Title: PYRROLO-PYRIDINE DERIVATIVES FOR THE TREATMENT OF DISORDERS ASSOCIATED WITH INAPPROPRIATE IKK1 ACTIVITY

Abstract: The present invention relates to pyrrolo-pyridine derivatives of formula (I) combinations, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, combinations, compositions and medicaments in the treatment of disorders associated with inappropriate kinase activity, in particular disorders associated with inappropriate IKK1 activity.

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Applicants (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB); SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania 19101 (US).

Inventors/Applicants (for US only): BALDWIN, Ian, Robert [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB); BAMBOROUGH, Paul [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB); CHRISTOPHER, John, Andrew [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB); HAMADI, Ahmed, Moktar [FR/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB); LACKEY, Karen, Elizabeth [US/US]; GlaxoSmithKline, Five Moore Drive, Research Triangle Park, North Carolina 27709 (US).


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PYRROLO-PYRIDINE DERIVATIVES FOR THE TREATMENT OF DISORDERS ASSOCIATED WITH INAPPROPRIATE IKK1 ACTIVITY

FIELD OF THE INVENTION
The present invention relates to pyrrolo-pyridine derivatives, combinations, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, combinations, compositions and medicaments in the treatment of disorders associated with inappropriate kinase activity, in particular disorders associated with inappropriate IKK1 activity.

BACKGROUND TO THE INVENTION
An important large family of enzymes is the protein kinase enzyme family. Currently, there are about 500 different known protein kinases. Protein kinases serve to catalyze the phosphorylation of an amino acid side chain in various proteins by the transfer of the \( \gamma \)-phosphate of the ATP-Mg\(^{2+} \) complex to said amino acid side chain. These enzymes control the majority of the signaling processes inside cells, thereby governing cell function, growth, differentiation and destruction (apoptosis) through reversible phosphorylation of the hydroxyl groups of serine, threonine and tyrosine residues in proteins. Studies have shown that protein kinases are key regulators of many cell functions, including signal transduction, transcriptional regulation, cell motility, and cell division. Several oncogenes have also been shown to encode protein kinases, suggesting that kinases play a role in oncogenesis. These processes are highly regulated, often by complex intermeshed pathways where each kinase will itself be regulated by one or more kinases. Consequently, aberrant or inappropriate protein kinase activity can contribute to the rise of disease states associated with such aberrant kinase activity including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune and nervous systems. Due to their physiological relevance, variety and ubiquitousness, protein kinases have become one of the most important and widely studied family of enzymes in biochemical and medical research.

The protein kinase family of enzymes is typically classified into two main subfamilies: Protein Tyrosine Kinases and Protein Serine/Threonine Kinases, based on the amino acid residue they phosphorylate. The protein serine/threonine kinases (PSTK), includes cyclic AMP- and cyclic GMP-dependent protein kinases, calcium and phospholipid dependent protein kinase, calcium- and calmodulin-dependent protein kinases, casein kinases, cell division cycle protein kinases and others. These kinases are usually cytoplasmic or associated with the particulate fractions of cells, possibly by anchoring proteins. Aberrant protein serine/threonine kinase activity has been implicated or is suspected in a number of pathologies such as rheumatoid arthritis, psoriasis, septic shock, bone loss, many cancers and other proliferative diseases. Accordingly, serine/threonine kinases and the signal transduction pathways which they are part of are important targets for drug design. The tyrosine kinases phosphorylate tyrosine residues. Tyrosine kinases play an equally important role in
cell regulation. These kinases include several receptors for molecules such as
growth factors and hormones, including epidermal growth factor receptor, insulin
receptor, platelet derived growth factor receptor and others. Studies have indicated
that many tyrosine kinases are transmembrane proteins with their receptor domains
located on the outside of the cell and their kinase domains on the inside. Much work
is also in progress to identify modulators of tyrosine kinases as well.

Nuclear factor κB (NF-κB) belongs to a family of closely related dimeric transcription
factor complexes composed of various combinations of the Rel/NF-κB family of
polypeptides. The family consists of five individual gene products in mammals, RelA
(p65), NF-κB1 (p50/ p105), NF-κB2 (p49/ p100), c-Rel, and RelB, all of which can
form hetero- or homodimers. These proteins share a highly homologous 300 amino
acid “Rel homology domain” which contains the DNA binding and dimerization
domains. At the extreme C-terminus of the Rel homology domain is a nuclear
translocation sequence important in the transport of NF-κB from the cytoplasm to the
nucleus. In addition, p65 and cRel possess potent transactivation domains at their C-
terminal ends.

The activity of NF-κB is regulated by its interaction with a member of the inhibitor IκB
family of proteins. This interaction effectively blocks the nuclear localization
sequence on the NF-κB proteins, thus preventing migration of the dimer to the
nucleus. A wide variety of stimuli activate NF-κB through what are likely to be
multiple signal transduction pathways. Included are bacterial products (LPS), some
viruses (HIV-1, HTLV-1), inflammatory cytokines (TNFα, IL-1), environmental and
oxidative stress and DNA damaging agents. Apparently common to all stimuli
however, is the phosphorylation and subsequent degradation of IκB. IκB is
phosphorylated on two N-terminal serines by the recently identified IκB kinases (IKK-
α and IKK-β). IKKα is also known as IKK1. IKK-β is also known as IKK2. Site-
directed mutagenesis studies indicate that these phosphorylations are critical for the
subsequent activation of NF-κB in that once phosphorylated the protein is flagged for
degradation via the ubiquitin-proteasome pathway. Free from IκB, the active NF-κB
complexes are able to translocate to the nucleus where they bind in a selective
manner to preferred gene-specific enhancer sequences. Included in the genes
regulated by NF-κB are a number of cytokines and chemokines, cell adhesion
molecules, acute phase proteins, immunoregulatory proteins, eicosanoid
metabolizing enzymes and anti-apoptotic genes.

It is well-known that NF-κB plays a key role in the regulated expression of a large
number of pro-inflammatory mediators including cytokines such as TNF, IL-1β, IL-6
and IL-8, cell adhesion molecules, such as ICAM and VCAM, and inducible nitric
oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of
leukocytes at sites of inflammation and in the case of iNOS, may lead to organ
destruction in some inflammatory and autoimmune diseases.
The importance of NF-κB in inflammatory disorders is further strengthened by studies of airway inflammation including asthma, in which NF-κB has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyperresponsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF-κB, one may speculate that these effects are mediated through an inhibition of NF-κB.

Further evidence for a role of NF-κB in inflammatory disorders comes from studies of rheumatoid synovium. Although NF-κB is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF-κB is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF-κB has been shown to be activated in human synovial cells in response to stimulation with TNF-α or IL-1β. Such a distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., J. Biol. Chem., 271, 31496-31501 (1996). Expression of IKK-β has been shown in synoviocytes of rheumatoid arthritis patients and gene transfer studies have demonstrated the central role of IKK-β in stimulated inflammatory mediator production in these cells. See Aupperle et al. J. Immunology 1999. 163:427-433 and Aupperle et al. J. Immunology 2001;166:2705-11. More recently, the intra-articular administration of a wild type IKK-β adenoviral construct was shown to cause paw swelling while intra-articular administration of dominant-negative IKKβ inhibited adjuvant-induced arthritis in rat. See Tak et al. Arthritis and Rheumatism 2001, 44:1897-1907.

The NF-κB/Rel and IκB proteins are also likely to play a key role in neoplastic transformation and metastasis. Family members are associated with cell transformation in vitro and in vivo as a result of over expression, gene amplification, gene rearrangements or translocations. In addition, rearrangement and/or amplification of the genes encoding these proteins are seen in 20-25% of certain human lymphoid tumors. Further, NF-κB is activated by oncogenic ras, the most common defect in human tumors and blockade of NF-κB activation inhibits ras mediated cell transformation. In addition, a role for NF-κB in the regulation of apoptosis has been reported strengthening the role of this transcription factor in the regulation of tumor cell proliferation. TNF, ionizing radiation and DNA damaging agents have all been shown to activate NF-κB which in turn leads to the upregulated expression of several anti-apoptotic proteins. Conversely, inhibition of NF-κB has been shown to enhance apoptotic-killing by these agents in several tumor cell types. As this likely represents a major mechanism of tumor cell resistance to chemotherapy, inhibitors of NF-κB activation may be useful chemotherapeutic agents as either single agents or adjunct therapy. NF-κB is constitutively activated in
estrogen-receptor (ER)-negative breast cancer and thus is considered a potential therapeutic target for this type of neoplasia (Ciucci et al, 2006, Mol. Pharmacol., 70 1812-1821). Recent reports have implicated NF-κB as an inhibitor of skeletal cell differentiation as well as a regulator of cytokine-induced muscle wasting (Guttridge et al. Science; 2000; 289: 2363-2365), as important in activation of oestrogen-responsive genes (Park et al 2005, Cell 18: 71-82) and as a link between RANK signaling and Cyclin D1 Expression during mammary gland development (Cao et al; Cell 107; 763-775), further supporting the potential of NFκB inhibitors as novel cancer therapies.

Thus compounds which are inhibitors of kinase activity, in particular inappropriate IKK1 activity are therefore potentially useful in the treatment of disorders associated with inappropriate kinase activity, in particular inappropriate IKK1 activity including autoimmune diseases, inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease); osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, alkylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restonosis, diabetes, glomerulonephritis, cancer (e.g. cancers which when treated with inhibitors of IKK function will promote cell death, including neoplastic diseases such as solid tumours, skin cancer, melanoma, lymphoma and diseases in which angiogenesis play a role), cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiectasia.

The present inventors have discovered novel pyrrolo-pyridine compounds, which inhibit the activity of one or more protein kinases, in particular IKK1. Such pyrrolo-pyridine derivatives are therefore expected to be useful in the treatment of disorders associated with inappropriate kinase activity.

**BRIEF SUMMARY OF THE INVENTION**

In one aspect of the present invention, there is provided a compound of formula (I) or a salt or solvate thereof:

![Chemical Structure](image)

(I)

wherein
R\(^1\) is
(a) a heteroaryl group selected from:
indole, indazole, pyridine, pyrazole, benzothiazole, indolene, isoxazole,
oxadiazole (each of which may be substituted one or more times with one or
more substituents independently selected from -C\(_{1-3}\)alkyl, -COOC\(_{1-6}\)alkyl and -
halogen)
or
(b) phenyl, (substituted by one or two substituents independently selected
from:
-C\(_{1-6}\)alkyl, -OH, -halogen -CN, -CONHC\(_{1-6}\)alkyl, -CONHC\(_{3-7}\)cycloalkyl, -C\(_6\)
alkyleneSO\(_2\)NH\(_2\), -OC\(_1-3\)alkyleneCONH\(_2\), -C\(_{1-6}\)hydroxyalkyl, -NHSO\(_2\)C\(_1-
6\)alkyl, -NHCOC\(_1-3\)alkyleneNR\(^1\)R\(^2\), -X-phenyl, a 5 membered heteroaryl group
(optionally substituted by C\(_{1-3}\)alkyl), -Y-C\(_1-3\)alkylene NHCOC\(_1-6\)alkyl)

X is -OC\(_{1-3}\)alkylene-, -SO\(_2\)- or -NHCO-;

R\(^1\) and R\(^-\) together with the nitrogen to which they are joined form a
morpholine ring;

Y = a bond (i.e. is absent), or -CONH- or -NHCO-

with the proviso that R\(^1\) is not

\[ \text{Diagram} \]

In a further aspect, there is provided a compound of formula (I), or a salt, or solvate
thereof for use in therapy, in particular in the treatment of a disorder mediated by
inappropriate IKK1 activity.

In a further aspect of the invention there is provided a compound of formula (I) or a
salt, or solvate thereof for use in the treatment of cancer.

In a further aspect, there is provided a pharmaceutical composition comprising a
compound of formula (I) or a salt, or solvate thereof, and one or more of
pharmacologically acceptable carriers, diluents and excipients.
In a further aspect, there is provided a method of treating a disorder mediated by inappropriate IKK1 activity which method comprises administering a compound of formula (I) or a salt, or solvate thereof.

In a further aspect there is provided a method of treating cancer comprising administering a compound of formula (I) or a salt, or solvate thereof.

In a further aspect there is provided the use of a compound of formula (I), or a salt, or solvate thereof in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate IKK1 activity.

In a further aspect there is provided the use of a compound of formula (I) or a salt, or solvate thereof in the manufacture of a medicament for the treatment of cancer.

In a further aspect there is provided a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent.

In a further aspect there is provided a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, for use in therapy.

In a further aspect there is provided a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent, for use in treating a disorder mediated by inappropriate IKK1 activity.

In a further aspect there is provided a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent, for use in treating cancer.

In a further aspect there is provided the use of a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent, in the manufacture of a medicament for the treatment of a disorder mediated by inappropriate IKK1 activity.

In a further aspect there is provided the use of a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent, in the manufacture of a medicament for the treatment of cancer.
In a further aspect there is provided a method of treating a disorder mediated by inappropriate IKK1 activity comprising administering a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent.

In a further aspect there is provided a method of treating cancer comprising administering a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent.

In a further aspect there is provided a pharmaceutical composition comprising a combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent, particularly at least one anti-neoplastic agent and one or more of pharmaceutically acceptable carriers, diluents and excipients.

DETAILED DESCRIPTION OF THE INVENTION
As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein the term "alkyl" refers to a straight- or branched-chain hydrocarbon radical having the specified number of carbon atoms, so for example as used herein, the terms "C₁₃C₃ alkyl" and "C₁₆C₆ alkyl" refer to an alkyl group, as defined above, containing at least 1, and at most 3 or 6 carbon atoms respectively. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, n-hexyl and the like.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo(-Br), and iodo(-I).

As used herein, the term "haloalkyl" refers to an alkyl group as defined above containing the specified number of carbon atoms, substituted with at least one halo group, halo being as defined herein. Examples of such branched or straight chained haloalkyl groups useful in the present invention include, but are not limited to, methyl,
ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halos, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term “alkylene” refers to a straight or branched chain divalent hydrocarbon radical having the specified number of carbon atoms. Thus for example, the term “C₁,₃ alkylene” refers to an alkylene group, as defined above, which contains at least 1, and at most 3, carbon atoms respectively. Examples of “alkylene” as used herein include, but are not limited to, methylene, ethylene, n-propylene and n-butylene.

As used herein, the term “C₃-C₇ cycloalkyl” refers to a non-aromatic cyclic hydrocarbon ring having from 3 to 7 carbon atoms. Exemplary “C₃-C₇ cycloalkyl” groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term “alkoxy” refers to the group RₙO-, where Rₙ is alkyl as defined above and the terms “C₁,₆ alkoxy” refer to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms. Exemplary “C₁,₆ alkoxy” groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isoproxy, n-butoxy, and t-butoxy.

As used herein, the term “haloalkoxy” refers to the group RₙO-, where Rₙ is haloalkyl as defined above and the term “C₁,₆ haloalkoxy” refers to a haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1, and at most 6, carbon atoms. Exemplary C₁,₆ haloalkoxy groups useful in the present invention include, but is not limited to, trifluoromethoxy.

As used herein, the term “C₁,₆ hydroxyalkyl” refers to a straight or branched chain hydrocarbon containing at least 1, and at most 6 carbon atoms substituted with at least one hydroxy, hydroxy being as defined herein. Examples of branched or straight chained “C₁,₆ hydroxyalkyl” groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more hydroxyl groups.

As used herein, the term “heteroaryl” refers to a mono or bicyclic aromatic ring system, having the specified number of ring members. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen heteroatoms. Examples of “heteroaryl” groups used herein include but are not limited to furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl.
As used herein, the term “optionally” means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and event(s) that do not occur.

As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

The term “kinase inhibitor” is used to mean a compound which inhibits one or more kinase enzymes. In one embodiment the kinase is IKK1.

The term “kinase mediated disease” or “disorder associated with inappropriate kinase activity” is used to mean any disease state mediated or modulated by kinase mechanisms, in particular those mediated by IKK1.

As used herein, the term “substituted” refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

In one embodiment R₁ is:

![Chemical Structures](image-url)
In one embodiment, $R^1$ is phenyl, monosubstituted by SO$_2$NH$_2$, -CH$_2$SO$_2$NH$_2$, -NHCOC$_2$H$_5$ (wherein $R^1$ and $R^2$ together with the nitrogen to which they are joined form a morpholine ring), -C(CH$_3$)$_2$OH, -NHSO$_2$CH$_3$, CH$_2$NHSO$_2$C$_4$-alkyl, -NHCOphenyl, -NHCOC$_2$H$_5$, CONH($($CH$_2$)$_3$NHCOOC$_2$-alkyl, -CH$_3$, -OCH$_2$CONH$_2$, -OCH$_2$phenyl, -SO$_2$phenyl, -CONHCH$_3$.

In one embodiment, the phenyl is monosubstituted in the meta or para position.

In a further embodiment, $R^1$ is phenyl (disubstituted by OH and CN), phenyl

(3-disubstituted by Cl and F), phenyl (disubstituted by CH$_3$ and

phenyl (disubstituted by CH$_3$ and

While embodiments for each variable have generally been listed above separately for each variable, the invention includes those compounds in which several or each variable in formula (I) is selected from all embodiments for each variable. Therefore, this invention is intended to include all combinations of embodiments for each variable.

Specific examples of compounds of the present invention include:

5-(1H-indol-6-yi)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;
2-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
5-[4-(1-hydroxyethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
N-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
5-(1H-indol-4-yi)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;
N-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]benzamide;
5-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
1-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
N-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]-2-(4-morpholinyl)acetamide;
5-(3-cyano-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-cyclopropylbenzamide;
3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-cyclopropyl-4-methylbenzamide;
5-(2-methyl-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(1H-indazol-6-yi)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(1H-pyrazol-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
N-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
5-[2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-
carbonitrile;
5-[4-[[phenylmethyl]oxy]phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(2-methylphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzamide;
5-(6-fluoro-3-pyridinyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-[4-(phenylsulfonyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(3-chloro-5-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(3.5-dimethyl-4-isoxazolyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
2-[[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]oxy]acetamide;
1,1-dimethyl ethyl (3-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]amino)-3-
oxopropyl)carbamate;
1,1-dimethyl ethyl (3-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]amino)-3-
oxopropyl)carbamate;
1,1-dimethyl ethyl [[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methyl] carbanate;
1,1-dimethyl ethyl 5-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,3-dihydro-1H-indole-1-
carboxylate;
1,1-dimethyl ethyl [3-[[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]carbonyl]
amino)propyl]carbamate
and salts and solvates thereof.

Particular compounds of formula (I) are
5-(1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;
and salts and solvates thereof.

Certain of the compounds described herein may contain one or more chiral atoms, or
may otherwise be capable of existing as two enantiomers. The compounds of this
invention include mixtures of enantiomers as well as purified enantiomers or
enantiomerically enriched mixtures. Also included within the scope of the invention
are the individual isomers of the compounds represented by formula (I) above as well
as any wholly or partially equilibrated mixtures thereof. The present invention also
covers the individual isomers of the compounds represented by the formulas above
as mixtures with isomers thereof in which one or more chiral centers are inverted.
Also, it is understood that any tautomers and mixtures of tautomers of the
compounds of formula (I) are included within the scope of the compounds of formula
(I).
It is to be understood that reference to compounds of formula (I) above, following herein, refers to compounds within the scope of formula (I) as defined above unless specifically limited otherwise.

The present invention also covers salts of the compounds of formula (I). Typically, the salts of the present invention are pharmaceutically acceptable salts. For a review on suitable salts, see Berge et al. J. Pharm. Sci. 1977, 66, 1-19. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, malaleic, formic, acetic, propionic, furmaric, citric, tartaric, lactic, benzoic, salicylic, glutamaic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable base addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) or hexanoate salt.

A pharmaceutically acceptable base addition salt can be formed by a reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration.

Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the compound of formula (I).

Other non-pharmaceutically acceptable salts, e.g. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I). Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by
filtration or may be recovered by evaporation of the solvent. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will be readily understood that they are each preferably provided in substantially pure form, for example, at least 60% pure, more suitably at least 75% pure and preferably at least 85% pure, especially at least 98% pure (% in a weight for weight basis).

While it is possible that, for use in therapy, a compound of formula (I), as well as salts and solvates thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provide a pharmaceutical composition comprising a compound of the formula (I) or a salt or solvate thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula (I) and salts and solvates thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of the formula (I), and/or salts and solvates thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).
Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an alginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, academia mucilage or solutions of cellullosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and
compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

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

The compounds of formula (I), and salts and solvates thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of formula (I) and salts, and solvates thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polylactals, polydiacydropyrans, polycyanoacrylates and cross-linked or amphiphatic block copolymers of hydrogels.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).
Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or as enemas.

Dosage forms for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

Pharmaceutical compositions adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

The compound of formula (I) may be formulated as a fluid formulation for delivery from a fluid dispenser, for example a fluid dispenser having a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity. A fluid dispenser of the aforementioned type is described and illustrated in WO05/044354, the entire content of which is hereby incorporated herein by reference. The dispenser has a housing which houses a fluid discharge device
having a compression pump mounted on a container for containing a fluid formulation. The housing has at least one finger-operable side lever which is movable inwardly with respect to the housing to cam the container upwardly in the housing to cause the pump to compress and pump a metered dose of the formulation out of a pump stem through a nasal nozzle of the housing. In one embodiment, the fluid dispenser is of the general type illustrated in Figures 30-40 of WO05/044354.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound of formula (I) (and salts and solvates) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound (or salt or solvate) is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol compositions, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol compositions can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) and salts and solvates thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, cellulose octaacetate and/or metals salts of stearic acid such as magnesium or
calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanneplein 25, 8017 JD Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of e.g. the dry powder composition can be administered by inhalation via the device such as the DISKUS™ device, marketed by GlaxoSmithKline. The DISKUS™ inhalation device is for example described in GB 2242134 A, and in such a device at least one container for the pharmaceutical composition in powder form (the container or containers preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: a means of defining an opening station for the said container or containers; a means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray compositions.

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

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of composition in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the composition, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of formula (I) for the treatment of diseases associated with inappropriate kinase activity, will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The compounds of formula (I) and salts and solvates thereof, are believed to have utility in disorders associated with inappropriate kinase activity as a result of inhibition of protein kinase activity.

The present invention thus also provides a compound of formula (I) or a salt or solvate thereof, for use in therapy, and particularly in the treatment of disorders associated with inappropriate kinase activity, in particular, inappropriate IKK1 activity.

The inappropriate kinase activity referred to herein is any kinase activity that deviates from the normal kinase activity expected in a particular mammalian subject. Inappropriate kinase activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of kinase activity. Such inappropriate activity may result then, for example, from over expression or mutation of the protein kinase leading to inappropriate or uncontrolled activation.
The present invention is directed to methods of regulating, modulating, or inhibiting kinase for the prevention and/or treatment of disorders related to unregulated kinase activity. In particular, the compounds of the present invention can also be used in the treatment of disorders associated with inappropriate kinase activity, including cancer.

Disorders associated with inappropriate IKK1 activity include autoimmune diseases, inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease); osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, alkylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer (e.g. cancers which when treated with inhibitors of IKK function will promote cell death, including neoplastic diseases such as solid tumours, skin cancer, melanoma, lymphoma and diseases in which angiogenesis play a role), cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiectasia.

A further aspect of the invention provides a method of treatment of a disorder associated with inappropriate kinase activity, comprising administering a compound of formula (I) or a salt, or solvate thereof. In one embodiment, the kinase is IKK1. In one embodiment the disorder is cancer (e.g. cancers which when treated with inhibitors of IKK function will promote cell death, including neoplastic diseases such as solid tumours, skin cancer, melanoma, lymphoma and diseases in which angiogenesis play a role).

A further aspect of the present invention provides the use of a compound of formula (I), or a salt or solvate thereof in the manufacture of a medicament for the treatment of a disorder associated with inappropriate kinase activity. In one embodiment the kinase is IKK1. In one embodiment the disorder is cancer (e.g. cancers which when treated with inhibitors of IKK function will promote cell death, including neoplastic diseases such as solid tumours, skin cancer, melanoma, lymphoma and diseases in which angiogenesis play a role).

The compound of formula (I) for use in the instant invention and their salts and solvates thereof may be used alone or in combination with one or more other therapeutic agents. The invention thus provides in a further aspect a combination comprising a compound of formula (I) or a salt or solvate thereof with a further therapeutic agent or agents, compositions and medicaments comprising the combination and use of the combination, compositions and medicaments in therapy,
in particular in the treatment of diseases associated with inappropriate kinase activity, in particular IKK1.

In particular, where the disorder is cancer, combination with at least one other anti-cancer therapy is envisaged. Combination therapy is rapidly becoming the norm in cancer treatment, rather than the exception. Oncologists are continually looking for anti-neoplastic compounds which when utilized in combination provides a more effective and/or enhanced treatment to the individual suffering the effects of cancer. Typically, successful combination therapy provides improved and even synergistic effect over monotherapy.

In particular, in anti-cancer therapy, combination with other anti-neoplastic agent (including chemotherapeutic, hormonal or antibody agents) is envisaged as well as combination with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a salt or solvate thereof, and the use of at least one other cancer treatment method. Preferably, combination therapies according to the present invention comprise the administration of at least one compound of formula (I) or a salt or solvate thereof, and at least one other pharmaceutically active agent, preferably an anti-neoplastic agent. The compound(s) of formula (I)) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order (including administration on different days according to the therapy regimen) and by any convenient route. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

In one embodiment, the further anti-cancer therapy is at least one additional anti-neoplastic agent.

Any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be utilized in the combination. Typical anti-neoplastic agents useful include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signalling inhibitors.

Anti-microtubule or anti-mitotic agents:
Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti-cancer agents that operate at the G2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.


Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel q.v., prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.
Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin’s Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin’s and non-Hodgkin’s malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosuppression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

**Platinum coordination complexes:**
Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, oxaliplatin, cisplatin and carboplatin.

Cisplatin, cis-diaminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma.

**Alkylating agents:**
Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not
limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin’s disease.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin’s disease, and non-Hodgkin’s lymphomas.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin’s Disease.

**Antibiotic anti-neoplastic**: Antibiotic anti-neoplastic are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthracyclins such as daunorubicin and doxorubicin; and bleomycins.
Dactinomycin, also known as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm’s tumor and rhabdomyosarcoma.

5 Daunorubicin, (8S-cis)-8-acetyl-10-[(3-amino-2,3,6-trIDEOXY-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihYDROXY-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi’s sarcoma.

10 Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trIDEOXY-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihYDROXY-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of Streptomyces verticillus, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas.

Topoisomerase II inhibitors:

25 Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

35 Etoposide, 4′-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers.

Teniposide, 4′-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in
combination with other chemotherapy agents in the treatment of acute leukemia in children.

**Antimetabolite neoplastic agents:**

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimitabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mercaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Other fluoropyrimidine analogs include 5-fluorodeoxyuridine (fluorouridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amin o-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2′,2′-difluorodeoxycytidine (gemcitabine).

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®.Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2′-deoxy-2′, 2′-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at
S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer.

Methotrexate, N-[4[[2,4-diamino-6-pteridinyl] methyl][methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dehydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin’s lymphoma, and carcinomas of the breast, head, neck, ovary and bladder.

Topoisomerase I inhibitors:
Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-{(4-piperidinopiperidino) carbonyloxy}-1H-pyran[3‘,4‘,6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®. Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irinotecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyran[3‘,4‘,6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer.

Hormones and hormonal analogues:
Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in
cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrozole, vorozole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagonists such as goserelin acetate and luponide.

**Signal transduction pathway inhibitors:**

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal transduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, ret, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.


Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku are also useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), Current Opinion in Immunology. 8

Also useful in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras, thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 – 102; and BioChim. Biophys. Acta, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kniases, Breast cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

**Anti-angiogenic agents:**

(i) Anti-angiogenic agents including non-receptor-kinase angiogenesis inhibitors may also be useful. Anti-angiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function, endostatin and angiostatin);

**Immunotherapeutic agents:**

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). Immunotherapy approaches, including for example ex-
vivo and in-vivo approaches to increase the immunogenecity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

**Proapoptotic agents:**

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention.

**Cell cycle signalling inhibitors**

Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent which is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

In a further embodiment, the at least one anti-neoplastic agent agent is a diterpenoid.

In a further embodiment, the at least one anti-neoplastic agent is a vinca alkaloid.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent, which is a platinum coordination complex.
In a further embodiment, the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

In a further embodiment, the at least one anti-neoplastic agent is carboplatin.

In a further embodiment, the at least one anti-neoplastic agent is vinorelbine.

In a further embodiment, the at least one anti-neoplastic agent is paclitaxel.

In one embodiment, the combination of the present invention comprises a compound of formula I and salts or solvates thereof and at least one anti-neoplastic agent which is a signal transduction pathway inhibitor.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase VEGFR2, TIE2, PDGFR, BTK, erbB2, EGFr, IGF-1, TrkA, TrkB, TrkC, or c-fms.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase Rafk, akt, or PKC-zeta.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a non-receptor tyrosine kinase selected from the src family of kinases.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of c-src.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

In a further embodiment the signal transduction pathway inhibitor is a dual EGFr/erbB2 inhibitor, for example N-[3-Chloro-4-[(3-fluorobenzyl) oxy]phenyl]-6-[5-[[2-(methanesulphonyl) ethyl]amino]methyl]-2-furyl]-4-quinazolinamine (structure below):
In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent which is a cell cycle signaling inhibitor.

In further embodiment, cell cycle signaling inhibitor is an inhibitor of CDK2, CDK4 or CDK6.

The compounds of formula (I), or salts and solvates thereof and the at least one anti-neoplastic agent may be employed in combination concomitantly or sequentially in any therapeutically appropriate combination. The combination may be employed in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both compounds or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

The combination of the present invention may also include at least one additional cancer treatment therapy in combination concomitantly or sequentially in any therapeutically appropriate combination with the combinations of the present invention. The additional cancer treatment therapy may include radiation therapy, surgical therapy and/or at least one additional chemotherapeutic therapy including administration of at least one additional anti-neoplastic agent.

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

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

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

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

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I). Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

Compounds of Formula I can be prepared according to the synthetic sequences illustrated in the scheme below and further detailed in the Examples section following.
React Intermediate 1 and an appropriate R¹-boronic acid or ester with a Palladium catalyst [eg dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) (PdCl₂(dpff)) in the presence of a base (eg aqueous sodium carbonate); solvent: 1,4-dioxane - water (1:1) at elevated temperature (eg 140°C); under these conditions the phenylsulphonyl group is cleaved to give compounds (I).

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

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

- g (grams);
- mg (milligrams);
- L (liters);
- mL (milliliters);
- μL (microliters);
- M (molar);
- mM (millimolar);
- MHz (megahertz);
- Hz (Hertz);
- mol (moles);
- mmol (millimoles);
- rt (room temperature);
- min (minutes);
- h (hours);
- DMSO (dimethylsulfoxide).

¹H NMR spectra were recorded on a Bruker AVANCE-400, or a Bruker DPX 400. Chemical shifts are expressed in parts per million (ppm, δ units). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).
LCMS were recorded on Waters ZQ mass spectrometers, typically under the following conditions: Column: 3.3cm x 4.6mm ID, 3µm ABZ+PLUS, Flow Rate: 3ml/min, Injection Volume: 5μl, room temperature, UV Detection Range: 215 to 330nm, Solvent A: 0.1% Formic Acid + 10mM aqueous ammonium acetate, Solvent B: MeCN: Water 95:5 +0.05% Formic Acid, using the solvent gradient tabulated below:

<table>
<thead>
<tr>
<th>Gradient</th>
<th>Time (min)</th>
<th>A%</th>
<th>B%</th>
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<td>0.70</td>
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<td>100</td>
</tr>
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<td></td>
<td>4.80</td>
<td>100</td>
<td>0</td>
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</table>

Preparative mass-directed HPLC refers to methods where the material was purified by High Performance Liquid Chromatography, typically using a Supelco LCABZ++ column whose dimensions are 30mm internal diameter by 150mm in length, with a stationary phase particle size of 12µm. Solvent A: Water + 0.1% Formic Acid, Solvent B: MeCN: Water 95:5 +0.05% Formic Acid. The purification was performed over a 10 minute solvent gradient (typically 0-30%, 5-30%, 15-55%, 30-80%, or 50-90% solvent B in A) at a flow-rate of 40 mL / minute. Mass detection and collection was performed using a MicroMass ZQ Mass Spectrometer.

Microwave reactions were performed using a microwave reactor such as a Personal Chemistry SmithCreator or SmithSynthesizer, or a Biotage Initiator 60.

**Compounds**

**Compound 1: 5-(1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

5-Bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (Intermediate 1, for a synthesis see Graczyk, P.; Palmer, V.; Khan, A. Int. Patent Appl. WO 2004/101565 A2, 1.88g, 5.19 mmol) was dissolved in 1,4-dioxane (47 mL) to give a 0.11 M stock solution.
A mixture of 5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (Intermediate 1, 0.98 mL of a 0.11 M stock solution, 0.11 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (40 mg, 0.165 mmol), PdCl$_2$(dpf) (9mg, 0.011 mmol) and Na$_2$CO$_3$ (0.40 mL of a 2M aqueous solution) in water (1mL) and 1,4-dioxane (1mL) was heated at 140°C for 15 minutes in a sealed vial in a microwave reactor. The reaction mixture was filtered through a 1g silica plug and washed several times with methanol. The resulting mixture was concentrated under vacuum, and the residue dissolved with a solution of DMSO:Methanol (1:1, 1 mL) and filtered, before purification by preparative mass-directed HPLC to give the title compound as a solid (8.8 mg, 31%); $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 6.45 - 6.50 (m, 1 H) 7.37 - 7.43 (m, 2 H) 7.66 (d, 1 H) 7.74 (br. s, 1 H) 8.28 (d, 1 H) 8.47 (d, 1 H) 8.72 (d, 1 H) 11.20 (br. s, 1 H) 12.86 (br. s, 1 H); m/z: 259.08 [M+H]$^+$. 

**Compound 2: 4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide**

![Chemical Structure](image)

A mixture of 5-bromo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (Intermediate 1, 0.98 mL of a 0.11 M stock solution, 0.11 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (47 mg, 0.165 mmol), PdCl$_2$(dpf) (9mg, 0.011 mmol) and Na$_2$CO$_3$ (0.40 mL of a 2M aqueous solution) in water (1mL) and 1,4-dioxane (1mL) was heated at 140°C for 15 minutes in a sealed vial in a microwave reactor. The reaction mixture was filtered through a 1g silica plug and washed several times with methanol. The resulting mixture was concentrated under vacuum, and the residue dissolved with a solution of DMSO:Methanol (1:1, 1 mL) and filtered, before purification by preparative mass-directed HPLC to give the title compound as a solid (11mg, 22%); $^1$H NMR (400 MHz, DMSO-d$_6$) δ ppm 7.44 (br. s, 2 H) 7.92 (d, 2 H) 8.03 (d, 2 H) 8.46 (d, 1 H) 8.53 (s, 1 H) 8.78 (d, 1 H) 12.81 (br. s, 1 H); m/z: 299.00 [M+H]$^+$. 

**Compound 3: 1-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide**
Compound 3 was synthesized using a similar procedure to that described for compound 1 using 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide (49 mg, 0.165 mmol). Compound 3 was obtained as a solid (12.7 mg, 37%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 4.38 (s, 2 H) 6.91 (br. s, 2 H) 7.41 (d, 1 H) 7.46 - 7.55 (m, 1 H) 7.72 - 7.86 (m, 2 H) 8.35 (d, 1 H) 8.48 - 8.53 (m, 1 H) 8.72 (d, 1 H) 12.75 (br. s, 1 H); m/z: 313.03 [M+H]+.

**Compound 4: 5-[4-(1-hydroxyethyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

Compound 4 was synthesized using a similar procedure to that described for compound 1 using [4-(1-hydroxyethyl)phenyl]boronic acid (28 mg, 0.165 mmol). Compound 4 was obtained as a solid (12 mg, 41%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 1.36 (d, 3 H) 4.72 - 4.84 (m, 1 H) 5.22 (d, 1 H) 7.46 (d, 2 H) 7.74 (d, 2 H) 8.31 (d, 1 H) 8.48 (s, 1 H) 8.70 (d, 1 H) 12.88 (br. s, 1 H); m/z: 264.07 [M+H]+.

**Compound 5: N-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide**

Compound 5 was synthesized using a similar procedure to that described for compound 1 using {4-[(methylsulfonyl)amino]phenyl}boronic acid (36 mg, 0.165 mmol). Compound 5 was obtained as a solid (16.3 mg, 48%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 3.04 (s, 3 H) 7.33 (d, 2 H) 7.78 (d, 2 H) 8.30 (d, 1 H) 8.47 (s, 1 H) 8.69 (d, 1 H); m/z: 313.04 [M+H]+.
Compound 6: 5-(1H-indol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

Compound 6 was synthesized using a similar procedure to that described for compound 1 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (40 mg, 0.165 mmol). Compound 6 was obtained as a solid (14.1 mg, 50%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 6.57 (br. s, 1 H) 7.09 - 7.30 (m, 2 H) 7.35 - 7.57 (m, 2 H) 8.25 (d, 1 H) 8.50 (s, 1 H) 8.70 (d, 1 H) 11.34 (br. s, 1 H) 12.92 (br. s, 1 H); m/z: 259.05 [M+H]+.

Compound 7: 3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide

Compound 7 was synthesized using a similar procedure to that described for compound 1 using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (47 mg, 0.165 mmol). Compound 7 was obtained as a solid (9 mg, 27%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 7.43 (br. s, 2 H) 7.70 (t, 1 H) 7.84 (d, 1 H) 8.07 (d, 1 H) 8.24 (t, 1 H) 8.41 (d, 1 H) 8.53 (s, 1 H) 8.77 (d, 1 H) 12.96 (br. s, 1 H); m/z: 298.9 [M+H]+.

Compound 8: N-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]benzamide

Compound 8 was synthesized using a similar procedure to that described for compound 1 using $N$-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
yl)phenyl]benzamide (54 mg, 0.165 mmol). Compound 8 was obtained as a solid (2.4 mg, 7 %); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 7.53 - 7.64 (m, 3 H) 7.82 (d, 2 H) 7.94 (d, 2 H) 7.97 - 8.01 (m, 2 H) 8.34 (d, 1 H) 8.48 (d, 1 H) 8.74 (d, 1 H) 10.38 (s, 1 H) 12.90 (br. s, 1 H); m/z: 339.32 [M+H]+.

**Compound 9: 5-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

\[ \text{\includegraphics[width=0.5\textwidth]{compound9.png}} \]

Compound 9 was synthesized using a similar procedure to that described for compound 1 using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (40 mg, 0.165 mmol). Compound 9 was obtained as a solid (5.9 mg, 21 %); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 7.66 (d, 1 H) 7.78 (dd, 1 H) 8.08 - 8.21 (m, 2 H) 8.34 (d, 1 H) 8.48 (d, 1 H) 8.75 (d, 1 H) 12.90 (s, 1 H); m/z: 260.06 [M+H]+.

**Compound 10: 1-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide**

\[ \text{\includegraphics[width=0.5\textwidth]{compound10.png}} \]

Compound 10 was synthesized using a similar procedure to that described for compound 1 using 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide (49 mg, 0.165 mmol). Compound 10 was obtained as a solid (8.4 mg, 24 %); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 4.34 (s, 2 H) 6.89 (s, 2 H) 7.50 (d, 2 H) 7.83 (d, 2 H) 8.35 (d, 1 H) 8.50 (s, 1 H) 8.73 (d, 1 H) 12.92 (br. s, 1 H); m/z: 313.04 [M+H]+.

**Compound 11: N-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]-2-(4-morpholiny)acetamide**
Compound 11 was synthesized using a similar procedure to that described for compound 1 using 2-(4-morpholiny)-N-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolanylphenyl)acetamide (57 mg, 0.165 mmol). Compound 11 was obtained as a solid (13.1 mg, 33 %); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 2.65 (br. s, 4 H) 3.31 (br. s, 2 H) 3.64 - 3.74 (m, 4 H) 7.39 - 7.55 (m, 2 H) 7.73 (d, 1 H) 7.95 - 8.05 (m, 1 H) 8.27 (d, 1 H) 8.50 (s, 1 H) 8.69 (d, 1 H) 9.96 (br. s, 1 H) 12.94 (br. s, 1 H); m/z: 362.08 [M+H]^+.

**Compound 12: 5-(3-cyano-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

Compound 12 was synthesized using a similar procedure to that described for compound 1 using 2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (41 mg, 0.165 mmol). Compound 12 was obtained as a solid (8.4 mg, 29 %); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 7.12 (d, 1 H) 7.95 (d, 1 H) 8.12 (s, 1 H) 8.37 (s, 1 H) 8.47 (s, 1 H) 8.69 (s, 1 H) 11.26 (br. s, 1 H) 12.88 (br. s, 1 H); m/z: 258.96 [M-H]^-.  

**Compound 13: 3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-cyclopropylbenzamide**

Compound 13 was synthesized using a similar procedure to that described for compound 1 using {3-[[cyclopropylamino]carbonyl]phenyl}boronic acid (34 mg, 0.165...
mmol). Compound 13 was obtained as a solid (11 mg, 34 %); $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.55 - 0.65 (m, 2 H) 0.72 - 0.79 (m, 2 H) 2.81 - 2.93 (m, 1 H) 7.54 - 7.63 (m, 1 H) 7.85 (d, 1 H) 7.95 (d, 1 H) 8.18 (s, 1 H) 8.43 (d, 1 H) 8.51 (s, 1 H) 8.60 (d, 1 H) 8.78 (d, 1 H) 12.96 (s, 1 H); m/z: 303.05 [M+H]+.

**Compound 14: 3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-cyclopropyl-4-methylbenzamide**

![Compound 14](image)

Compound 14 was synthesized using a similar procedure to that described for compound 1 using N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (50 mg, 0.165 mmol). Compound 14 was obtained as a solid (16 mg, 46 %); $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.52 - 0.60 (m, 2 H) 0.65 - 0.73 (m, 2 H) 2.30 (s, 3 H) 2.78 - 2.90 (m, 1 H) 7.42 (d, 1 H) 7.74 - 7.82 (m, 2 H) 8.10 (d, 1 H) 8.41 (d, 1 H) 8.44 (d, 1 H) 8.51 (s, 1 H) 12.93 (br. s, 1 H); m/z: 317.09 [M+H]+.

**Compound 15: 5-(2-methyl-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

![Compound 15](image)

Compound 15 was synthesized using a similar procedure to that described for compound 1 using 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazole (46 mg, 0.165 mmol). Compound 15 was obtained as a solid (6.1 mg, 19 %); $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.84 (s, 3 H) 7.84 (dd, 1 H) 8.15 (d, 1 H) 8.32 (d, 1 H) 8.44 (d, 1 H) 8.51 (s, 1 H) 8.80 (d, 1 H) 12.95 (br. s, 1 H); m/z: 291.0 [M+H]+.

**Compound 16: 5-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**
Compound 16 was synthesized using a similar procedure to that described for compound 1 using 1H-indazol-6-ylboronic acid (27 mg, 0.165 mmol). Compound 16 was obtained as a solid (6.7 mg, 24 %); 1H NMR (400 MHz, DMSO-d6) δ ppm 7.54 (d, 1 H) 7.84 - 7.92 (m, 2 H) 8.12 (s, 1 H) 8.40 (d, 1 H) 8.50 (s, 1 H) 8.77 (d, 1 H) 13.20 (br. s, 1 H); m/z: 260.06 [M+H]+.

**Compound 17: 5-(1H-pyrazol-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

Compound 17 was synthesized using a similar procedure to that described for compound 1 using 1H-pyrazol-3-ylboronic acid (19 mg, 0.165 mmol). Compound 17 was obtained as a solid (5.0 mg, 22 %); 1H NMR (400 MHz, DMSO-d6) δ ppm 6.92 (br. s, 1 H) 7.83 (br. s, 1 H) 8.45 (br. s, 2 H) 8.91 (br. s, 1 H) 13.00 (br. s, 1 H); m/z: 210.01 [M+H]+.

**Compound 18: 5-(1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile**

Compound 18 was synthesized using a similar procedure to that described for compound 1 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (32 mg, 0.165 mmol). Compound 18 was obtained as a solid (6.1 mg, 27 %); 1H NMR (400 MHz, DMSO-d6) δ ppm 8.12 (br. s, 1 H) 8.31 (d, 1 H), 8.41 (s, 1 H) 8.72 (d, 1 H) 12.68 (br. s, 1 H) 13.01 (br. s, 1 H); m/z: 210.07 [M+H]+.

**Compound 19: N-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide**
Compound 19 was synthesized using a similar procedure to that described for compound 1 using {3-[(methylsulfonyl)amino]phenyl}boronic acid (36 mg, 0.165 mmol). Compound 19 was obtained as a solid (12.7 mg, 37%); $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 3.06 (s, 3 H) 7.26 (dd, 1 H) 7.47 (t, 1 H) 7.50 - 7.58 (m, 2 H) 8.27 (d, 1 H) 8.50 (s, 1 H) 8.66 (d, 1 H); m/z: 313.02 [M+H]+.

The following compounds of formula (I) were prepared by a similar procedure to that described for Compound 1 using Intermediate 1 and the appropriate boronic acid or ester.

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**BIOLOGICAL DATA**

**IKK1 Time-Resolved Fluorescence Resonance Energy Transfer Assay**

Recombinant human IKK1 (residues 1-785) was expressed in baculovirus as a C-terminal 6HIS-tagged fusion protein, and its activity was assessed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Briefly, IKK1 (typically 5-10 nM final) diluted in assay buffer (50 mM HEPES, 10 mM MgCl₂, 1 mM CHAPS pH 7.4 with 1 mM DTT and 0.01% w/v BSA) was added to wells containing
various concentrations of compound or DMSO vehicle (less than 5% final). The reaction was initiated by the addition of GST-IκBα substrate (25 nM final)/ATP (1 μM final), in a total volume of 6 μl. The reaction was incubated for 30 minutes at room temperature, then terminated by the addition of stop reagent (3 μl) containing 50 mM EDTA and detection reagents in buffer (100 mM HEPES pH 7.4, 150 mM NaCl and 0.1% w/v BSA). Detection reagents comprise antiphosphoserine-IκBα-32/36 monoclonal antibody 12C2 (Cell Signalling Technology, Beverly Massachusetts, USA) labelled with W-1024 europium chelate (Wallac OY, Turku, Finland) and an allophycocyanin-labelled anti-GST antibody (Prozyme, San Leandro, California, USA). The reaction mixture (9 μl total volume) was further incubated for at least 60 minutes at room temperature. The degree of phosphorylation of GST-IκBα was measured using a suitable time-resolved fluorimeter such as Packard Discovery (Perkin-Elmer Life Sciences, Pangbourne, Berkshire, UK), Wallac Viewlux (Perkin-Elmer Life Sciences, Pangbourne, Berkshire, UK) or Rubystar (BMG, Aylesbury, Buckinghamshire, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

IKK2 Time-Resolved Fluorescence Resonance Energy Transfer Assay
Recombinant human IKK2 (residues 1-737) is expressed in baculovirus as a C-terminal GST-tagged fusion protein, and its activity is assessed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Briefly, IKK2 (typically 2-5 nM final) diluted in assay buffer (50 mM HEPES, 10 mM MgCl₂, 1 mM CHAPS pH 7.4 with 1 mM DTT and 0.01% w/v BSA) is added to wells containing various concentrations of compound or DMSO vehicle (less than 5% final). The reaction is initiated by the addition of GST-IκBα substrate (25 nM final)/ATP (1 μM final), in a total volume of 6 μl. The reaction is incubated for 30 minutes at room temperature, then terminated by the addition of stop reagent (3 μl) containing 50 mM EDTA and detection reagents in buffer (100 mM HEPES pH 7.4, 150 mM NaCl and 0.1% w/v BSA). Detection reagents comprise antiphosphoserine-IκBα-32/36 monoclonal antibody 12C2 (Cell Signalling Technology, Beverly Massachusetts, USA) labelled with W-1024 europium chelate (Wallac OY, Turku, Finland) and an allophycocyanin-labelled anti-GST antibody (Prozyme, San Leandro, California, USA). The reaction mixture (9 μl total volume) is further incubated for at least 60 minutes at room temperature. The degree of phosphorylation of GST-IκBα is measured using a suitable time-resolved fluorimeter such as Packard Discovery (Perkin-Elmer Life Sciences, Pangbourne, Berkshire, UK), Wallac Viewlux (Perkin-Elmer Life Sciences, Pangbourne, Berkshire, UK) or Rubystar (BMG, Aylesbury, Buckinghamshire, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

The activity of the compound of the invention as a JNK1 inhibitor is determined by the following in vitro assay:
Fluorescence anisotropy kinase binding assay

The kinase enzyme, fluorescent ligand (FL) and a variable concentration of test compound are incubated together to reach thermodynamic equilibrium under conditions such that in the absence of test compound the fluorescent ligand is significantly (>50%) enzyme bound and in the presence of a sufficient concentration (>10 x K_i) of a potent inhibitor the anisotropy of the unbound fluorescent ligand is measurably different from the bound value.

The concentration of kinase enzyme is preferably 2 x K_i. The concentration of fluorescent ligand required depends on the instrumentation used, and the fluorescent and physicochemical properties. The concentration used must be lower than the concentration of kinase enzyme, and preferably less than half the kinase enzyme concentration.

Recombinant full length human JNK1α1 L26318 (Genbank) is expressed in baculovirus as a N-terminal His (6)-tagged fusion protein. This enzyme (JNK1) was activated in 50 mM Tris/HCl pH 7.5, 0.1 mM EGTA, 0.1 % beta-mercaptoethanol, 0.1 mM sodium vanadate, 10 mM magnesium acetate, 0.1 mM ATP with 100 nM active MKK4 and MKK7beta at 30 degrees Celsius for 30 minutes. Following activation, the JNK1 is purified by, Ni-NTA agarose chromatography. The JNK1 is then dialyzed into storage buffer ( 50 mM Tris/HCl pH 7.5, 270 mM Sucrose, 150 mM NaCl, 0.1 mM EGTA, 0.1 % beta-mercaptoethanol, 0.03 % Brij-35, 1 mM benzamidine, 0.2 mM PMSF), snap frozen in liquid nitrogen and stored at -70 degrees Celsius.

A typical protocol is:

All components are dissolved in buffer of composition 50 mM HEPES, pH 7.5, 1 mM CHAPS, 1 mM DTT, 10 mM MgCl_2 with final concentrations of 4.25 nM JNK1α1 (26.56 nM of 16% competent enzyme) and 2 nM fluorescent ligand (FL):

(see below for details of its synthesis). This reaction mixture is added to wells containing various concentrations of test compound (0.28 nM - 16.6 μM final) or DMSO vehicle (< 3% final) in black 384 well microtitre plates and equilibrated for 30-
300 minutes at room temperature. Fluorescence anisotropy is read in Molecular Devices Acquest (excitation 530 nm/emission 580 nm).

Definitions:  
$K_i$ = dissociation constant for inhibitor binding  
$K_r$ = dissociation constant for fluorescent ligand binding

**Intermediate 1: Synthesis of Fluorescent ligand - 2-{[4-(Aminomethyl)phenyl]amino}-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one**

A mixture of 6-(2,6-dichlorophenyl)-8-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Klutchko et al, J. Med. Chem., 1998, 41, 3276) (247 mg, 0.64 mmol), N-[(4-aminophenyl)methyl]acetamide (317 mg, 1.92 mmol) and HCl in dioxane (4M, 0.16 mL, 0.64 mmol) in ethylene glycol (5 mL) is stirred at rt for 3 h, and then at 100°C for 21.5 h. After cooling to rt, the mixture is added to water (20 mL), and the resulting light-yellow solid (150 mg) isolated by filtration and washed with water (5 mL).

The light-yellow solid is partitioned into three equal portions, and to each is added H$_2$O (2 mL) and concentrated HCl (37% aq, 0.2 mL). Each portion is heated in a microwave reactor for 15 mins at 150°C, followed by the addition of DMSO (1 mL to each portion), and further heating in a microwave reactor for 15 min at 150°C. The three portions are combined and concentrated in vacuo. The crude material is dissolved in DMSO / MeOH (1:1), and purified by preparative HPLC to yield the title compound.

**14-{[4-{[6-(2,6-Dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino}phenyl]methyl}[amino]-2-oxoethyl]-16,16,18,18-tetramethyl-6,7,7a,8a,9,10,16,18-octahydrobenzo[2",3""]indolizino[8",7":5',6']pyrano[3',2':3,4]pyrido[1,2-a]indol-5-ium-2-sulfonate**
2-[[4-(Aminomethyl)phenyl]amino]-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]
pyrimidin-7(8H)-one (3.3 mg, 7.74 umol) is dissolved in dimethylformamide (250 ul),
diluted with water (250 ul) and solid sodium hydrogen carbonate added to saturation.
Cy3B-hydroxysuccinimide ester (Amersham Biosciences, 5 mg, 6.5 umol) is added
as a solution in dimethylformamide (400ul total) and the mixture agitated gently for 2
h, after which time analysis by analytical HPLC (Waters Spherisorb ODS2, 30 to 60%
B/1h, where A = 0.1% Trifluoroacetic acid in water and B= 0.1% Trifluoroacetic acid
in 90% acetonitrile/10% water) showed complete removal of the active ester. The
reaction mixture is evaporated to dryness in vacuo, the residue re-dissolved in acetic
acid/acetonitrile/water (1/5/4, 2 ml) and filtered. The solution is purified in two
portions by preparative reverse phase HPLC (Phenomenex Jupiter C18, 10u, 300A,
250 x 21.2mm) using a 25 to 65% B gradient over 1h and detection at 214nm.
Fractions containing the product are analysed by ES LC/MS and reverse phase
HPLC, pooled and then evaporated to dryness.

The compounds of the P13K may be tested to determine their inhibitory activity at
P13Ka, P13Kδ, p13Kβ and P13Kγ according to the following.

For all P13K isoforms:

1. Cloning, expression, purification, and characterization of the human Class 1a
phosphoinositide 3-kinase isoforms: Meier, T.I., Cook, J.A.; Thomas, J.E.;
Radding, J.A.; Horn, C.; Lingaraj, T.; Smith, M.C. Protein Expr. Purif., 2004,
35(2), 218.

2. Competitive fluorescence polarization assays for the detection of
phosphoinositide kinase and phosphatase activity. Drees, B.E.; Weipert, A.;
Hudson, H.; Ferguson, C.G.; Chakravarty, L.; Prestwich, G.D. Comb. Chem.
Using assays as above or similar thereto the following results are obtained:

**Table 1: IKK-1 data.**

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For those compounds of the invention which were tested in assays similar to those described above, the activities below were

IKK-2: IC50 range: 355 nM to > 25 uM
JNK-1: IC50 range: 19 nM to 2.69 uM
P13Kgamma: IC50 range: 102 nM to > 10 uM
CLAIMS

1. A compound of formula (I) or a salt or solvate thereof:

\[
\text{R}^1
\]

wherein

10 R\(^1\) is
(a) a heteroaryl group selected from:
indole, indazole, pyridine, pyrazole, benzothiazole, indolene, isoxazole,
oxadiazole (each of which may be substituted one or more times with one or
more substituents independently selected from -C\(_{1-3}\)-alkyl, -COOC\(_{1-6}\)-alkyl and
halogen)
or
(b) phenyl, (substituted by one or two substituents independently selected from:
-C\(_{1-6}\)-alkyl, -OH, -halogen -CN, -CONHC\(_{1-6}\)-alkyl, -CONHC\(_{3-7}\)-cycloalkyl, -C\(_{0-3}\)-
alkyleneSO\(_2\)NH\(_2\), -OC\(_{1-3}\)-alkyleneCONH\(_2\), -C\(_{1-6}\)-hydroxyalkyl, -NH\(_2\)SO\(_2\)C\(_{1-6}\)-alkyl,
-NHCOC\(_{1-3}\)-alkyleneNR\(^1\)R\(^2\), -X-phenyl, a 5 membered heteraryl group
(optionally substituted by C\(_{1-3}\)-alkyl), -Y-C\(_{1-3}\)-alkylene NHCOOC\(_{1-6}\)-alkyl)

20 X is -OC\(_{1-3}\)-alkylene-, -SO\(_2\)- or -NHCO-;

R\(^1\) and R\(^1\) together with the nitrogen to which they are joined form a
morpholine ring;

Y = a bond (i.e. is absent), or -CONH- or -NHCO-

25 with the proviso that R\(^1\) is not

\[
\text{CONH-}
\]

2. A compound according to claim 1 wherein R\(^1\) is
or a salt or solvate thereof.

3. A compound according to claim 1 wherein $R^1$ is phenyl, monosubstituted by -SO$_2$NH$_2$, -CH$_2$SO$_2$NH$_2$, -NHOCH$_2$NR'R'' (wherein $R'^1$ and $R''^1$ together with the nitrogen to which they are joined form a morpholine ring), -

$$\text{CONH}$$

10 C(CH$_3$)$_2$OH, -NH$_2$SO$_2$CH$_3$, CH$_2$NHOOC$_{1,4}$alkyl, -NHOphenyl, -NHCO(CH$_2$)$_2$NHOOC$_{1,4}$alkyl, CONH((CH$_2$)$_3$NHOOC$_{1,4}$alkyl, -CH$_3$, -OCH$_2$CONH$_2$, -OCH$_2$phenyl, -SO$_2$phenyl, -CONHCH$_3$, or a salt or solvate thereof.

4. A compound according to claim 3 or a salt or solvate thereof wherein the phenyl is substituted in the meta or para position.

5. A compound according to claim 1 wherein $R^1$ is phenyl (dissubstituted by OH and CN), phenyl (dissubstituted by Cl and F), phenyl (dissubstituted by CH$_3$ and

$$\text{CONH}$$

20 thereof.

6. A compound according to claim 1 selected from:
5-(1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;
25 1-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
5-(4-(1-hydroxyethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
N-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
5-(1H-indol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;
N-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]benzamide;
5-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
1-[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
N-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]-2-(4-morpholinyl)acetamide;
5-(3-cyano-4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-cyclopropylbenzamide;
3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-cyclopropyl-4-methylbenzamide;
5-(2-methyl-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(1H-pyrazol-3-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
N-[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methanesulfonamide;
5-[2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-
carbonitrile;
5-[4-[(phenylmethyl)oxy]phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(2-methylphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzamide;
5-(6-fluoro-3-pyridinyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-[4-(phenylsulfonyl)phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(3-chloro-5-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
5-(3,5-dimethyl-4-isoxazolyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
2-[[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]oxy]acetamide;
1,1-dimethylethyl (3-[[3-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]amino]-3-
oxopropyl)carbamate;
1,1-dimethylethyl (3-[[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]amino]-3-
oxopropyl)carbamate;
1,1-dimethylethyl [[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]methyl]
carbamate;
1,1-dimethylethyl 5-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,3-dihydro-1H-indole-1-
carboxylate;
1,1-dimethylethyl [3-[[4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl]carbonyl] 
amino)propyl]carbamate;
and salts or solvates thereof.

7. A compound according to claim 6 selected from;
30
5-(1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
4-(3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide;
and salts and solvates thereof.
8. A pharmaceutical composition, comprising: a compound as claimed in any one of claims 1 - 7, or a salt, or solvate thereof, and one or more of pharmaceutically acceptable carriers, diluents and excipients.

9. A compound as claimed in any of claims 1 - 7, or a salt or solvate thereof for use in therapy.

10. A compound as claimed in any of claims 1 - 7, or a salt or solvate thereof for use in treating a disorder mediated by at least one of inappropriate IKK1 activity.

11. A compound as claimed in any of claims 1 - 7, or a salt or solvate thereof for use in treating cancer.

12. A method of treating a disorder mediated by inappropriate IKK1 activity, comprising administering a compound as claimed in any one of claims 1 - 7, or a salt, or solvate thereof.

13. A method according to claim 12 wherein the disorder mediated by inappropriate IKK1 activity is cancer.

14. Manufacture of a compound as claimed in any of claims 1 - 7, or a salt or solvate in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate IKK1 activity.

15. Use according to claim 14 wherein the disorder mediated by at least one of inappropriate IKK1 activity is cancer.

16. A combination comprising a compound of formula (I) or a salt or solvate thereof and at least one anti-neoplastic agent.

17. A combination according to claim 16, wherein the at least one anti-neoplastic agent is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

18. The combination according to claim 17, wherein at least one anti-neoplastic agent is an anti-microtubule agent.

19. The combination according to claim 17 of claim 1, wherein at least one anti-neoplastic agent is a diterpenoid.
20. The combination according to claim 17, wherein at least one anti-neoplastic agent is a vinca alkaloid.

21. The combination according to claim 17, wherein at least one anti-neoplastic agent is a platinum coordination complex.

22. The combination according to claim 17, wherein at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

23. The combination according to claim 17, wherein at least one anti-neoplastic agent is paclitaxel.

24. The combination of claim 17, wherein at least one anti-neoplastic agent is carboplatin.

25. The combination of claim 17, wherein at least one anti-neoplastic agent is vinorelbine.

26. The combination of claim 17, wherein at least one anti-neoplastic agent is a signal transduction pathway inhibitor.

27. The combination of claim 17, wherein the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase selected from the group consisting of VEGFR2, TIE2, PDGFR, BTK, IGFR-1, erbB2, EGFR, TrkA, TrkB, TrkC, and c-fms.

28. The combination of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of rafk, akt, and PKC-zeta.

29. The combination of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a non-receptor tyrosine kinase selected from the src family of kinases.

30. The combination of claim 29, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

31. The combination of claim 29, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.
32. The combination of claim 29, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

33. The combination of claim 26 wherein at least one anti-neoplastic agent is:

34. The combination of claim 17, wherein at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

35. The combination of claim 33, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

36. A combination comprising a compound of formula (I) or a salt or solvate thereof and at least one further therapeutic agent.

37. A combination as claimed in claims 16 – 36 for use in therapy.

38. A combination as claimed in claims 16 – 36 for use in treating a disorder mediated by inappropriate IKK1 activity.


40. Use of a combination as claimed in claims 16 – 36 in the manufacture of a medicament for the treatment of a disorder mediated by inappropriate IKK1 activity.

41. Use of a combination as claimed in claims 16 – 36 in the manufacture of a medicament for the treatment of cancer.

42. A method of treating a disorder mediated by inappropriate IKK1 activity comprising administering a combination as claimed in claims 16 - 36.

43. A method of treating cancer comprising administering a combination as claimed in claims 16 - 36.
44. A pharmaceutical composition comprising a combination as claimed in claims 16 – 34 and one or more of pharmaceutically acceptable carriers, diluents and excipients.
A. CLASSIFICATION OF SUBJECT MATTER
INV. CO7D471/04 A61P25/00 A61P9/00 A61P31/18

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
CO7D A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>PHILIP DG COISH ET AL: &quot;Small molecule inhibitors of IKK kinase activity&quot; EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 16, no. 1, 1 January 2006 (2006-01-01), pages 1-12, XP002449699 ISSN: 1354-3776 the whole document</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 8 August 2008

Date of mailing of the international search report: 14/08/2008

Authorized officer: Gregoire, Ariane
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