before being dried for scintillation counting.

Compounds were tested at the concentrations detailed below in duplicate against all kinases and the percent activity compared to control was calculated. Where inhibition was high an IC₅₀ was determined. IC₅₀ values for Compound (1) against the kinases described herein are outlined in Table A and Table B.
Substrates were:

A: 250 µM GGMEDIYFEFMGGKKK
B: 30 µM KKKNRTLSVA
C: 0.1 mg/ml Poly (Glu, Tyr) 4:1
D: KKLNRRTLSFAEPG
E: 30 µM KKLNRRTLSVA
F: 250 µM KKKSPGEYVNIEFG
G: 250 µM KVEKIGETYGWYK
H: 30 µMGRPRTSSFAEGKK
I: 200 µMRRLSFAEPG
J: 100 µM KTFCGTPEYLAPEVRREPRILSEEQEMFRDFDYIAD WC
K: 100 µM AMARAASAAALARRR
L: 2 mg/ml caesin
M: 100 µM KKVRSRSGLYRSPSMPENLNPR
N: 0.1 mg/ml Histone H1
O: 50 µM ERMRPRKRQGVSRRV
P: 100 µM KTFCGTPEYLAPEVRREPRILSEEQEMFRDFDYIADWC
Q: 250 µM KVEKIGETYGWYK
R: 30 µM KKKNRTLSVA
S: 30 µM GRPRTSSFAEGKK

Enzyme buffers were:

A: 20 mM MOPS, 1 mM EDTA, 0.01% Brij-35, 5% glycerol, 0.1% β-mercaptoethanol, 1 mg/ml BSA

Assay buffers were:

A: 8 mM MOPS, pH 7.0, 0.2 mM EDTA, 30 mM NaCl, 10 mM MgAcetate
B: 8 mM MOPS, pH 7.0, 0.2 mM EDTA, 10 mM MgAcetate
C: 20 mM Hepes, pH 7.4, 0.03% Triton-X-100, 10 mM MgAcetate.
D: 50 mM Tris, pH 7.5, 0.1 mM EGTA, 0.1 mM Na3VO4, 10 mM MgAcetate
E: 20 mM Hepes, pH 7.4, 0.03% Triton-X-100, 0.1 mg/ml phosphatidylserine, 10 µg/ml diacylglycerol, 10 mM MgAcetate.
F: 20 mM HEPES, pH 7.4, 0.03% Triton-X-100, 0.1 mM CaCl2, 0.1 mg/ml phosphatidylserine, 10 µg/ml diacylglycerol, 10 mM MgAcetate.
G: 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na_3VO_4, 10 mM Mg acetate.

EXAMPLE 14

Anti-proliferative Activity

The anti-proliferative activities of 1-cyclopropyl-3-[3-(5-morpholin-4-y lmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea can be determined by measuring the ability of the compound to inhibit cell growth in a number of cell lines.

Inhibition of cell growth is measured using the Alamar Blue assay (Nociari, M. M., Shalev, A., Benias, P., Russo, C. *Journal of Immunological Methods* 1998, 213, 157-167). The method is based on the ability of viable cells to reduce resazurin to its fluorescent product resorufin. For each proliferation assay cells are plated onto 96 well plates and allowed to recover for 16 hours prior to the addition of inhibitor compounds for a further 72 hours. At the end of the incubation period 10% (v/v) Alamar Blue is added and incubated for a further 6 hours prior to determination of fluorescent product at 535nM ex / 590nM em. In the case of the non-proliferating cell assay cells are maintained at confluence for 96 hour prior to the addition of inhibitor compounds for a further 72 hours. The number of viable cells is determined by Alamar Blue assay as before. IC50 values can then be calculated. In addition, any morphological changes are recorded.

Cell lines can be selected based on the disease or kinase of interest and can be obtained from the ECACC (European Collection of cell Cultures), ATCC (American Type Culture Collection), DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH - the German Collection of Microorganisms and Cell Cultures) or other such cell bank.

EXAMPLE 15

**General Colony Forming Assay Protocol for 1-Cyclopropyl-3-r3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl] -urea**

The effect of various treatment treatments of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea on adherent tumour cell lines can be assessed in a clonogenic assay. Cell lines can be selected based on the disease or kinase of interest can be obtained from the ECACC (European Collection of cell Cultures), ATCC (American Type Culture Collection), DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH - the German Collection of Microorganisms and Cell Cultures) or other such cell bank.
Cells were seeded at a concentration of 75 to 100 cells/ml relevant culture media onto 6 or 24 well tissue culture plates and allowed to recover for 16 h.

1-Cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea or vehicle control (DMSO) can be added to duplicate wells to give a final DMSO concentration of 0.1%. Following compound addition, colonies are allowed to grow out for between 10 and 14 days for optimum discrete colony counting. Colonies are fixed in 2ml Carnoys fixative (25% Acetic Acid, 75% Methanol) and stained in 2ml 0.4% w/v crystal violet. The number of colonies in each well are counted. Only multi-cellular colonies of approximately 50 cells or more which show proliferation from a single cell to a colony of many cells (i.e. complete cell cycles including successful cytokinesis) are scored. Single multi-nucleated (polyploid) cells are not scored. IC50 values are calculated by sigmoidal dose-response (variable slope) IC50 curves using Prism Graphpad Software.

EXAMPLE 16

**Western Blotting Assay to determine the inhibition of phosphorylation of the downstream substrates of the Kinases described herein**

Using this protocol, it can be shown whether phosphorylation of direct downstream substrates of a specific kinase in relevant cells is observed, and either inhibited or increased, when cells are treated with 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea.

Following compound treatment at a final concentration of 0.1% DMSO, cells are harvested and lysed in ice cold triton lysis buffer. Lysates are cleared by centrifugation and a sample of the supernatant removed for protein determination. Equivalent amounts of protein lysate has SDS sample buffer and DTT added and are boiled for 5 minutes.

Samples are resolved by SDS PAGE, blotted onto nitrocellulose filters, blocked with 5% non-fat milk or equivalent blocking buffer and incubated overnight with the specific antibodies to phosphorylated and non-phosphorylated proteins at 4°C. Secondary antibodies are used such as anti-rabbit and anti-mouse IgG, HRP linked (Cell Signalling Technology) and detection achieved using ECLPLUS reagents (Amersham Bioscience). Alternative secondary antibodies used can beIRDye® conjugated and detection achieved using the Odyssey Infrared Imaging System (LI-COR Biosciences).
General Method for Preservative Efficacy Test

The Preservative Efficacy Test can be performed as described in European Pharmacopoeia 5th edition Chapter 5.1.3 'Efficacy of Antimicrobial Preservation'. The test consists of challenging the preparation with a prescribed inoculum of suitable micro-organisms including 2 bacterial strains and 2 fungal strains.

Two bacterial strains are used:

*Pseudomonas aeruginosa* ATCC 9027; NCIMB 8626; CIP 82.1 18.

*Staphylococcus aureus* ATCC 6538; NCTC 10788; NCIMB 9518; CIP 4.83.

Preparatory to the test, inoculate the surface of Trypcase-soy agar (agar medium B (2.6.12), commercially available) for bacteria with the recently grown stock culture of each of the specified micro-organisms. Incubate the bacterial cultures at 30-35 °C for 18-24 h. Subcultures may be needed after revival before the micro-organism is in its optimal state, but it is recommended that their number be kept to a minimum. To harvest the bacterial cultures, use a sterile suspending fluid, containing 9 g/l of sodium chloride R (SRIP, 1963, p 181), for dispersal and transfer of the surface growth into a suitable vessel. Add sufficient suspending fluid to reduce the microbial count to about 10^8 microorganisms per millilitre.

Remove immediately a suitable sample from each suspension and determine the number of colony-forming units per millilitre (CFU/ml) in each suspension by plate count or membrane filtration. This value serves to determine the inoculum and the baseline to use in the test. The suspensions shall be used immediately.

To count the viable micro-organisms in the inoculated products, use the agar medium used for the initial cultivation of the respective micro-organisms. Inoculate a series of containers of the product to be examined, each with a suspension of one of the test organisms to give an inoculum of 10^5 to 10^6 micro-organisms per millilitre or per gram of the preparation. The volume of the suspension of inoculum does not exceed 1 per cent of the volume of the product. Mix thoroughly to ensure homogeneous distribution. Maintain the inoculated product at 20-25 °C, protected from light. Remove a suitable sample from each container, typically 1 ml or 1 g, at zero hour and at appropriate intervals according to the type of the product and determine the number of viable micro-organisms by plate count or membrane filtration. Ensure that any residual antimicrobial activity of the product is eliminated by dilution, by filtration or by the use of a specific inactivator. When dilution procedures are used, due allowance is made for the reduced sensitivity in the recovery of small numbers of viable micro-organisms. When a specific inactivator is used, the ability of the system to support the growth of the test organisms
is confirmed by the use of appropriate controls. The procedure is validated to verify its ability to demonstrate the required reduction in count of viable micro-organisms.

**EXAMPLE 18**

**Preservative Efficacy Test**

The test was carried out by Tepnel Scientific Services, according to the method described in European Pharmacopoeia 5th edition Chapter 5.1.3 'Efficacy of Antimicrobial Preservation'. The test consisted of challenging the preparation with a prescribed inoculum of suitable micro-organisms including 2 bacterial strains and 2 fungal strains. Standardised organism are inoculated into the product, and after suitable exposure periods pour-plate or spread plate viable counts are performed. The number of surviving organism per ml or g of product is calculated and, from this, the efficacy of the preservative is determined. The results for the two bacterial strains are laid out below in Example 18A-D.

For each bacterial organism (*Pseudomonas aeruginosa* ATCC 9027 and *Staphylococcus aureus* ATC 6538) inoculate two Tryptone Soya Agar (TSA) slopes and incubate for 30-35 °C for 18-24 hours. After incubation harvest the organisms using Sterile Buffered Sodium Chloride Peptone Solution (BSCPS) to wash the growth into sterile universal bottles. For bacterial organisms, adjust the optical density at 650 nm (A$_{650}$) as measured on a calibrated Spectrophotometer to read between the values 1.15-1.34 for *P. aeruginosa* and 0.75-1.00 for *S. aureus* (viable count 1-2 x 10$^5$). In order to produce a concentration of approximately 1 x 10$^6$ bacterial per ml or g of test preparation, dilute the concentrated suspensions obtained 1 in 10 with BSCPS and use an inoculum of the diluted suspension equivalent to 1% of the sample volume or weight.

Vials containing 52mg of Compound I (free base) as a lyophilised powder, produced according to Example 18 (xi), are reconstituted with 5.1mL of appropriate diluent (either 5% Dextrose solution or 0.9% Sodium chloride solution) to give a 10mg/mL solution. These solutions are then further diluted with the same diluent, to give test products containing 2mg/mL and 8mg/mL solutions of Compound I in either 5% Dextrose Solution or 0.9% Sodium Chloride Solution.

Inoculate into portions of the product sufficient microbial suspension to produce a final concentration of approx. 10$^6$ organisms per g or ml (e.g. 0.5ml of a 10$^8$ suspension into 50ml product). The limit for inoculum level is 10$^5$ to 10$^6$ cfu/ml or g for the Ph. Eur. The volume of the inoculum must be 1% of the sample weight or volume. Separate portions of the product are
used for each organism. Introduce the same volume of inoculum into equivalent quantities of
BSCPS or inactivation medium (Buffered Sodium Chloride Peptone Water + 3% Tween) for
each organism for control counts. Ensure that mixing thoroughly evenly disperses the
organisms. Place the inoculated products in a 20-25 °C incubator. Remove 1mL or 1g
quantities at appropriate time intervals (6 hour, 24 hour, 7 day, 14 day and 28 day).

Prepare 10-fold dilutions of sample in inactivator solution to an appropriate level e.g. $10^4$ or
$10^5$ for initial counts, less for subsequent counts depending on the kill level achieved at the
previous point. Carry out viable counts by pour-plate method or spread plate method onto the
relevant agar plate (TSA for bacteria). All counts must be preformed in duplicate. Incubate
TSA plates at 30-35 °C for 5 days for each organism under test.

Viable counts are carried out on the control preparations as soon as possible after inoculation
but not more than 1 hour after preparation. These are carried out to determine the initial
number of organisms used and the suitability of the culture media used; these counts are also
carried out in duplicate.

Compare the counts obtained at each time point for each organism and for each sample dilution
with the control count, taking into account the dilution factor, and express any reduction as a
log value. Undertake calculation using pairs of plates with the highest counts, but less than 300
cfu per plate for bacteria (e.g. $10^2$ product dilation yields 31 colonies and a product count on
3.1 x $10^3$ cfu/ml).

**Example 18A**

**Sample**

2.0g/ml Compound I as Lactate salt in citrate buffer (prepared as outlined in Example 18 (xi))
in dextrose solution

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Log Reduction: (Sample)/(A/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>6 hour</td>
<td>0.5 [2/NT]</td>
</tr>
<tr>
<td>24 hour</td>
<td>0.6 [3/1]</td>
</tr>
<tr>
<td>7 day</td>
<td>1.7 [NT/3]</td>
</tr>
</tbody>
</table>
Key:
A : Minimum log reduction to comply with 'A' criteria for Parenteral and Ophthalmic preparations
B : Minimum log reduction to comply with 'B' criteria for Parenteral and Ophthalmic preparations.
NT: No test required for this organism at this timepoint/criteria combination.
ND: No decrease of log reduction compared to previous timepoint.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Log Reduction: (Sample)/[A/B]</th>
<th>S. aureus</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hour</td>
<td>0.1 [2/NT]</td>
<td>2.2 [2/NT]</td>
<td></td>
</tr>
<tr>
<td>24 hour</td>
<td>0.5 [3/1]</td>
<td>4.2 [3/1]</td>
<td></td>
</tr>
<tr>
<td>7 day</td>
<td>2.2 [NT/3]</td>
<td>&gt;5.2 [NT/3]</td>
<td></td>
</tr>
<tr>
<td>14 day</td>
<td>2.5 [NT/NT]</td>
<td>&gt;5.2 [NT/NT]</td>
<td></td>
</tr>
<tr>
<td>28 day</td>
<td>3.5 [ND/ND]</td>
<td>&gt;5.2 [ND/ND]</td>
<td></td>
</tr>
</tbody>
</table>

Key:
A : Minimum log reduction to comply with 'A' criteria for Parenteral and Ophthalmic preparations
B : Minimum log reduction to comply with 'B' criteria for Parenteral and Ophthalmic preparations.
NT: No test required for this organism at this timepoint/criteria combination.
ND: No decrease of log reduction compared to previous timepoint.

Example 18B

Sample
2.0g/ml Compound I as Lactate salt in citrate buffer (prepared as outlined in Example 18 (xi)) in saline solution

Example 18C
Sample
8.0g/ml Compound I as Lactate salt in citrate buffer (prepared as outlined in Example 18 (xi)) in dextrose solution

Testing Results

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Log Reduction: (Sample)/[A/B]</th>
<th>S. aureus</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hour</td>
<td>0.1 [2/NT]</td>
<td>&gt;5.2 [2/NT]</td>
<td></td>
</tr>
<tr>
<td>24 hour</td>
<td>0.5 [3/1]</td>
<td>&gt;5.2 [3/1]</td>
<td></td>
</tr>
<tr>
<td>7 day</td>
<td>0.7 [NT/3]</td>
<td>&gt;5.2 [NT/3]</td>
<td></td>
</tr>
<tr>
<td>14 day</td>
<td>1.5 [NT/NT]</td>
<td>&gt;5.2 [NT/NT]</td>
<td></td>
</tr>
<tr>
<td>28 day</td>
<td>&gt;4.9 [ND/ND]</td>
<td>&gt;5.2 [ND/ND]</td>
<td></td>
</tr>
</tbody>
</table>

Key:
A: Minimum log reduction to comply with 'A' criteria for Parenteral and Ophthalmic preparations
B: Minimum log reduction to comply with 'B' criteria for Parenteral and Ophthalmic preparations.
NT: No test required for this organism at this timepoint/criteria combination.
ND: No decrease of log reduction compared to previous timepoint.

Example 18D

Sample
8.0g/ml Compound I as Lactate salt in citrate buffer (prepared as outlined in Example 18 (xi)) in saline solution

Testing Results

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Log Reduction: (Sample)/[A/B]</th>
<th>S. aureus</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hour</td>
<td>0.2 [2/NT]</td>
<td>1.6 [2/NT]</td>
<td></td>
</tr>
<tr>
<td>24 hour</td>
<td>0.2 [3/1]</td>
<td>3.6 [3/1]</td>
<td></td>
</tr>
<tr>
<td>7 day</td>
<td>1.4 [NT/3]</td>
<td>&gt;5.2 [NT/3]</td>
<td></td>
</tr>
<tr>
<td>14 day</td>
<td>2.9 [NT/NT]</td>
<td>&gt;5.2 [NT/NT]</td>
<td></td>
</tr>
<tr>
<td>28 day</td>
<td>4.9 [ND/ND]</td>
<td>&gt;5.2 [ND/ND]</td>
<td></td>
</tr>
</tbody>
</table>

Key:
A: Minimum log reduction to comply with 'A' criteria for Parenteral and Ophthalmic preparations
B: Minimum log reduction to comply with 'B' criteria for Parenteral and Ophthalmic preparations.

NT: No test required for this organism at this timepoint/criteria combination.
ND: No decrease of log reduction compared to previous timepoint.

CONCLUSION

The test demonstrates that Compound I has antimicrobial activity against S. aureus and P. aeruginosa.

EXAMPLE 19

Minimum inhibitory concentration (MIC) Test Method

The cultures are streaked on Trypticase Soya Agar (TSA) for aerobic cultures and Cation adjusted Mueller Hinton Agar (MHA-Difco) with 5% sheep blood for fastidious cultures.

Aerobic cultures were incubated at 37 °C for about 18-24 hours. Fastidious cultures were incubated CO₂ incubation (5% CO₂) at 37 °C for about 18-24 hours. Three to four well isolated colonies are taken and saline suspensions are prepared in sterile densimat tubes. The turbidity of the culture was adjusted to 0.5-0.7 Mc Farland standard (1.5 x 10⁸ CFU/ml). The cultures were diluted 10 fold in saline to get an inoculum size of approximately 1-2 x 10⁷ organisms/ml.

1 mg/ml concentrations of stock solution of compound are prepared in dimethylsulfoxide/distilled water/solvent given in National Committee for Clinical Laboratory Standards (NCCLS) manual. Serial two fold dilutions of the compounds and standard drugs are prepared as per NCCLS manual. Stock solution was changed according to the needs of the experiment. Two ml of respective compound concentrations are added to 18 ml of Molten Mueller Hinton agar to get the required range, for example 0.015 µg/ml - 16 µg/ml. For fastidious cultures 1 ml of sheep blood was added in Molten Mueller Hinton agar. For control MHA and MHA with 5% sheep blood plates without antibiotic for each set are prepared. One MHA and MHA with 5% sheep blood plate without antibiotic for determining quality check for media was prepared.

1 µl of each culture on each plate are replicated with the help of replicator (Denley’s multipoint replicator). The spots are allowed to dry and the plates are incubated for about 18-24 hours at 37°C. Fastidious cultures are incubated at 37 °C in CO₂ incubator. The results were noted comparing with the control plates. The concentration of compound at which there is complete
disappearance of growth spot or formation of less than 10 colonies per spot was considered as Minimum Inhibitory Concentration (MIC). The MICs of Quality Control (QC) strains were plotted on the QC chart for agar dilution method. If the MICs were within the range, the results interpreted by comparing MICs of standards against all organisms with those of test compounds.

Strains which can be used in this method include Staphylococcus aureus ATCC 29213; Enterococcus faecalis ATCC 29212; Eschericia coli ATCC 25922; and Pseudomonas aeruginosa ATCC 27853.

NCCLS disc diffusion assay using 10µg discs of Gentamicin (Difco) against Pseudomonas aeruginosa ATCC 27853. A zone diameter of 16-21 mm was considered for optimum cation (Magnesium and Calcium) content of the media. The diameter was plotted in the media QC chart.

**EXAMPLE 20**

Methods Of Testing For Pain Reducing Or Pain Preventing Activity

(I) Inflammatory hyperalgesia test

Mechanical hyperalgesia can be examined in a rat model of inflammatory pain. Paw withdrawal thresholds to an increasing pressure stimulus are measured by the Randal-Selitto technique using an analgesymeter (Ugo Basile, Milan), in naïve animals prior to an intraplantar injection of complete Freund's complete adjuvant (FCA) into the left hind paw. 24 h later paw withdrawal thresholds are measured again prior to (predose) and then from 10 min to 6 h following drug or vehicle administration. Reversal of hyperalgesia in the ipsilateral paw is calculated according to the formula:

\[
\% \text{ reversal} = \frac{\text{postdose threshold} - \text{predose threshold}}{\text{naïve threshold} - \text{predose threshold}} \times 100
\]

(ii) Neuropathic hyperalgesia test

Mechanical hyperalgesia can be examined in a rat model of neuropathic pain induced by partial ligation of the left sciatic nerve. Approximately 14 days following surgery mechanical withdrawal thresholds of both the ligated (ipsilateral) and non-ligated (contralateral) paw are measured prior to (predose) and then from 10 min to 6 h following drug or vehicle administration. Reversal of hyperalgesia at each time point is calculated according to the formula:
\[
\% \text{ reversal} = \frac{\text{ipsilateral threshold postdose} - \text{ipsilateral threshold predose}}{\text{contralateral threshold predose} - \text{ipsilateral threshold predose}} \times 100
\]

All experiments are carried out using groups of 6 animals. Stock concentrations of drugs are dissolved in distilled water and subsequent dilutions were made in 0.9% saline for subcutaneous administration in a volume of 4 ml kg \(^{-1}\). All drugs are made up in plastic vials and kept in the dark.

Statistical analysis are carried out on withdrawal threshold readings (g) using ANOVA with repeated measures followed by Tukey's HSD test. Efficacy refers to the maximal reversal of hyperalgesia observed at the doses used.

(iii) Testing the effects of compounds of formula (I) a Rat Model of Bone Cancer Pain

Adult female rats are given intra-tibial injections of MRMZ-I rat mammary gland carcinoma cells (3µl, 10⁷ cells/ml). The animals typically gradually develop mechanical hyperalgesia, mechanical allodynia (skin sensitivity to non-noxious stimuli) and hind limb sparing, beginning on day 12-14 following cell injection. A compound of formula (I) (e.g. at a dose of 10 and 30 µg/kg s.c.) is administered 3 times a week from the day of cell injection, and the extent of inhibition of hind limb sparing and mechanical allodynia is determined in comparison to vehicle-treated controls.

EXAMPLE 21

Minimum Bactericidal Dilution

Organisms to be tested are grown on slants and transferred to an agar plate by streaking to form a lawn. Colonies are scraped off the agar plates using a sterile inoculating loop and suspended in phosphate buffered solution (PBS) and diluted to 5 x 10⁶ CFU/ml.

EXAMPLE 22

Residual Skin Testing

Residual skin testing can be performed by evenly coating the surface of a skin patch with 20µl of the active solution. Skin samples are allowed to evaporate for 1 minute, 15 minutes, 60 minutes, 120 minutes, 240 minutes, 360 minutes, 480 minutes, and 14 hours with the lid off the Petri plate. At the appropriate time point, skin samples were inoculated with 10µl of a 1:10 dilution of a microbial suspension (e.g. the 18 hour inoculum of 1.0E+08 CFUs/mL), evenly covering the entire area and the sample recovered and allowed to sit 5 minutes. At this time the
skin is extracted using sterile forceps and placed in a sterile centrifuge tube containing 10 ml of a sampling solution and vortexed for 30 seconds. An aliquot of the extracted sample containing any microbials from the skin is plated onto a trypticase soy agar plate using a spiral plater (typically 50µl in exponential mode).

The agar plates are incubated at 37°C overnight (18 hours) and CFUs are counted. CFUs/mL established by Baseline Count are calculated and compared to CFUs/mL for antibacterial solutions to determine the log reductions. The Baseline Count was achieved by evenly spreading 10µl of the diluted bacterial suspension on a square of the Skin and processed in accordance with the above procedure, except no active solution was added.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 23

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

(iii) Injectable Formulation I

A parenteral composition for administration by injection can be prepared by dissolving a compound of the formula (I) (e.g. in a salt form) in water containing 10% propylene glycol to give a concentration of active compound of 1.5% by weight. The solution is then sterilised by filtration, filled into an ampoule and sealed.

(iv) Injectable Formulation II

A parenteral composition for injection is prepared by dissolving in water a compound of the formula (I) (e.g. in salt form) (2 mg/ml) and mannitol (50 mg/ml), sterile filtering the solution and filling into sealable 1 ml vials or ampoules.

(v) Injectable formulation III
A formulation for i.v. delivery by injection or infusion can be prepared by dissolving the compound of formula (I) (e.g. in a salt form) in water at 20 mg/ml. The vial is then sealed and sterilised by autoclaving.

(Vi) Injectable formulation IV

A formulation for i.v. delivery by injection or infusion can be prepared by dissolving the compound of formula (I) (e.g. in a salt form) in water containing a buffer (e.g. 0.2 M acetate pH 4.6) at 20 mg/ml. The vial is then sealed and sterilised by autoclaving.

(viii) Lyophilised formulation I

Aliquots of formulated compound of formula (I) or a salt thereof as defined herein are put into 50 mL vials and lyophilized. During lyophilisation, the compositions are frozen using a one-step freezing protocol at (-45 °C). The temperature is raised to -10 °C for annealing, then lowered to freezing at -45 °C, followed by primary drying at +25 °C for approximately 3400 minutes, followed by a secondary drying with increased steps if temperature to 50 °C. The pressure during primary and secondary drying is set at 80 millitor.

(vii) Lyophilised formulation II

Aliquots of formulated compound of formula (I) or s salt thereof as defined herein are put into 50 mL vials and lyophilized. During lyophilisation, the compositions are frozen using a one-step freezing protocol at (-45 °C). The temperature is raised to -10 °C for annealing, then lowered to freezing at -45 °C, followed by primary drying at +25 °C for approximately 3400 minutes, followed by a secondary drying with increased steps if temperature to 50 °C. The pressure during primary and secondary drying is set at 80 millitor.

(ix) Lyophilised Formulation for use in i.v. administration III

An aqueous buffered solution is prepared by dissolving 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-lH-benzoimidazol-2-yl)-lH-pyrazol-4-yl]-urea L-lactic acid salt at a concentration of 12.86mg/ml in a 0.02M citric acid buffer corrected to a pH of 4.5 with sodium hydroxide or hydrochloric acid.

The buffered solution is filled, with filtration to remove particulate matter, into a container (such as class 1 glass vials) which is then partially sealed (e.g. by means of a Florotec stopper).

If the compound and formulation are sufficiently stable, the formulation is sterilised by autoclaving at 121°C for a suitable period of time. If the formulation is not stable to
autoclaving, it can be sterilised using a suitable filter and filled under sterile conditions into sterile vials. The solution is freeze dried using a suitable cycle: for example

Freezing - freeze to -40°C over 2 hours and hold at -40°C for 3 hours.
Primary drying - ramp -40°C to -30°C over 8 hours and hold at -30°C for 7 hours.
Secondary drying - ramp to +30°C over 4 hours and hold at +30°C for 8-10 hours

On completion of the freeze drying cycle the vials are back filled with nitrogen to atmospheric pressure, stoppered and secured (e.g. with an aluminium crimp). For intravenous administration, the freeze dried solid can be reconstituted into a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose. The solution can be dosed as is, or can be injected into an infusion bag (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

(x) Subcutaneous Injection Formulation

A composition for sub-cutaneous administration is prepared by mixing a compound of the formula (I), or a salt thereof as defined herein, with pharmaceutical grade corn oil to give a concentration of 5 mg/ml. The composition is sterilised and filled into a suitable container.

(xii) Lyophilised Formulation for use in i.v. administration IV

An aqueous buffered solution is prepared by dissolving 13 mg/ml of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea L-lactic acid salt (equivalent to 10mg of free base) in 20 mg/ml citric acid anhydrous buffer corrected to a pH of 4.5 with 2M aqueous sodium hydroxide or 2M aqueous hydrochloric acid.

5 ml of the solution of 1-cyclopropyl-3-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea L-lactic acid salt (containing 65.9 mg of the L-lactate salt which equates to 52 mg the free base) in approximately 100 mM (e.g. 104 mM) citrate buffer pH 4.5 was filled into 20 ml type I glass vials and lyophilised. The solution is freeze dried using a suitable cycle for example:
On completion of the freeze drying cycle the vials are back-filled with nitrogen to around atmospheric pressure (e.g. just below (95%)), stoppered and secured (e.g. with an aluminium crimp). For intravenous administration, the freeze dried solid can be reconstituted into a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose. The solution can be dosed as is, or can be injected into an infusion bag (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

**Equivalents**

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.
CLAIMS

1. A compound of Formula (I), or salts, solvates or tautomers thereof, for use:

a) in the prophylaxis or treatment of a disease state or condition mediated by a kinase, or a mutated form thereof, which is:

5 "a member of the AXL family, such as AxI, Mer and Sky, in particular Mer.
▪ a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, theta, iota, lambda and mu (α, βI and βII), γ, δ, ε, ζ, η, θ, ι, λ, and μ), in particular PKC-mu (PKCµ) or PKC-gamma (PKCγ)
▪ a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-stimulating factor 1 receptor (M-CSF-IR or FMS)
▪ a member of the Mitogen- and stress-activated kinase family such as MSK 1 and MSK2, in particular MSK2
▪ a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as DRAK1 and DRAK2, in particular DRAK1

10 "a Salt-inducible kinase (SIK)
▪ a member of the 90kDa ribosomal S6 kinase family such as RSK1 -4, in particular RSK2, RSK3, RSK4
▪ a member of the p21 activated kinase (PAK) family in particular PAK5
▪ a member of the Brain specific kinase family, Brain specific kinases 1 and 2
▪ (BRSK1/2), in particular BrSK2, or
▪ a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular TLK2; or

b) as an antibacterial agent; or

c) as a neuroprotective agent, as an immunosuppressive agent or as anti-osteolytic agent; or

d) in the prophylaxis or treatment of a disease or condition selected from the following:

▪ pain;
▪ coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF), hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease, lung injury;
a disease state or condition resulting in excessive bone formation, Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients;

- proliferative vitreoretinopathy, liver fibrosis, renal failure, irritable bowel syndrome (IBS), oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy;
- cerebral ischemia, Coffin-Lowry syndrome, Borna disease, spinocerebellar ataxia type 14 (SCA14), schizophrenia, transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, pancreatitis and metal (e.g. lead) poisoning;
- pancreatic adenocarcinoma, gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases;
- adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts; and
- allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

wherein the compound of Formula (I) is:

![Formula (I)](image)

2. A compound of Formula (I), or salts, solvates or tautomers thereof, as defined in claim 1 for use as an antibacterial agent.

3. A compound of Formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for use in the prophylaxis or treatment of a Gram-positive bacterial infection.
4. A compound of Formula (I) and salts, solvates or tautomers thereof, as defined in claim 1 for use in the prophylaxis or treatment of a Gram-negative bacterial infection.

5. The lactate or citrate salt or mixture thereof (in particular lactate salt) of the compound of formula (I) for use in the prophylaxis or treatment of an infection as defined in claim 3 or claim 4.

6. A crystalline form of lactate salt of the compound of formula (I) for use in the prophylaxis or treatment of an infection as defined in claim 3 or claim 4.

7. A compound of Formula (I), or salts, solvates or tautomers thereof, as defined in claim 1 for use in the prophylaxis or treatment of a disease state or condition caused by S. aureus.

8. A compound of Formula (I), or salts, solvates or tautomers thereof, as defined in claim 1 for use in the prophylaxis or treatment of a disease state or condition caused by P. aeruginosa.

9. A compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for use in the treatment of infection such as streptococcal infection including strep throat, impetigo, erysipelas, scarlet fever, infection from surgical procedures, hospital acquired lung infection, skin infection, diabetic foot infection, soft tissue infection, bone infection, joint infection, ear infection including otitis media, eye infection including conjunctivitis and blepharoconjunctivitis, urinary tract infection including catheter infection, venous catheter insertions, prosthesis infection, respiratory tract infection including upper respiratory tract infection, lower respiratory tract infection; tonsillitis; meningitis; cellulitis; diverticulitis; endocarditis; osteomyelitis; pseudomembranous colitis; bronchitis e.g. tracheobronchitis; sinusitis; laryngitis; pneumonia including community acquired pneumonia, bronchopneumonia and legionellosis (Legionnaires’ disease); sepsis; septic arthritis; cellulitis; osteomyelitis; epiglottitis; exacerbation of existing chronic obstructive pulmonary disease (COPD); botulism; food poisoning; gonorrhoea; septicemia including meningococcal septicaemia; typhoid fever; paratyphoid fever; foodborne illness including food poisoning; toxic shock syndrome (TSS); gastrointestinal diseases including diarrhoea, dysentery-like conditions; ankylosing spondylitis; scalded skin syndrome; peptic ulcers; chronic gastritis; duodenitis; gas gangrene; enterotoxemia; tetanus; anthrax; listeriosis; necrotizing fascitis; tuberculosis; bacteremia, chancroid, shigellois, leprosy and dysentery.

10. A compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for use in the treatment of pneumonia.
11. A compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for use in the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having antibacterial activity.

12. The use of a compound of formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for the manufacture of a medicament for the prophylaxis or treatment of a Gram-positive bacterial infection.

13. The use of a compound of Formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for the manufacture of a medicament for the prophylaxis or treatment of a Gram-negative bacterial infection.

14. The use of a compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition caused by *S. aureus*.

15. The use of a compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition caused by *P. aeruginosa*.

16. The use of a compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for the manufacture of a medicament for use in the prophylaxis or treatment of infection such as streptococcal infection including strep throat, impetigo, erysipelas, scarlet fever, infection from surgical procedures, hospital acquired lung infection, skin infection, diabetic foot infection, soft tissue infection, bone infection, joint infection, ear infection including otitis media, eye infection including conjunctivitis and blepharoconjunctivitis, urinary tract infection including catheter infection, venous catheter insertions, prosthesis infection, respiratory tract infection including upper respiratory tract infection, lower respiratory tract infection; tonsillitis; meningitis; cellulitis; diverticulitis; endocarditis; osteomyelitis; pseudomembranous colitis; bronchitis e.g. tracheobronchitis; sinusitis; laryngitis; pneumonia including community acquired pneumonia, bronchopneumonia and legionellosis (Legionnaires' disease); sepsis; septic arthritis;cellulitis; osteomyelitis; epiglottitis; exacerbation of existing chronic obstructive pulmonary disease (COPD); botulism; food poisoning; gonorrhoea; septicemia including meningococcal septicaemia; typhoid fever; paratyphoid fever; foodborne illness including food poisoning; toxic shock syndrome (TSS); gastrointestinal diseases including diarrhoea, dysentery-like conditions; ankylosing spondylitis; scalded skin syndrome;
peptic ulcers; chronic gastritis; duodenitis; gas gangrene; enterotoxemia; tetanus; anthrax; listeriosis; necrotizing fascitis; tuberculosis; bacteremia, chancroid, shigellosis, leprosy and dysentery.

17. A method for the prophylaxis or treatment of a Gram-positive bacterial infection, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.

18. A method for the prophylaxis or treatment of a Gram-negative bacterial infection, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.

19. A method for the prophylaxis or treatment of a disease state or condition caused by S. aureus; which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.

20. A method for the prophylaxis or treatment of a disease state or condition caused by P. aeruginosa; which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1.

21. A method for the prophylaxis or treatment of infection such as streptococcal infection including strep throat, impetigo, erysipelas, scarlet fever, infection from surgical procedures, hospital acquired lung infection, skin infection, diabetic foot infection, soft tissue infection, bone infection, joint infection, ear infection including otitis media, eye infection including conjunctivitis and blepharoconjunctivitis, urinary tract infection including catheter infection, venous catheter insertions, prosthesis infection, respiratory tract infection including upper respiratory tract infection, lower respiratory tract infection; tonsillitis; meningitis; cellulitis; diverticulitis; endocarditis; osteomyelitis; pseudomembranous colitis; bronchitis e.g. tracheobronchitis; sinusitis; laryngitis; pneumonia including community acquired pneumonia, bronchopneumonia and legionellosis (Legionnaires’ disease); sepsis; septic arthritis; cellulitis; osteomyelitis; epiglottitis; exacerbation of existing chronic obstructive pulmonary disease (COPD); botulism; food poisoning; gonorrhoea; septicemia including meningococcal septicaemia; typhoid fever; paratyphoid fever; foodborne illness including food poisoning; toxic shock syndrome (TSS); gastrointestinal diseases including diarrhoea, dysentery-like conditions; ankylosing spondylitis; scalded skin syndrome; peptic ulcers; chronic gastritis; duodenitis; gas gangrene; enterotoxemia; tetanus; anthrax; listeriosis; necrotizing fascitis;
tuberculosis; bacteremia, chancroid, shigellosis, leprosy and dysentery, which method
comprises administering to a patient in need thereof a therapeutically effective amount of a
compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.

22. A compound of Formula (I), or salts, solvates or tautomers thereof, for use in the
prophylaxis or treatment of a disease state or condition mediated by a kinase, or a mutated form
thereof, which is:

- a member of the AXL family, such as AxI, Mer and Sky, in particular Mer.
- a member of the PKC family known as alpha, beta-I, beta-II, gamma, delta, epsilon,
zeta, eta, theta, iota, lambda and mu (α, β (βI and βII), γ, δ, ε, ζ, η, θ, i, λ, and μ), in
  particular PKC-mu (PKCμ) or PKC-gamma (PKCγ)
- a member of the CSF-1/PDGF receptor subfamily in particular macrophage colony-
  stimulating factor 1 receptor (M-CSF-IR or FMS)
- a member of the Mitogen- and stress-activated kinase family such as MSK 1 and
  MSK2, in particular MSK2
- a member of the DAP kinase-related apoptosis-inducing protein kinase family, such as
  DRAK1 and DRAK2, in particular DRAK1
- a Salt-inducible kinase (SIK)
- a member of the 90kDa ribosomal S6 kinase family such as RSK -4, in particular
  RSK2, RSK3, RSK4
- a member of the p21 activated kinase (PAK) family in particular PAK5
- a member of the Brain specific kinase family, Brain specific kinases 1 and 2
  (BRSKI/2), in particular BrSK2, or
- a member of the Tousled-like kinase (TLK) family such as TLK1 or TLK2 in particular
  TLK2

23. A compound of Formula (I) or salts, solvates or tautomers thereof, for use in the
prophylaxis or treatment of a disease or condition selected from the following:

- pain;
coronary artery disease, myocardial contraction, cardiomyopathy (e.g. dilated cardiomyopathy), cardiac remodelling, and heart failure such as congestive heart failure (CHF), hypertension including chronic hypoxic pulmonary hypertension (PHTN) disorders, systemic vascular diseases and a range of lung conditions such as bronchiolitis, interstitial lung disease, lung injury;

a disease state or condition resulting in excessive bone formation, Paget's disease, and other diseases in which bone resorption mediates morbidity including prosthesis failure, osteolytic sarcoma, and tumor metastasis to bone; osteolytic disease associated with bone metastasis and other bone diseases in patients;

proliferative vitreoretinopathy, liver fibrosis, renal failure, irritable bowel syndrome (IBS), oxidative stress-related neurodegenerative disorders and diabetic nephro- and neuropathy;

cerebral ischemia, Coffin-Lowry syndrome, Borna disease, spinocerebellar ataxia type 14 (SCA14), schizophrenia, transplant rejection, organ transplantation, resistance to transplantation, in graft vs. host disease, pancreatitis and metal (e.g. lead) poisoning;

pancreatic adenocarcinoma, gastric adenocarcinomas; invasive and/or metastatic breast cancer; metastasis from ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, hairy cell leukemia, in particular bone metastases;

adenopathy (lymphadenopathy), hepatosplenomegaly, and circulating lymphoblasts; and

allodynia including mechanical allodynia and EtOH or opiate withdrawal-associated allodynia, and hyperalgesia, in particular thermal hyperalgesia and hyperalgesia during EtOH or opiate withdrawal (also known as EtOH or opiate withdrawal-associated hyperalgesia).

wherein the compound of Formula (I) is as defined in claim 1.

24. A compound of Formula (I) or salts, solvates or tautomers thereof, as defined in claim 1 for use as a neuroprotective agent, as an immunosuppressive agent or as anti-osteolytic agent.
25. The lactate or citrate salt or mixture thereof (in particular lactate salt) of the compound of formula (I) for use in the prophylaxis or treatment of a disease as defined in the preceding claims.

26. A crystalline form of lactate salt of the compound of formula (I) for use in the prophylaxis or treatment of a disease as defined in the preceding claims.

27. A compound of Formula (I), or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition as defined in claim 1, and wherein the disease state or condition is as defined in claim 23.

28. A compound of Formula (I), or salts, solvates or tautomers thereof, for use in the prophylaxis or treatment of a disease state or condition as defined in claim 1, and wherein the disease state or condition is cancer.

29. A compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for use in the treatment of pain.

30. A compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for use in the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

31. A compound of the formula (I) or salts, solvates or tautomers thereof, for use in the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against a kinase which is as defined in claim 1.

32. The use of a compound of formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition defined in claim 1.

33. The use of a compound of Formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the prophylaxis or treatment of a disease as defined in claim 23.

34. The use of a compound of the formula (I) or salts, solvates or tautomers thereof, for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition as defined in claim 1; and wherein the disease state or condition is selected from cancer.
35. The use of a compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for the manufacture of a medicament for the treatment of pain.

36. The use of a compound of the formula (I) or salts, solvates or tautomers thereof, as defined in claim 1, for the manufacture of a medicament for use in the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF).

37. A method for the prophylaxis or treatment of a disease state or condition as defined in claim 1, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

38. A method for the prophylaxis or treatment of a disease as defined in claim 2, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.

39. A method for the treatment or prophylaxis of a disease state or condition as defined in claim 1; and wherein the disease state or condition is selected from cancer, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof.

40. A method of treating pain in a patient such as a mammal (e.g. human), which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.

41. A method for the treatment of heart disease and its manifestations, including coronary artery disease, cardiomyopathy, myocardial contraction, congestive heart failure, cardiac hypertrophy, cardiac remodelling, and heart failure such as congestive heart failure (CHF), which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula (I) or salts, solvates or tautomers thereof as defined in claim 1.
A. CLASSIFICATION OF SUBJECT MATTER

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

INV. A61K31/4184 A61P25/00 A61P31/04 A61P35/00

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/070195 A (ASTEX THERAPEUTICS LTD [GB]; BERDINI VALERIO [GB]; CARR MARIA GRAZIA []) 6 July 2006 (2006-07-06) cited in the application page 82, line 6 - page 83, line 5 page 84, lines 3-18 page 84, line 27 - page 85, line 15 page 86, lines 1-20 page 90; table 3 page 130, line 15 - page 132, line 16 figures 1-6 claims 1,2,39,42,43,45,49-63</td>
<td>1,9,10, 16,21-41</td>
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Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search

31 August 2009

Date of mailing of the international search report

08/09/2009

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Herdemann, Matthias
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