(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2013 (21.02.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/024282 A2

(51) **International Patent Classification**:
A61K 31/506 (2006.01) *A61K 31/4184* (2006.01)
A61K 31/519 (2006.01) *A61K 31/437* (2006.01)
A61K 31/427 (2006.01) *A61P 35/00* (2006.01)
A61K 31/404 (2006.01)

(21) **International Application Number**:
PCT/GB2012/051978

(22) **International Filing Date**:
14 August 2012 (14.08.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1114051.4 15 August 2011 (15.08.2011) GB

(71) **Applicant** *(for all designated States except US)*: **DOMAINEX LIMITED** [GB/GB]; 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GH (GB).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **NEWTON, Gary** [GB/GB]; c/o Domainex Limited, 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GH (GB). **PERRIOR, Trevor** [GB/GB]; c/o Domainex Limited, 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GH (GB). **ASHWORTH, Alan** [GB/GB]; c/o The Institute of Cancer Research:, Royal Cancer Hospital, 123 Old Brompton Road, London SW7 3RP (GB). **LORD, Christopher James** [GB/GB]; c/o The Institute of Cancer Research:, Royal Cancer Hospital, 123 Old Brompton Road, London SW7 3RP (GB).

(74) **Agents**: **SCOTT, Susan Margaret** et al.; Abel and Imray, 20 Red Lion Street, London WC1R 4PQ (GB).

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

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2013/024282 A2

(54) **Title**: COMPOUNDS AND THEIR USES

(57) **Abstract**: The invention provides a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, for use in a method of treating a cancer that is dependent on the PI3kinase pathway. The invention further provides a method of treating cancer in an individual in whom the cancer is dependent on the PI3kinase pathway, comprising administering to the individual a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε.

Compounds and their uses

This invention relates to compounds that are inhibitors of one or both of the kinases TBK1 and IKKε (otherwise referred to as I-kappa-B-kinase-3 (IKK3), or down-regulators of the expression of one or both of TBK1 and IKKε, and their use in the treatment of cancers that are dependent on the PI3kinase-pathway. The invention also relates to methods of diagnosis, methods of determining the susceptibility of a cancer to particular treatments, and methods of determining suitability of particular treatments.

There are approximately 500 different known protein kinases. Protein kinases serve to catalyze the phosphorylation of an amino-acid side-chain in various substrate proteins. Studies have shown that protein kinases play a key role in many cell functions, including signal transduction, transcriptional regulation, cell motility, and cell division.

The PI3kinase signalling pathway is an important cell survival pathway which involves a number of protein kinases, and also lipid kinases of the phosphoinositide 3-kinase (PI3 kinase) family whose primary role is to phosphorylate inositol lipids. The phosphorylated inositol lipids subsequently play an important signalling role by membrane recruitment of effectors having phosphoinositide-recognition motifs. Increased signalling through this pathway is seen in many tumours (Holmes, *Nature Reviews Drug Discovery*, 2011, **10**, 563-564; Engleman, *Nature Reviews Cancer*, 2009, **9**, 550-562; Stephens *et al.*, *Current Opinion in Pharmacology*, 2005, **5**, 357-365).

Three different classes of PI3 kinases have been identified. All members of the family share a common function in phosphorylating the 3'OH group of phosphatidylinositols (PtdIns), however they act preferentially on different PtdIns substrates. The PI3 kinases that are most commonly implicated in cancer are the class I PI3 kinases (Engleman, **2009**).

PI3kinase signalling by class I PI3 kinases is driven by the kinase function of the p110 catalytic domain which primarily converts PtdIns(4,5)P_2 into PtdIns(3,4,5)P_3. Proteins that contain a pleckstrin homology (PH) domain become associated with the cell membrane by binding to PtdIns(3, 4,5)P_3, and when localised here they can become further activated by

other proteins. A major pathway for transduction of the downstream signal from PI3kinase involves the activation of AKT. AKT becomes associated with the cell membrane via its PH domain, from where it can become activated by phopsphorylation of Threonine 308 and Serine 473 by PDK-1, and the mTOR/Rictor complex (mTorc2), respectively. AKT can then provide a powerful growth/survival signal by phosphorylation of a number of proteins including TSC-2, which indirectly activates the mTOR/Raptor complex (mTorc1), GSK3β and members of the FOXO family of proteins (Engleman, **2009**; Stephens *et al.*, **2005**)

Although AKT is the PI3kinase pathway downstream effector most widely implicated in cancer, there are also AKT independent pathways, which include the Bruton tyrosine kinase (BTK), the TEC families of non-receptor tyrosine kinases and serum- and glucocorticoid-regulated kinases (SGKs) (Qui *et al.*, *Oncogene*, 2000, **19**, 5651-5661; Vasudevan *et al.*, *Cancer Cell*, 2009, **16** (1), 21-32).

There are 4 isoforms of the catalytic p110 subunit α, β γ, δ all of which contain binding sites for a regulatory subunit, p85-related proteins in the case of the class IA catalytic subunits p110α, p110β and p110δ and p101 or the closely related p84-p87 subunit in the case of the class IB isotype p110γ. The class I catalytic subunits also contain a binding site for Ras proteins. There are a number of mechanisms by which the PI3kinase pathway can be activated in cancer:

Receptor tyrosine kinases, such as EGFR or Erb-2, can activate the PI3 kinase pathway by recruiting the regulatory subunit thereby releasing the auto-inhibitory role that this would normally play (Nagata *et al.*, *Cancer Cell*, 2004, **6(2)**, 117-27). This mechanism of activation is primarily associated with class IA isoforms (Williams *et al.*, *Biochem. Soc. Trans*, 2009, **37**, 615-626).

The p110 isoforms can be activated directly by binding to activated Ras proteins. This is the primary mode of activation for p110γ, and may also be required for activation of p110β (Kang *et al*, PNAS, 2006, **103** (5) 1289-1294, Andrews *et al*, Science Signalling, 2007, **407**, cm2, "PI3K Class IB Pathway").

Mutations in the one of the PI3 kinase catalytic subunits can result in constituitive activation of the pathway (Engleman, 2009).

Mutations in the regulatory p85 subunit can result in loss of its inhibitory activity and hence constitutive activation of the pathway (Engleman, 2009).

One of the PI3 Kinase catalytic subunits may be over-expressed resulting in amplification of signalling through the PI3 kinase pathway (Engleman 2009).

Loss or inactivation of key phosphatases such as PTEN, which reverse the action of the PI3 kinases by dephophorylating the 3 position of PtdIns(3, 4,5)P_3 can increase flux through the PI3 kinase pathway (Engleman, 2009; Nagata *et al.*, *Cancer Cell*, 2004, **6(2)**, 117-27).

A downstream kinase such as PDK-1 or AKT may be over-expressed or possess an activating mutation (Engleman, 2009).

Phosphatase and tensin homolog (PTEN) is a key enzyme that inhibits signalling through the PI3kinase pathway and it therefore has tumour suppressing effects. Mutation in the *PTEN* gene (*PTEN*(-) mutation) inactivates the enzyme and leads to increased flux through the pathway. PTEN is one of the most commonly mutated or lost tumour suppressors in human cancer. PTEN loss has been reported in endometrial cancer (35%) and glioblastoma (54%) as well as in other cancer types such as breast (32%), colo-rectal carcinoma (30%), prostate (27%) and lung cancer (19%) (Frattini *et al.*, *Br. J. Cancer*, 2007, **97(8)**, 1139-45; Nagata *et al.*, 2004). Low levels of PTEN are also reported in a number of cancers. This can occur for example as the result of the loss of one functional copy of the PTEN gene, often described as haploinsufficiency. It is believed that low levels of PTEN can contribute significantly to the oncogenic state especially when accompanied by other changes/mutations that are able to further activate the PI3 kinase pathway (Ying *et al.*, *Cancer Discovery*, 2011, **1** (2), 158-169; Nagata *et al.*, 2004). It has also been shown that receptor tyrosine kinase signalling can deactivate PTEN. It has been shown that part of the mechanism of action of the Erb2 antibody trastuzumab involves inhibition of Src kinase activity. Src kinase is believed to be responsible for deactivating PTEN in breast cancers where Erb2 is over-expressed, by phophorylation of key tyrosine residues on PTEN. Furthermore, loss of PTEN has been shown to be associated with resistance to trastuzumab, and inhibition of PI3 kinase signalling can increase sensitivity to trastuzumab in PTEN deficient cells (Nagata *et al.*, 2004).

PI3kinases increase flux through the PI3kinase pathway, and so PI3 kinase activating mutations are oncogenic, for example mutations classified as *PIK3CA* (catalytic – alpha polypeptide) leads to enhanced signalling through the pathway. *PIK3CA* mutation can be found in a range of malignancies such as colon, lung, ovarian, liver, brain, stomach and breast cancers (Samuels *et al.*, *Science*, 2004, **304(5670)**, 554; Engleman, 2009). Genetic amplification of PIK3CA is also found in a number of tumour types including head and neck, squamous cell lung carcinoma, cervical, gastric and oesophageal (Engleman, 2009).

I-kappa-B-kinase epsilon, IKKε, (also known as IKKε, I-kappa-B-kinase-3 (IKK3), or inducible I-kappa-B-kinase (IKKi)), and TANK Binding Kinase-1, TBK1 (also known as T2K or NF-kappa B-activating kinase), are serine-threonine kinases.

Aberrant IKKε activity has been linked to a number of disease states including cancer and obesity. Studies have shown that the gene encoding IKKε (*IKBE*) is amplified and over-expressed in certain breast cancer cell lines and patient-derived tumours. Furthermore suppression of *IKBE* gene expression in these cell lines induces cell death (Boehm *et al.*, *Cell*, 2007, **129**, 1065-1079). IKKε has also been shown to phosphorylate the estrogen receptor, and its activity has been linked to tamoxifen resistance in breast cancer tumours (Guo *et al.*, *The Journal of Biological Chemistry*, 2010, 285, 3676-3684). IKKε is also frequently over-expressed in human ovarian cancer lines and primary tumours. Moreover IKKε over-expression renders cells resistant to cis-platin, whereas IKKε knockdown restores cis-platin sensitivity (Guo *et al.*, *The American Journal of Pathology*, 2009, 175, 324-333). These observations suggest that IKKε inhibitors may show efficacy in the treatment of certain cancers.

TBK1 has been linked to various cancer states although the published literature has not defined its exact role, or the appropriate clinical setting for use of a TBK-1 inhibitor. The levels of TBK1 mRNA and protein are elevated in certain malignant colon and breast cancer cells. TBK1 is also recruited and activated by the RalB/Sec5 effector complex: in cancer cells, constitutive engagement of this pathway via chronic RalB activation, restricts the initiation of apoptotic programmes. The proto-oncogene *KRAS* (which encodes the protein K-Ras) is mutated in a wide array of human tumours, most of which are aggressive and respond poorly to standard therapies. The knockdown of TBK1 in a number of K-Ras

dependant tumour cell lines has been shown to cause cell death. Although it is known that K-Ras can activate the PI3 kinase pathway it is believed that cell lines which have K-Ras mutations are not necessarily addicted to the PI3 kinase pathway. For example it has been shown in pancreatic ductal adenocarcinoma (PDAC) that low levels of PTEN are also required for activation of the PI3 kinase pathway (Ying *et al.*, 2011).

Both IKKε and TBK1 have been shown to phosphorylate and activate AKT in a number of cancer cell lines (Ou *et al.*, *Molecular Cell*, 2011, 41, 458-70; Xie *et al.*, *PNAS*, 2011, 108, 16, 6474-6479). AKT is a major signalling kinase and is generally considered to be one of the enzymes involved in the PI3kinase pathway. Despite this it has been shown that not all tumour cell lines that are dependent on the PI3kinase pathway have high levels of activated AKT nor do they all respond to AKT knockdown (Vasudevan *et al.*, 2009). Ou *et al.* reported that shRNA knockdown of TBK1 in a number of NSCLC cell lines inhibited cell survival and that K-Ras mutation status alone was not sufficient to determine sensitivity. They also reported that a small molecule dual inhibitor of TBK1 and IKKε kinase showed greater efficacy in cell lines that were susceptible to TBK-1 shRNA knockdown. Those cell lines which showed enhanced sensitivity to TBK-1 inhibition also showed reduction of AKT phosphorylation following treatment with the small molecule inhibitor, although the authors were unable to determine what factors conferred sensitivity to TBK-1 inhibition.

There remains a need for improved treatments of cancers. It is important for clinicians to know which mechanisms are driving the malignancy in a particular patient, and to use the appropriate treatment. For example a drug that targets PI3kinase signalling pathway will be effective in tumours that use the pathway, but not effective in tumours that do not use it.

The invention provides a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, for use in a method of treating a cancer that is dependent on the PI3kinase pathway. It has surprisingly been found by the current inventors that cancers that are deficient in PTEN activity are sensitive to compounds that are inhibitors of TBK1 and IKKε. It has also been found by the current inventors that cancers which are deficient in PTEN activity are sensitive to down-regulation of the expression of TBK1. From the data obtained by the current inventors, it is anticipated that such cancers are also are sensitive to down-regulation of the expression of IKKε. It has

also been found by the current inventors that cancers with overactive PI3kinase signalling are sensitive to TBK1 and IKKε inhibitors. From the data obtained by the current inventors, it is anticipated that cancers with overactive PI3kinase signalling are sensitive to down-regulation of the expression of one or both of TBK1 and IKKε. In particular, the current inventors found that a human cell line in which both alleles of *PTEN* had been inactivated was lethally susceptible to siRNA inhibition of TBK1. That result demonstrates that TBK1 activity is necessary for the survival of cells that are deficient in PTEN. The inventors also found that TBK1 inhibitor compounds were selectively toxic to *PTEN* (-/-) cell lines over *PTEN* (+/+) cells lines, showing that TBK1 activity is necessary for the survival of cells that are deficient in PTEN, but not for cells that have normally functional PTEN. The inventors have further found that breast tumour cell models that have *PTEN* and/or *PIK3CA* defects are more sensitive to TBK1 inhibitors than tumour cell models with defects in other genes.

The findings demonstrate that a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, is effective in the treatment of a cancer that is dependent on the PI3kinase pathway. In particular, a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, is effective in the treatment of a cancer that has a defect in one or both of the *PTEN* and *PIK3CA* genes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the Normalised Percent Inhibition (NPI) scores following the knockdown of 714 kinase genes with a panel of siRNAs in HCT116 human tumour cells in which both alleles of PTEN had been deactivated (PTEN-/-) and HCT116 human tumour cells with wildtype PTEN (PTEN +/+)..

Figures 2 (a) to (c) show the effects of small molecule dual inhibitors of the kinase domain of TBK1 and IKKε on (PTEN-/-)-HCT116 and (PTEN +/+)-HCT116 human tumour cells. (a) shows the results for DMA-A, (b) shows the results for DMX-B and (c) shows the results for DMX-C.

Figure 3 (a) shows the effect on survival fraction for escalating concentrations of the TBK1/IKKε inhibitor DMX-C on an ovarian tumour cell line which contains deactivating mutations in the PTEN gene.

Figures 3 (b) to (d) show the effects on survival fractions for escalating concentrations of the TBK1/IKKε inhibitor DMX-C on breast tumour cell lines which contains deactivating mutations in the PTEN gene.

Figure 3 (e) shows the effect on survival fraction for escalating concentrations of the TBK1/IKKε inhibitor DMX-C on a breast tumour cell lines which contains both deactivating mutations in the PTEN gene and activating mutations in the PIK3CA gene.

Figures 4(a) to (c) show the effects on survival fractions for escalating concentrations of the TBK1/IKKε inhibitor DMX-C on breast tumour cell lines which contains activating mutations in the PIK3CA gene.

Figures 5 (a) to (e) show the effects on survival fractions for escalating concentrations of the TBK1/IKKε inhibitor DMX-C on breast tumour cell lines with wildtype PTEN and PIK3CA genes.

Figure 6 (a) shows SF80 (concentration at which 80% of cells survive) and (b) shows SF50 (concentration at which 50% of cells survive) results for DMX-C in cell lines with PTEN and/or PIKCA mutations and those with wild type PTEN and PIKCA.

Figure 7 shows the results of a study into TBK1 sensitising to BEZ235 (a dual PI3kinase, mTOR inhibitor), the graph shows the survival fraction results for T47D breast tumour cells exposed to various concentrations of BEZ235 in the presence or absence of TBK-1 siRNA , with siRNA targeting PIK3CA used as a positive control.

TBK1 and IKKε have overlapping substrate specificities and it is believed that they have similar binding sites. Accordingly, many compounds that are inhibitors of one of TBK1 and IKKε are also inhibitors of the other. Compounds that are strong inhibitors of both TBK1 and IKKε are particularly advantageous compounds for use in the current invention.

The cancer to be treated may be a cancer that is deficient in PTEN activity. For example, the cancer may have reduced amounts of PTEN, or a level of PTEN function that is lower than PTEN function in normal cells in the individual. Expression levels of PTEN protein can be

established by western blotting, or *in situ* hybridization, using commercially available antibodies to PTEN. For example, the cancer may include at least some cells carrying a loss of function mutation in the *PTEN* gene. The presence or absence of loss of function mutations may be assessed by determining the presence or absence of one or more mutations or polymorphisms in a nucleic acid sequence encoding at least a portion of the PTEN enzyme. The presence of such mutations can be established by Sanger Sequencing or Next Generation (Massively Parallel or Deep) Sequencing, or the use of mutation-specific PCR assays. The copy number of each gene (and thus loss of heterozygosity in the case of *PTEN*) can be established by Fluorescent In Situ Hybridisation (FISH).

The cancer may be a cancer that has overactive PI3kinase signalling. For example, the level of PI3kinase signalling can be assessed by a functional assay known to or readily developed by the person skilled in the art.

For example, the cancer may include at least some cells carrying an activating *PIK3CA* mutation. The presence or absence of an activating *PIK3CA* mutation may be assessed by determining the presence or absence of one or more mutations or polymorphisms in a nucleic acid sequence encoding at least a portion of the PI3kinase p110 catalytic subunit.

Overactive PI3 kinase signalling may be detected by an increase in phosphorylation of one or more of the downstream proteins, for example PDK-1 or mTOR. This can be measured in standard assay formats such as the use of a western blot, ELISA or *in situ* hybridization techniques, which all use commercially available phospho-protein specific antibodies.

Cancers with overactive PI3kinase signalling include endometrial cancer, glioblastoma, colorectal carcinoma, myeloma and leukemia, and cancers of the breast, prostate, lung (including non small cell lung cancer (NSCLC)), ovary, liver, brain and stomach; in particular, endometrial cancer, glioblastoma, breast cancer, including tamoxifen resistant breast cancer, ovarian cancer, including cis-platin resistant ovarian cancer. Compounds of the invention are expected to be particularly useful in the treatment of such cancers. Cancers in the treatment of which the compounds of the invention are especially useful include cancers harbouring Ras mutations and Ras-dependant tumours, and cancers with PTEN loss of function mutatons or *PIK3CA* gain of function mutations.

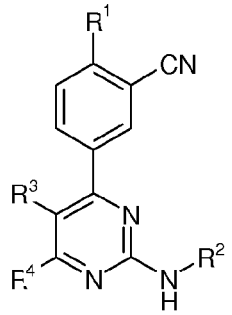
A compound for use in the invention may be a compound that is an inhibitor of one or both of TBK1 and IKKε. A compound is considered to be an inhibitor of TBK1 if it has an IC_{50} for inhibition of TBK-1 of <300nM. Preferred compounds have an IC_{50} for inhibition of TBK-1 of <100nM, particularly <50nM, more particularly <30nM. The IC_{50} for inhibition of TBK-1 can be assessed by assays known to the person skilled in the art, for example a luminescent kinase assay, or a time-resolved fluorescence assay. For example, a TBK-1 assay is available from Promega (Promega Corporation, 2800 Woods Hollow Road, Madison, WI53711-5399, USA, or see http://www.promega.com/). An example of an assay is described in the Examples section herein.

A compound is considered to be an inhibitor of IKKε if for inhibition of IKKε of <300nM; Preferred compounds have an IC_{50} for inhibition of IKKε of <100nM, particularly <50nM, more particularly <30nM. The IC_{50} for inhibition of IKKε can be assessed by assays known to the person skilled in the art, for example a luminescent kinase assay, or a time-resolved fluorescence assay. For example, an IKKε assay is available from Invitrogen (see http://www.invitrogen.com). An example of an assay is described in the Examples section herein.

A compound for use in the invention may be selective for TBK1 and/or IKKε over other kinases, or said compound may also inhibit other kinases. Some compounds have been found to be inhibitors of both TBK1 and IKKε.

Compounds that are inhibitors of one or both of TBK1 and IKKε include compounds selected from the group consisting of:

(a) compounds described in PCT/GB2011/001075 (published as WO2012/010826), that is to say compounds of Formula (I):



(I)

in which:

R^1 represents an aliphatic heterocyclyl group having 4, 5, 6 or 7 ring atoms, bonded to the phenyl group shown in formula I through a ring nitrogen atom, and optionally substituted by one or more substituents selected from halogen atoms; OH; =O; C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups, each optionally substituted by one or more substituents independently selected from halogen atoms and NR^aR^b groups; NO_2; CN; NR^aR^b; COR^c; $O.CO.R^c$; CO_2R^a; $NR^a.COR^c$; $NR^aCO_2R^b$; $C(=NH)NH_2$; SO_2R^c; $NR^aSO_2R^c$; and $CH(CF_3)NH_2$;

R^2 represents a phenyl or heteroaryl group which is optionally substituted by one or more substituents independently selected from:

halogen atoms;

NR^aR^b;

C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups, each optionally substituted by one or more substituents independently selected from halogen atoms and NR^aR^b groups; and

$-(CH_2)_p$-R' in which p is 0, 1, 2, 3 or 4 and R' represents one of the following substituents: OH; NO_2; CN; COR^c; $O.CO.R^c$; CO_2R^b; $NR^a.COR^c$; $NR^aCO_2R^b$; $C(=NH)NH_2$; SO_2R^c; $NR^aSO_2R^c$; and $CH(CF_3)NH_2$;

and/or which is optionally substituted on adjacent ring atoms by a group $-NR^a.CO.(CH_2)_n-$ or $-(CH_2)_n.CO.NR^a-$ forming a fused ring;

R^a represents a hydrogen atom or a C_{1-4}alkyl group;

R^b represents a hydrogen atom, a C_{1-4}alkyl group optionally substituted by a group NR^aR^a, or a cycloalkyl group in which a CH_2 moiety may be replaced by an oxygen atom or an NR^a group;

R^c represents a hydrogen atom, a group $-NR^aR^b$, or a C_{1-4}alkyl group optionally substituted by a group NR^aR^b;

or R^a and R^b together may, when attached to the same nitrogen atom, represent a $-(CH_2)_m-$ group in which a CH_2 moiety may be replaced by an oxygen atom or an $-NR^a-$ group;

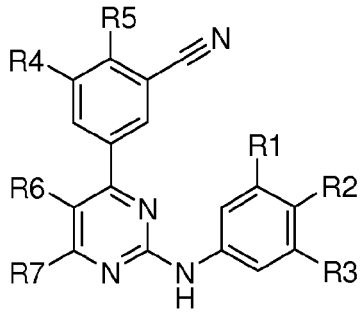
m represents 4 or 5;

n represents 1 or 2; and

each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group;

or a salt thereof.

(b) Compounds described in WO2011/046970, that is to say compounds of Formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein:

R1 , R2, R3, and R5 are independently chosen from the following groups: alkyl, alkylene, alkenyl, alkenylene, alkynyl, carbocycle, cycloalkyl, cycloalkenyl, heterocycle, aryl, heteroaryl, halo, hydro, hydroxyl, alkoxy, alkynyloxy, cycloalkyloxy, heterocycloxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, mercapto, alkylthio, arylthio, cycloalkylthio, arylalkyl, heteroarylalkyl, heteroarylalkenyl, arylalkynyl, haloalkyl, aldehyde, thiocarbonyl, O-carboxy, C-carboxy, carboxylic acid, ester, C-carboxy salt, carboxyalkyl, carboxyalkenylene, carboxyalkyl salt, carboxyalkoxy, carboxyalkoxyalkanoyl, amino, aminoalkyl, nitro, O-carbamyl, N- carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, aminothiocarbonyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, cyano, nitrile, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, sulfonamide,

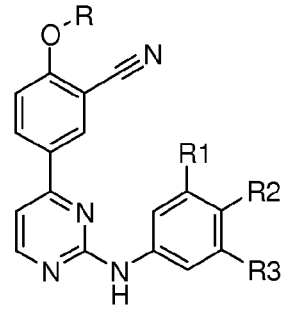
aminosulfonyl, aminosulfonyloxy, sulfonamidecarbonyl, alkanoylaminosulfonyl, trihalomethylsulfonyl, or trihalomethylsulfonamide,

wherein any of the foregoing groups are optionally substituted at least once with alkyl, alkylene, alkenyl, alkenylene, alkynyl, carbocycle, cycloalkyl, cycloalkenyl, heterocycle, aryl, heteroaryl, halo, hydro, hydroxyl, alkoxy, alkynyloxy, cycloalkyloxy, heterocycloxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, mercapto, alkylthio, arylthio, cycloalkylthio, arylalkyl, heteroarylalkyl, heteroarylalkenyl, arylalkynyl, haloalkyl, aldehyde, thiocarbonyl, O-carboxy, C-carboxy, carboxylic acid, ester, C-carboxy salt, carboxyalkyl, carboxyalkenylene, carboxyalkyl salt, carboxyalkoxy, carboxyalkoxyalkanoyl, amino, aminoalkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N- thiocarbamyl, C-amido, N-amido, aminothiocarbonyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, cyano, nitrile, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, sulfonamide, aminosulfonyl, aminosulfonyloxy, sulfonamidecarbonyl, alkanoylaminosulfonyl, trihalomethylsulfonyl, or trihalomethylsulfonamide,

or, R2 and either Rl or R3, together with the carbon atoms to which they are bound, form an optionally-substituted cycloalkyl, heterocycle, aryl, or heteroaryl;
R4 is independently chosen from hydro, halo, and an optionally-substituted group chosen from lower alkyl, haloalkyl, alkoxy, arylalkoxy, heteroarylalkoxy, and heterocycloalkoxy;
R6 and R7 are independently chosen from hydro, halo, and lower alkyl;
or R6, taken together with R7, form an aryl or heteroaryl ring.

Compounds of Formula (II) were reported to be inhibitors of both TBK1 and/or IKKε.

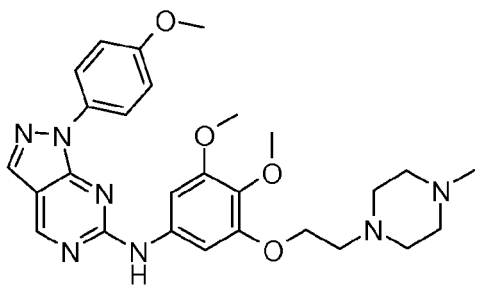
In particular, preferred compounds of group (b) have an ether group at R5 and are without further substitution at R4, R6 and R7, for example compounds of Formula (IIa):



(IIa)

wherein R is H, alkyl, substituted alkyl, substituted or un substituted heterocyclyl groups.

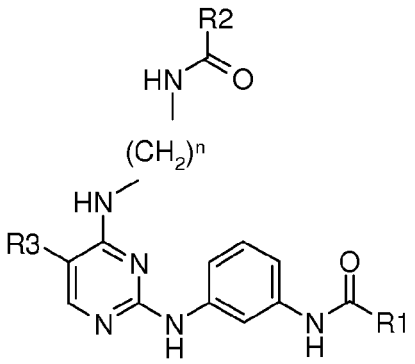
(c) the inhibitor compound described in Ou *et al.*, *Molecular Cell*, 2011, 41, 458-70, referred to herein as the compound of Formula (III):



(III)

Compound (III) was reported as having activity against both TBK1 and IKKε.

(d) Compounds described in WO2009/030890, that is to say compound of Formula (IV):



(IV)

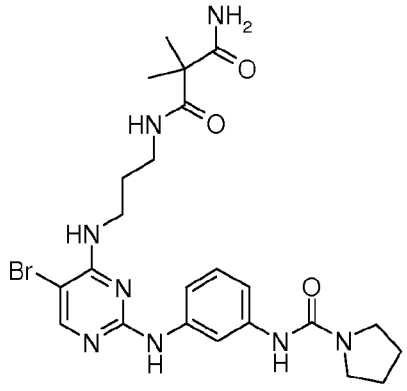
wherein n is from 2-6;

R1 is a 5 or 6 membered cyclic alkyl ring or aromatic cyclic ring, wherein optionally one or more carbons in the ring structure is substituted by an O, N or S;

R2 is a 5 or 6 membered cyclic alkyl ring or arromatic cyclic ring, wherein optionally one or more carbons in the ring structure is substituted by an O, N or S, or is a linear or branched substituted or unsubstituted C_1-C_6 alkyl, C_1-C_6 alkoxy or C_2-C_6 alkenyl, wherein when substituted the substituent group may be a $C(=O)NH_2$;COOH; OH, NH_2, NO_2, and R3 is a halo, H, CH_3, CN, NO_2.

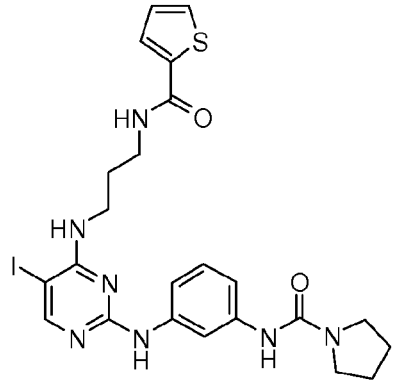
Compounds of Formula (IV) were reported as having activity against TBK1 and/or IKKε.

Preferred compounds of group (d) are the compounds:



BX-320

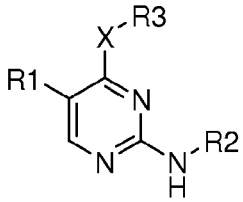
and



BX-795

BX-795 has also been reported in, for example, *J. Biol. Chem.*, 2009, 284(21), 14136–14146. The preferred compounds BX-320 and BX-795 were shown to inhibit TBK1 and IKKε.

(e) Compounds described in WO2009/122180, that is to say compound of Formula (V):



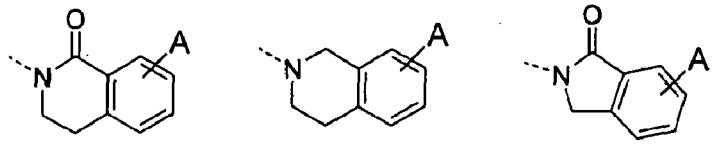
(V)

wherein: R^1 is C_{3-8}-cycloalkyl;

X is O, NR^7 or C_{3-6}-heterocycloalkyl;

R^2 is aryl, heteroaryl, fused or unfused aryl-C_{3-6}-heterocycloalkyl or fused or unfused heteroaryI-C_{3-6}- heterocycloalkyl, each of which is optionally substituted by one or more substitutents selected from aryl, heteroaryl, C_{1-6}-alkyl, C_{3-7}-cycloalkyl and a group A, wherein said C_{1-6}-alkyl group is optionally substituted by one or more substituents selected from aryl, heteroaryl, R^{10} and a group A, said heteroaryl group is optionally substituted by one or more R<10> groups; and wherein said C_{3-6}- heterocycloalkyl group optionally contains one or more groups selected from oxygen, sulfur, nitrogen and CO;

R^3 is C_{1-6}-alkyl optionally substituted by one or more substituents selected from aryl, heteroaryl, $-NR^4R^5$, $-OR^6$, $-NR^7(CO)R^6$, $-NR^7(CO)NR^4R^5$, $-NR^7SO2R^6$, $-NR^7COOR^7$, $-CONR^4R^5$, C_{3-6}-heterocycloalkyl and



wherein said aryl, heteroaryl and C_{3-6} -heterocycloalkyl groups are each optionally substituted by one or more substituents selected from -C_{1-6}-alkyl and a group A, wherein said -C_{1-6}-alkyl group is optionally substituted by one or more substituents selected from aryl, heteroaryl and a group A;

A is selected from halogen, hydroxyl, cyano, trifluoromethyl, alkoxy, $-NO_2$, $-NH_2$, $-NR^4R^5$, $-OR^6$, $-NR^7(CO)R^6$, $-NR^7(CO)NR^4R^5$, $-NR^7COOR^7$, $-NR^7(SO_2)R^6$, $-CO_2H$, $-(NR^7CSO_2)NR^4R^5$, $-COOR^7$, $-CONR^4R^5$, COR^6, $SO2NR^4R^5$ and $-SO_2CH_3$;

each R^4 and R^5 is independently selected from hydrogen, C_{3-7}-cycloalkyl, aryl, heteroaryl, C_{1-6}-alkyl and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO and optionally substituted by one or more R^{10} groups, wherein said C_{1-6}-alkyl is optionally substituted by one or more substituents selected from halogen, cyano, hydroxyl, aryl, heteroaryl, $-NR^8R^9$, $-NR^7(CO)R^6$, NR^7COOR^6, $-NR^7(SO_2)R^6$, $-COOR^6$, $-CONR^8R^9$, OR^{10}, $-SO2R^6$ and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO and optionally substituted by one or more or R^{10} groups; or

R^4 and R^5 together with the N to which they are attached form a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO, wherein said C_{3-6}-heterocycloalkyl ring may be saturated or unsaturated and is optionally substituted with one or more groups selected from NR^8R^9 and R^{10} groups;

each R^6 is independently selected from C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{4-7}-heterocycloalkyl, aryl and heteroaryl, each of which may be optionally substituted by one or more substituents selected from halogen, R^{10} and $-NR^8R^9$;

each R^7 is selected from hydrogen, C_{1-6}-alkyl and C_{3-7}-cycloalkyl, wherein said C_{1-6}-alkyl is optionally substituted by one or more halogens;

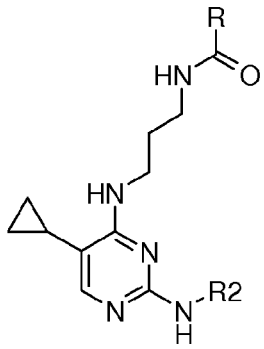
each of R^8 and R^9 is independently selected from hydrogen and C_{1-6}-alkyl, wherein said C_{1-6}-alkyl group is optionally substituted by one or more halogens; or

R^8 and R^9 together with the N to which they are attached form a C_{4-6}-heterocycloalkyl ring optionally further containing one or more heteroatoms selected from oxygen and sulfur, wherein said C_{4-6}-heterocycloalkyl ring is optionally substituted by one or more R^{10} groups; and

each R^{10} is selected from halogen, C_{3-7}-cycloalkyl and C_{1-6}-alkyl optionally substituted by one or more halogens, wherein where R^{10} is C_{1-6}-alkyl and two or more R^{10} groups are attached to the same carbon atom, the R^{10} groups may be linked to form a spiroalkyl group.

Compounds of Formula (V) were primarily reported as having activity against TBK1. From the disclosure of WO2009/122180, they appear also to have activity against IKKε

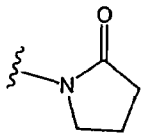
In particular, there are disclosed in WO2009/122180 compounds for Formula (Va):



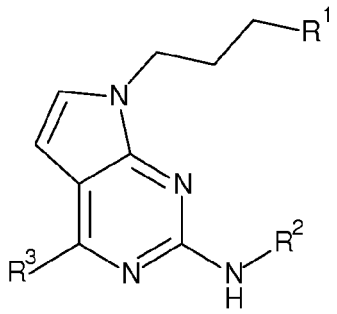
(Va)

wherein R is C_{1-6}-alkyl, C_{3-7}-cyloalkyl, C_{4-7}-heteroalkyl, heteroaryl, each of which may be optionally substituted by one of more substituents selected from halogen, R^{10} and $-NR^8R^9$;

and R^2 is an aryl or heteroaryl group each of which is optionally substituted by one or more substituents selected from Me, Cl, F, CN, NHCOMe, CF_3, COOH, $CONH_2$, OH, NH_2, $NHSO_2Me$, OCF_3, $-NHCOO^tBu$, $-CO_2Me$, $-NMe_2$, 4-methylpiperazin-1-yl, N-morpholinyl, (4-methylpiperazin-l-yl)-CO-, (N-morpholinyl)-CH_2CH_2O-, (imidazol-l-yl)-CH_2- and



(f) Compounds described in WO2010/100431, that is to say compound of Formula (VI):



(VI)

wherein: R^1 is $-NR^7(CO)R^{11}$;

R^2 is aryl, heteroaryl, fused aryl-C_{3-6} -heterocycloalkyl or fused heteroaryl-C_{3-6}-heterocycloalkyl, each of which is optionally substituted by one or more substitutents selected from aryl, heteroaryl, C_{1-6}-alkyl, C_{3-6} -heterocycloalkyl and a group A, wherein said C_{1-6}-alkyl group is in turn optionally substituted by one or more substituents selected from aryl, heteroaryl, C_{3-6}-heterocycloalkyl and a group A, said heteroaryl group is optionally substituted by one or more R^{10} groups; and wherein each C_{3-6}-heterocycloalkyl group is optionally substituted by one or more groups selected from C_{1-6}-alkyl, C_{1-6}-haloalkyl, and A, and which optionally contains one or more groups selected from oxygen, sulphur, nitrogen and CO;

R^3 is H, halogen, cyano or C_{1-6}-alkyl;

A is selected from halogen, hydroxyl, cyano, trifluoromethyl, $-NO_2$, $-NH_2$, $-NR^4R^5$, $-OR^6$, $-NR^7(CO)R^6$, $-NR^7(CO)NR^4R^5$, $-NR^7COOR^7$, $-NR^7(SO_2)R^6$, $-CO_2H$, $-NR^7(SO_2)NR^4R^5$, $-COOR^7$, $-CONR^4R^5$, COR^6 and $-SO_2CH_3$;

each R^4 and R^5 is independently selected from hydrogen, C_{3-7}-CycloalkyI, aryl, heteroaryl, C_{1-6}-alkyl and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO, and optionally substituted by one or more R^{10} groups, wherein said C_{1-6}-alkyl is optionally substituted by one or more substituents selected from halogen, cyano, hydroxyl, aryl, heteroaryl, $-NR^8R^9$, $-NR^7(CO)R^6$, $-NR^7COOR^6$, $-NR^7(SO_2)R^6$, $-COOR^6$, $-CONR^8R^9$, OR^{10}, $-SO_2R^6$ and a C_{3-6}-heterocycloalkyl ring optionally

further containing one or more groups selected from oxygen, sulfur, nitrogen and CO and optionally substituted by one or more or R^{10} groups; or

R^4 and R^5 together with the N to which they are attached form a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO, wherein said C_{3-6}-heterocycloalkyl ring may be saturated or unsaturated and is optionally substituted with one or more groups selected from NR^8R^9 and R^{10};

each R^6 is independently selected from C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{4-7}-heterocycloalkyl, aryl and heteroaryl, each of which may be optionally substituted by one or more substituents selected from halogen, R^{10} and -NR^8R^9;

each R^7 is selected from hydrogen, C_{1-6}-alkyl and C_{3-6}-cycloalkyl, wherein said C_{1-6}-alkyl is optionally substituted by one or more halogens;

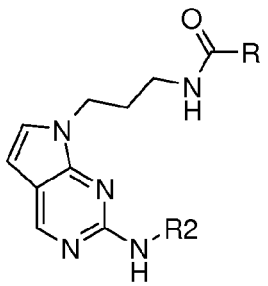
each of R^8 and R^9 is independently selected from hydrogen and C_{1-6}-alkyl, wherein said C_{1-6}-alkyl group is optionally substituted by one or more halogens; or

R^8 and R^9 together with the N to which they are attached form a C_{4-6}-heterocycloalkyl ring optionally further containing one or more heteroatoms selected from oxygen and sulfur, wherein said C_{4-6}-heterocycloalkyl ring is optionally substituted by one or more R^{10} groups; and

each R^{10} is selected from C_{3-7}-cycloalkyl and C_{1-6}-alkyl optionally substituted by one or more halogens, wherein where R^{10} is C_{1-6}-alkyl and two or more R^{10} groups are attached to the same carbon atom, the R^{10} groups may be linked to form a spiroalkyl group; and each R^{11} is independently selected from C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{4-7}-heterocycloalkyl, aryl and heteroaryl, each of which may be optionally substituted by one or more substituents selected from A.

Compounds of Formula (VI) were reported as having activity against TBK1 and/or IKKε.

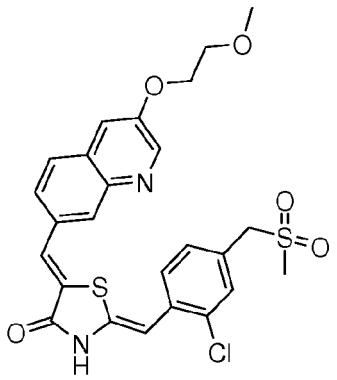
Preferred compounds of Formula (VI) include compounds of Formula (VIa):



(VIa)

wherein: R^2 is selected from aryl or heteroaryl, each of which is optionally substituted by one or more substitutents selected from halo, optionally substituted C_{3-7}-heterocycloalkyl, optionally substituted C_{1-6}-alkyl, heteroaryl, C_{1-6}-alkyl-C_{3-7} -heterocycloalkyl, CN, NHCO-C_{3-7}-heterocycloalkyl, CO-C_{3-7}- heterocycloalkyl and NHCO-C_{1-6}-alkyl, wherein said C_{3-7}-heterocycloalkyl is optionally substituted by one or more C_{1-6}-alkyl or A groups, and said C_{1-6}-alkyl is optionally substituted by one or more halo or NR^4R^5 groups;
and R is selected from cyclobutyl, thienyl, cyclopentyl, pyrazinyl, CH_2-cyclopropyl, sec-butyl, tetrahydrofuranyl, thiazolyl, cyclopropyl, isopropyl, cyclohexyl, CH_2-cyclopentyl and n-propyl.

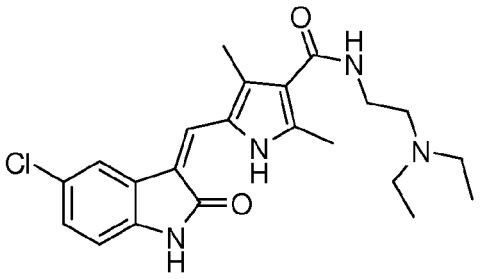
(g) Compound GSK2292978, of Formula (VII), disclosed in poster Richter *et al.*, "Assessing IKKε as a Novel Oncology Target", presented at AACR-NCI-EORTC 2009



(VII)

Compound (VII) was reported as having activity against both TBK1 and IKKε.

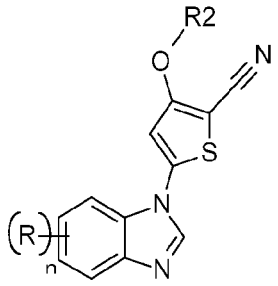
(h) Compound SU11652, of Formula (VIII), disclosed in a poster Wilkinson *et al.*, "High Throughput Compatible Cellular Assays for Interrogating Toll-Like Receptor Signaling Pathways", Invitrogen, Life Technologies Ltd, 3 Fountain Drive, Inchinnan Business Park Paisley PA4 9RF, UK (www.invitrogen.com).



(VIII)

Compound (VIII) was reported as being an inhibitor of TBK1.

(i) Compounds described in WO2005/075465 (also US 2007/014951), that is to say compounds of Formula (X):



(X)

wherein: n is 0, 1,2, 3, or 4 ;

each R^1 which may be the same or different, independently represents H, halogen or a group $(X)_a(Y)_bZ$;

X represents -O- or -CONH-;

a is 0 or 1;

Y represents C_{1-6}alkylene-;

b is 0 or 1;

Z represents hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{5-7} heterocyclyl, C_{1-6} alkoxyalkyl, C_{1-6} haloalkoxyalkyl;

R^2 represents a group $-(X^1)_c(Y^1)_dZ^1$;

Wherein X^1 represents $-C_{1-12}$ alkylene-;

c is 0 or 1;

Y^1 represents -O-;

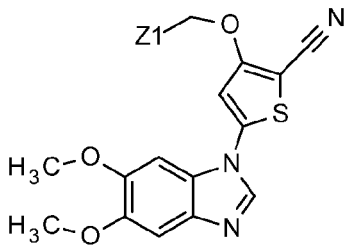
d is 0 or 1;

Z^1 represents H, aryl or heteroaryl each of which contains 5-14 ring atoms, C_{5-7} heterocyclyl, C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, (each of which aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl may be optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S0_2R^3$, C_{1-6} hydroxyalkyl);

R^3 represents H or C_{1-6} alkyl;

or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof.

Preferred compounds have the general of structure (Xa):



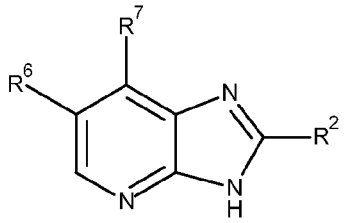
(Xa)

where Z^1 is aryl or heteroaryl each of which is optionally substituted by one of more substituents independently selected from halogen, CF_3, CH_2OH, SO_2CH_3, CH_3, OCH_3.

Compounds of this general structure are also described in Bamborough *et al.*, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6236–6240.

Compounds of Formula (X) were reported as being inhibitors of IKKε.

(j) Compounds described in Wang *et al*. Biorg. Med. Chem. Lett, 2012, **22**, 2063-2068, that is to say compounds of formula (XI)

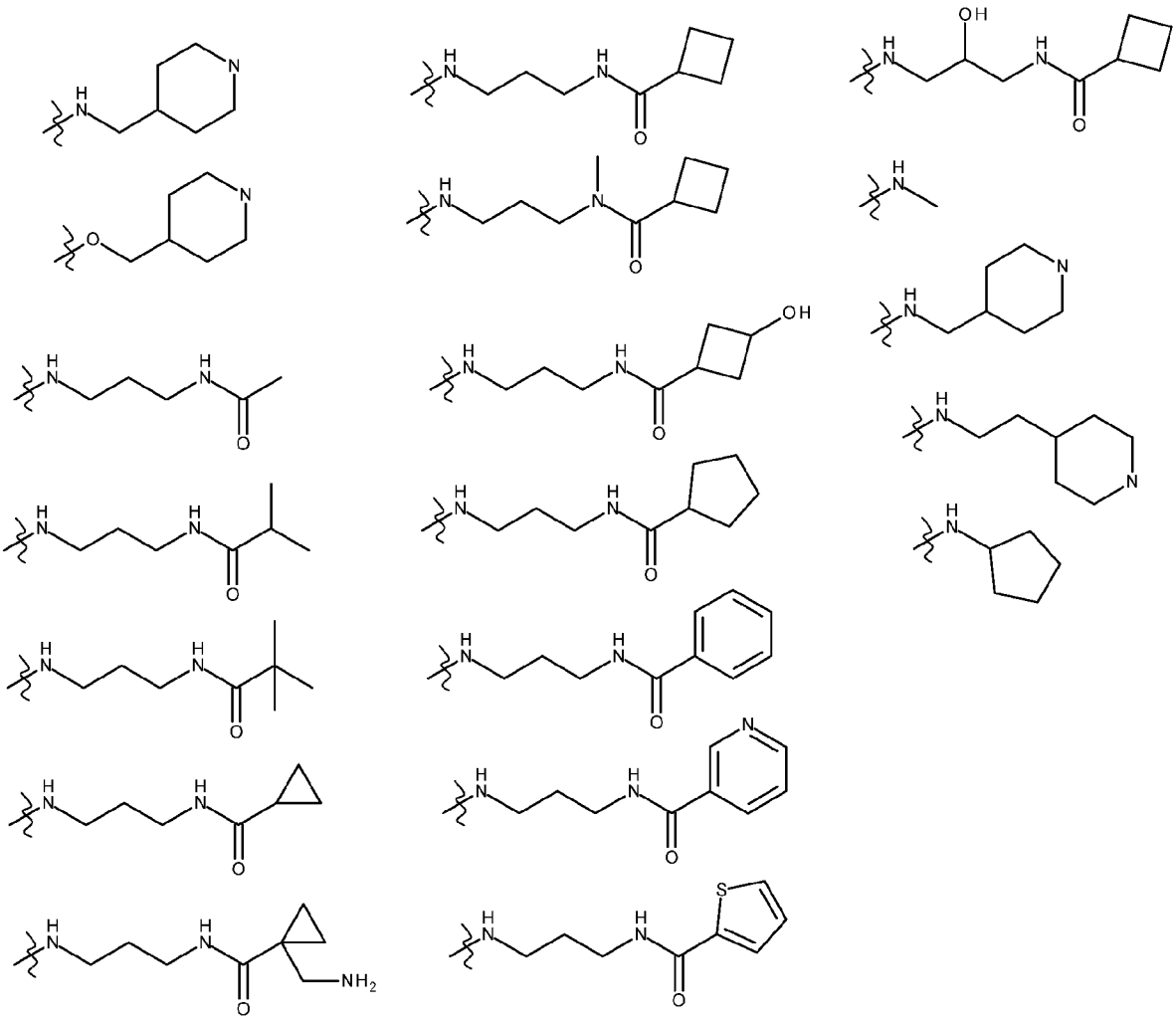


(XI)

wherein R^6 is Br, CN, $CONH_2$ or Cl;

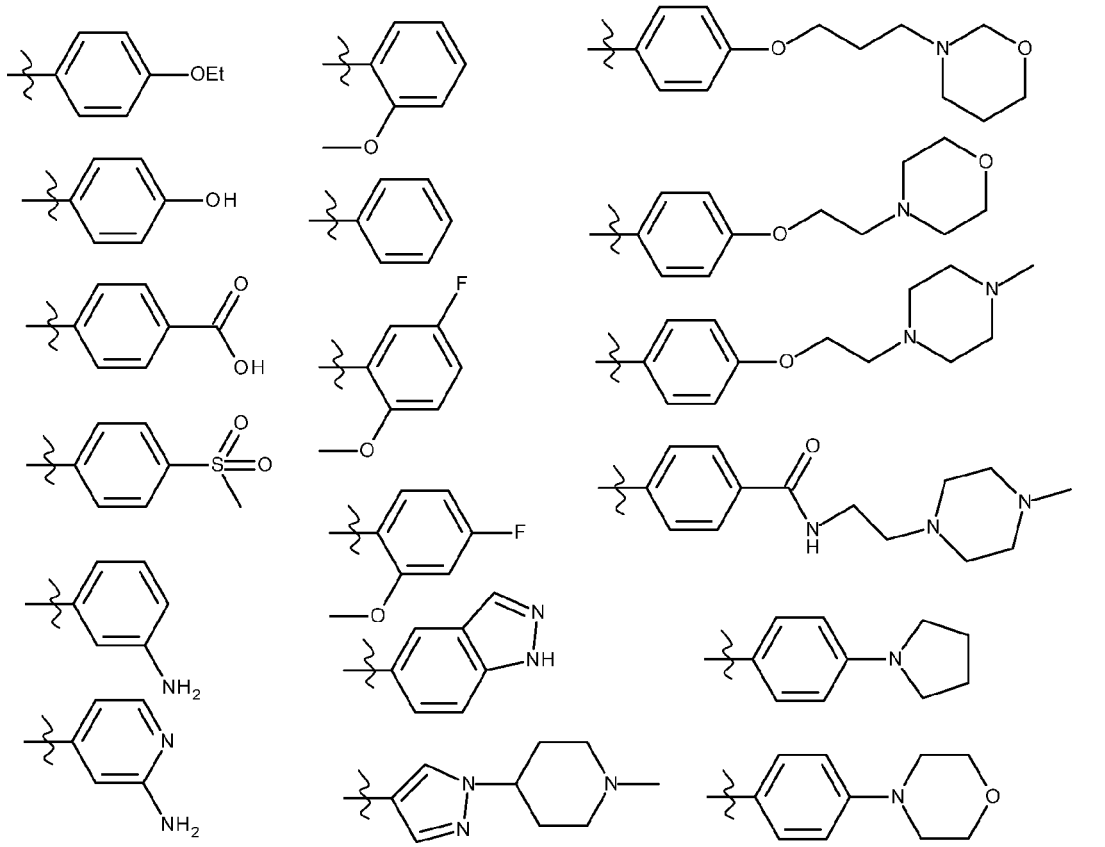
wherein R^7

represents



;

and wherein R^2 represents

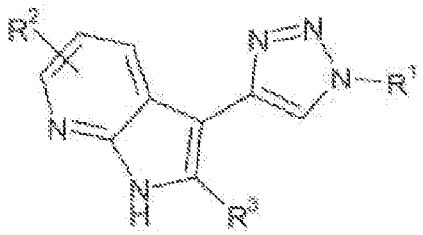


;

or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof.

(k) Compounds described in WO2010127754 (also published as US2012/0053178) that is to say:

1. Compounds of the formula (XII)



(XII)

in which R^1 denotes A, -[C(R^3)(R^4)]$_n$Ar, --[C(R^3)(R^4)]$_n$Het or --[C(R^3)(R^4)]$_n$Cyc,

R^2 denotes H, A, Hal, CN, -[C(R^3)$_2$]$_n$-Ar', -[C(R^3)$_2$]$_n$-Het', --[C(R^3)$_2$]$_n$-Cyc, OR^3 or N(R^3)$_2$,

R^3 denotes H or A,

R^4 denotes H, A, -[C(R^3)$_2$]$_n$$OR^3$, -[C($R^3$)$_2$]$_n$$COOR^3$, -[C($R^3$)$_2$]$_n$N($R^3$)$_2$ or -[C(R^3)$_2$]$_n$Het,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which one or two CH_2 groups may be replaced by O, N and/or S atoms and/or by --CH=CH-- groups and/or, in addition, 1-7 H atoms may be replaced by F,

Cyc denotes cycloalkyl having 3, 4, 5, 6 or 7 C atoms,

Ar denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, -[C(R^3)$_2$]$_n$$OR^3$, N($R^3$)$_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$ and/or S(O)$_n$A,

Ar' denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^3, N(R^3)$_2$, SR^3, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, $SO_2N(R^3)_2$, S(O)$_n$A, CO-Het_1, Het_1, [C(R^3)$_2$]$_n$N(R^3)$_2$, [C(R^3)$_2$]$_n$$Het_1$, O[C($R^3$)$_2$]$_n$N($R^3$)$_2$, O[C($R^3$)$_2$]$_n$$Het_1$, NHCOOA, $NHCON(R^3)_2$, NHCOO[C(R^3)$_2$]$_n$N(R^3)$_2$, NHCOO[C(R^3)$_2$]$_n$$Het_1$, NHCONH[C($R^3$)$_2$]$_n$N($R^3$)$_2$, NHCONH[C($R^3$)$_2$]$_n$$Het_1$, OCONH[C($R^3$)$_2$]$_n$N($R^3$)$_2$, OCONH[C($R^3$)$_2$]$_n$$Het_1$, CO-$Het_1$, CHO and/or COA,

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, and/or O and/or S atoms which is unsubstituted or mono- or disubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^S, SO_2NR^3 and/or S(O)$_n$A,

Het' denotes a mono-, bi- or tricyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms which is unsubstituted or may be mono- or disubstituted by Hal, A, OR^3, N(R^3)$_2$, SR^3, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, $SO_2N(R^3)_2$, S(O)$_n$A, CO-Het_1, Het_1, [C(R^3)$_2$]$_n$N(R^3)$_2$, [C(R^3)$_2$]$_n$$Het_1$, O[C($R^3$)$_2$]$_n$N($R^3$)$_2$, O[C($R^3$)$_2$]$_n$$Het_1$, NHCOOA, $NHCON(R^3)_2$, NHCOO[C(R^3)$_2$]$_n$N(R^3)$_2$, NHCOO[C(R^3)$_2$]$_n$Het.sup.1, NHCONH[C(R^3)$_2$]$_n$N(R^3)$_2$, NHCONH[C(R^3)$_2$]$_n$$Het_1$, OCONH[C($R^3$)$_2$]$_n$N($R^3$)$_2$, OCONH[C($R^3$)$_2$]$_n$$Het_1$, CO-$Het_1$, CHO, COA, =S, =NH, =NA and/or =O (carbonyl oxygen),

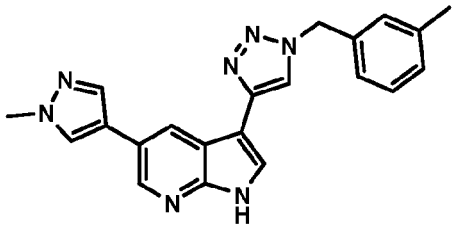
Het_1 denotes a monocyclic saturated heterocycle having 1 to 2 N and/or O atoms, which may be mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),

Hal denotes F, Cl, Br or I,

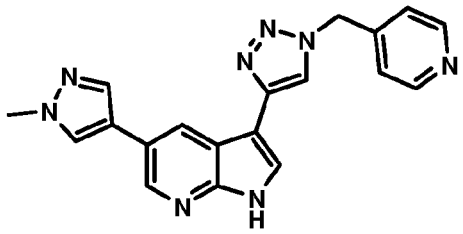
N denotes 0, 1 or 2,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

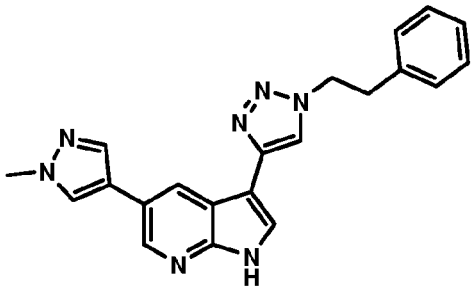
Preferred compounds have the following structures:



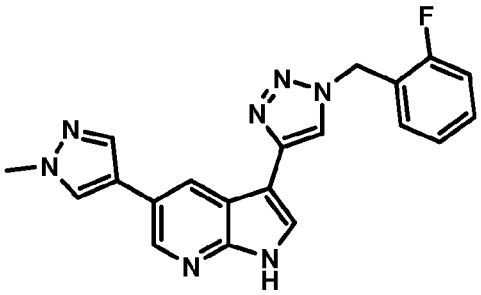
(XIIa)



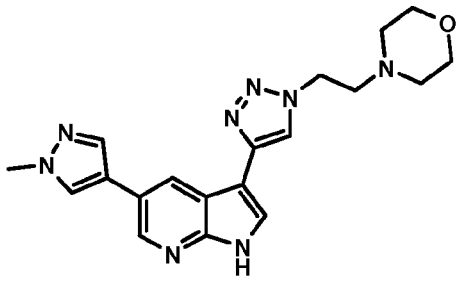
(XIIb)



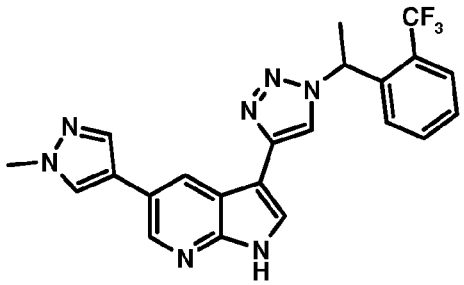
(XIIc)



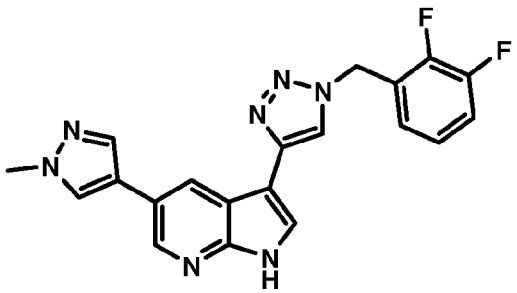
(XIId)



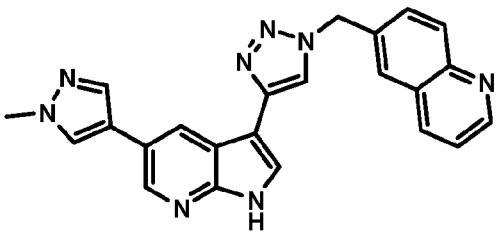
(XIIe)



(XIIf)



(XIIg)



(XIIh)

Further compounds are also described in WO2012059171.

A compound for use in the invention may be a compound that is a down-regulator of the expression of one or both of TBK1 and IKKε. Expression of one or both of TBK1 and IKKε may be down-regulated using anti-sense nucleic acid or RNAi technology, amongst other approaches. The use of these approaches to down-regulate gene expression is now well-established in the art. Anti-sense oligonucleotides may be designed to hybridise to the complementary sequence of nucleic acid, pre-mRNA or mature mRNA, interfering with the production of TBK1 or IKKε so that its expression is reduced or completely or substantially completely prevented. In addition to targeting coding sequence, anti-sense techniques may be used to target control sequences of a gene, e. g. in the 5' flanking sequence, whereby the anti-sense oligonucleotides can interfere with expression control sequences. The construction of anti-sense sequences and their use is described for example in Peyman and Ulman, *Chemical Reviews*, 1990, **90**, 543-584, and Crooke, *Ann. Rev. Pharmacol. Toxicol.* 1992, **32**, 329-376.

Oligonucleotides may be generated in vitro or ex vivo for administration or anti-sense RNA may be generated in vivo within cells in which down-regulation is desired. Thus, double-stranded DNA may be placed under the control of a promoter in a "reverse orientation" such that transcription of the anti-sense strand of the DNA yields RNA which is complementary to normal mRNA transcribed from the sense strand of the target gene. The complementary anti-sense RNA sequence is thought then to bind with mRNA to form a duplex, inhibiting translation of the endogenous mRNA from the target gene into protein. Whether or not this is the actual mode of action is still uncertain. However, it is established fact that the technique works.

The complete sequence corresponding to the coding sequence in reverse orientation need not be used. For example fragments of sufficient length may be used. It is a routine matter for the person skilled in the art to screen fragments of various sizes and from various parts of the coding or flanking sequences of a gene to optimise the level of anti-sense inhibition. It may be advantageous to include the initiating methionine ATG codon, and perhaps one or more nucleotides upstream of the initiating codon. A suitable fragment may have about 14-23 nucleotides, e. g. about 15, 16 or 17.

An alternative to anti-sense is to use a copy of all or part of the target gene inserted in sense, that is the same, orientation as the target gene, to achieve reduction in expression of the target

gene by co-suppression (see Angell & Baulcombe, *The EMBO Journal*, 1997, **16(12)**, 3675-3684; and Voinnet & Baulcombe, Nature , 1997, **389**, 553).

Double stranded RNA (dsRNA) has been found to be even more effective in gene silencing than both sense or antisense strands alone (Fire *et al.*, *Nature*, 1998, **391**, 806-811) [. dsRNA mediated silencing is gene specific and is often termed RNA interference (RNAi). RNA interference is a two-step process. First, dsRNA is cleaved within the cell to yield short interfering RNAs (siRNAs) of about 21-23nt length with 5' terminal phosphate and 3' short overhangs (-2nt). The siRNAs target the corresponding mRNA sequence specifically for destruction (Zamore, Nature *Structural Biology*, 2001, **8**, 746-750). RNAi may also be efficiently induced using chemically synthesized siRNA duplexes of the same structure with 3'-overhang ends (Zamore *et al.*, *Cell*, 2000, **101**, 25-33. Synthetic siRNA duplexes have been shown to specifically suppress expression of endogenous and heterologeous genes in a wide range of mammalian cell lines (Elbashir, *et al.*, *Nature*, 2001, **411**, 494-498).

Particular siRNA molecules that find use in the invention include RNAi reagents with the target sequence include:

5′-GAACGUAGAUUAGCUUAUA-3′ (TBK1) [SEQ ID NO. 1],
5-UGACAGAGAUUUACUAUCA-3′ (TBK1) [SEQ ID NO. 2],
5′-UAAAGUACAUCCACGUUAU-3′ (TBK1) [SEQ ID NO. 3],
5′-GGAUAUCGACAGCAGAUUA-3′ (TBK1) [SEQ ID NO. 4];
5′-ACAAACAGUUCAAGAAGUC-3′ (IKKε) [SEQ ID NO. 5],
5′-GGACCUGCUUCUCCACAUG-3′ (IKKε) [SEQ ID NO. 6],
5′-GAAGGCGGCUGCAGAACUG-3′ (IKKε) [SEQ ID NO. 7],
5′-GGCAGGAGCUAAUGUUUCG-3′ (IKKε) [SEQ ID NO. 8].

Whilst a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε may be used as the sole active agent, it is also possible for the compound to be used in combination with one or more further active agents. Such further active agents may be further compounds that are inhibitors of one or both of TBK1 and IKKε, or down-regulators of the expression of one or both of TBK1 and IKKε, or they may be different therapeutic agents, for example agents targeting one of the diseases mentioned above, particularly the same disease as that targeted by the compound of

the invention. A further therapeutic agent is selected from the group consisting of inhibitors of mTOR, inhibitors of PI3kinase, inhibitors of both mTOR and PI3kinase, inhibitors of AKT and inhibitors of PDK1. Examples of further therapeutic agents include: UCN01, (NVP)-BAG956, Celecoxib, OSU-03012, BX-795, BX-912, BX-320, AR-12, KP372-1, LY294002, PWT-458, PX-866, CAL-101, XL-147, ZSTK474, GDC-0941, (NVP)-BEZ235, AS-252424, TGX-221, XL-765, wortmannin, PI-103, Perifosine (KRX-0401), Triciribine (API-2), SR13688, AR-67 (DB-67), AR-42, GSK690693, KP372-1, A-443654, MK-2206, Rapamycin (Sirolimus), Temsirolimus (Torisel®, CCI-779), Everolimus (Afinitor®, RAD001), Deforolimus (Ridaforolimus, AP-23573), AZD-8055, OSI-027, INK-128, PP-242. These and further therapeutic agents are described in further detail in Chapell et al, *Oncotarget*, 2011, **2**, 135-164.

In certain cancers in which activation of the Ras/Raf/Mek/Erk pathway is important, for example those tumours containing activating mutations in *KRAS* or *BRAF,* inhibition of the Ras/Raf/Mek/Erk pathway in conjunction with inhibition of the PI3 kinase pathway could provide an important therapeutic strategy (Chappell, 2011; Engleman *et al.*, *Nat. Med.*, 2008, **14**, 1351-1356). A compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε may be used in combination with an inhibitor of the Ras/Raf/Mek/Erk pathway, in particular in tumours that contain activating mutations in this pathway. Examples of therapeutic agents that inhibit the Ras/Raf/Mek/Erk pathway are: Tipifarnib (Zarnesta™, R115777), Sorafenib (Nexavar®, BAY43-9006), AAL-881, LBT-613, RAF265, XL281, SB-590885, PLX-4720, PLX-4032, L-779,450, GW5074, SB-699393, CI-1040 (PD184352), PD0325901, XL518, Selumtinib (AZD6244, ARRY-142886), RDEA119 (BAY 869766), PD098059, U0126, SL-327. These and further therapeutic agents are described in further detail in Chapell, 2011.

The compound of the invention may be co-formulated with the additional agent, or it may be formulated separately and administered consecutively, simultaneously or sequentially with the additional agent.

The amount of active ingredient which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, including the type, species, age, weight, sex, and medical condition of the subject and the renal and hepatic function of the subject, and the particular cancer being treated, as well as its severity. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 mg per kg of body weight per day (mg/kg/day) to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day, for adult humans. For oral administration, the compositions are preferably provided in the form of tablets or other forms of presentation provided in discrete units containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The pharmaceutical formulations according to the invention include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous (bolus or infusion), and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered doses pressurized aerosols), nebulizers or insufflators, rectal, intraperitoneal and topical (including dermal, buccal, sublingual, and

intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, pills or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate, calcium sulfate, sorbitol, glucose and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. 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. Disintegrators include without limitation starch, methylcellulose, agar, bentonite, xanthan gum and the like. The compounds of the invention can also be

delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. For oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for nasal, aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives,

absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

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

Methods for the therapeutic delivery of si~RNA agents are well known to those skilled in the art, for example as described in Xie *et al.*, *Drug Discovery Today*, 2006 **11** (1-2), 67-73. "Harnessing *in vivo* siRNA delivery for drug discovery and therapeutic development".

In a further embodiment, the invention provides a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, for use in a method of treating a cancer that is dependent on the PI3kinase pathway comprising:

- identifying a cancer in the individual as being dependent on the PI3kinase pathway, and
- administering the compound to the individual.

The cancer may be a cancer as described above. The compound may be a compound as described above.

In a further embodiment, there is provided a method of treating cancer in an individual in whom the cancer is dependent on the PI3kinase pathway, comprising administering to the individual a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε. The cancer may be a cancer as described above. The compound may be a compound described above.

In a further embodiment, there is provided a method of treating cancer in an individual comprising:
- identifying the cancer as dependent on the PI3kinase pathway, and
- administering to the individual a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε.

The cancer may be a cancer as described above. The compound may be a compound as described above.

The invention further provides a method of determining the susceptibility of a cancer in an individual to treatment with a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, comprising determining whether the cancer is dependent on the PI3kinase pathway, whereby a dependence on the PI3kinase pathway indicates that the cancer in the individual has an increased susceptibility to a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε.

The cancer may be a cancer as described above. The compound may be a compound as described above.

The invention further provides a method of determining a suitable treatment for an individual with a cancer comprising:
determining whether the cancer is dependent on the PI3kinase pathway; and
determining a suitable treatment, whereby a compound that is an inhibitor of one or both of TBK1 and IKKε is suitable in the treatment of an individual with a cancer that is dependent on the PI3kinase pathway.

The cancer may be a cancer as described above. The compound may be a compound as described above.

A method of determining a suitable treatment may including determining that a particular treatment is not suitable in the subject. For example, if a cancer is found not to be dependent on the PI3kinase pathway, then an inhibitor of one or both of TBK1 and IKKε might not be suitable in the treatment of the individual.

The invention further provides a method of predicting the response of a cancer condition in an individual to a treatment with a compound that is an inhibitor of one or both of TBK1 and IKKε by determining whether the cancer is dependent on the PI3kinase pathway.
The cancer may be a cancer as described above. The compound may be a compound as described above.

In some embodiments, a cancer may be identified as dependent on the PI3kinase pathway by determining the presence in cancer cells from the individual of one or more variations, for example, polymorphisms or mutations, in a nucleic acid encoding a polypeptide that is a component of the PI3kinase pathway.
In some embodiments, a cancer may be identified as being deficient in PTEN activity by determining the presence in cancer cells from the individual of one or more variations, for example, polymorphisms or mutations, in a nucleic acid encoding a PTEN polypeptide.

In some embodiments, a cancer may be identified as having overactive PI3kinase signalling by determining the presence in cancer cells from the individual of one or more variations, for example, polymorphisms or *PIK3CA* mutations, in a nucleic acid encoding an overactive PI3 kinase p110 polypeptide.

In some embodiments, a cancer may be identified as being deficient in PTEN activity by determining the presence in cancer cells from the individual of one or more variations, for example, polymorphisms or mutations, in a nucleic acid encoding a PTEN polypeptide. A cancer may be identified as having overactive PI3kinase signalling by determining the presence in cancer cells from the individual of one or more variations, for example, polymorphisms or mutations, in a nucleic acid encoding an PI3 kinase p110 polypeptide, for

example *PIK3CA*, which polymorphisms or mutations cause the PI3 kinase to be overactive, or one or more variations in the nucleic acid controlling expression of a PI3 kinase p110 polypeptide, for example *PIK3CA,* which cause the PI3 kinase to be over-expressed. Sequence variations such as mutations and polymorphisms may include a deletion, insertion or substitution of one or more nucleotides, relative to the wild-type nucleotide sequence. In some embodiments, the variation may be a gene amplification. The one or more variations may be in a coding or non-coding region of the nucleic acid sequence and, may reduce or abolish the expression of a negatively regulating pathway component polypeptide, for example PTEN. The variant nucleic acid may encode a variant polypeptide which has reduced or abolished activity or may encode a wild-type polypeptide which has little or no expression within the cell, for example through the altered activity of a regulatory element. A variant nucleic acid may have one, two, three, four or more mutations or polymorphisms relative to the wild-type sequence. Furthermore, a cancer may be determined to be heterozygous or homozygous in mutant forms of one or more components, leading to a dependency on the PI3kinase pathway.

Various methods are available for determining, in a sample obtained from an individual, the presence or absence of a particular nucleic acid sequence, for example a nucleic acid sequence which has a mutation or polymorphism that reduces or abrogates the expression or activity of a PI3kinase pathway component, or that increases the expression or activity of a PI3kinase pathway component, as the case may be depending on the role that the component plays in the pathway or its control.

Furthermore, having sequenced nucleic acid of an individual or sample, the sequence information can be retained and subsequently searched without recourse to the original nucleic acid itself.

Thus, for example, scanning a database of sequence information using sequence analysis software may identify a sequence alteration or mutation.

Methods according to some aspects of the present invention may comprise determining the binding of an oligonucleotide probe to nucleic acid obtained from the sample, for example, genomic DNA, RNA or cDNA. The probe may comprise a nucleotide sequence which binds

specifically to a nucleic acid sequence which contains one or more mutations or polymorphisms and does not bind specifically to the nucleic acid sequence which does not contain the one or more mutations or polymorphisms, or vice versa.

The oligonucleotide probe may comprise a label and binding of the probe may be determined by detecting the presence of the label.

A method may include hybridisation of one or more (e. g. two) oligonucleotide probes or primers to target nucleic acid. Where the nucleic acid is double-stranded DNA, hybridisation will generally be preceded by denaturation to produce single-stranded DNA. The hybridisation may be as part of a PCR procedure, or as part of a probing procedure not involving PCR. An example procedure would be a combination of PCR and low stringency hybridisation.

Binding of a probe to target nucleic acid (e. g. DNA) may be measured using any of a variety of techniques at the disposal of those skilled in the art. For instance, probes may be radioactively, fluorescently or enzymatically labelled. Other methods not employing labelling of probe include examination of restriction fragment length polymorphisms, amplification using PCR, RN'ase cleavage and allele specific oligonucleotide probing. Probing may employ the standard Southern blotting technique. For instance, DNA may be extracted from cells and digested with different restriction enzymes. Restriction fragments may then be separated by electrophoresis on an agarose gel, before denaturation and transfer to a nitrocellulose filter. Labelled probe may be hybridised to the DNA fragments on the filter and binding determined.

Those skilled in the art are well able to employ suitable conditions of the desired stringency for selective hybridisation, taking into account factors such as oligonucleotide length and base composition, temperature and so on.

Suitable selective hybridisation conditions for oligonucleotides of 17 to 30 bases include hybridization overnight at 42 °C in 6X SSC and washing in 6X SSC at a series of increasing temperatures from 42 °C to 65 °C. Other suitable conditions and protocols are described in Molecular Cloning: a Laboratory Manual: 3rd edition, Sambrook & Russell (2001) Cold

Spring Harbor Laboratory Press NY and Current Protocols in Molecular Biology, Ausubel et al. eds. John Wiley & Sons (1992).

Nucleic acid, which may be genomic DNA, RNA or cDNA, or an amplified region thereof, may be sequenced to identify or determine the presence of polymorphism or mutation therein. A polymorphism or mutation may be identified by comparing the sequence obtained with the database sequence of the component, as set out above. In particular, the presence of one or more polymorphisms or mutations that cause abrogation or loss of function of the polypeptide component in the case, for example, of PTEN; or over-expression or constitutive (i.e. unregulated) function of the polypeptide component in the case, for example, of *PIK3CA* mutations; and thus the activation of the PI3kinase pathway as a whole, may be determined. Sequencing may be performed using any one of a range of standard techniques. Sequencing of an amplified product may, for example, involve precipitation with isopropanol, resuspension and sequencing using a TaqFS+ Dye terminator sequencing kit. Extension products may be electrophoresed on an ABI 377 DNA sequencer and data analysed using Sequence Navigator software.

A specific amplification reaction such as PCR using one or more pairs of primers may conveniently be employed to amplify the region of interest within the nucleic acid sequence, for example, the portion of the sequence suspected of containing mutations or polymorphisms. The amplified nucleic acid may then be sequenced as above, and/or tested in any other way to determine the presence or absence of a mutation or polymorphism which reduces PTEN function, or enhances PI3kinase function, or the overall flux through the PI3kinase pathway. The polymerase chain reaction (PCR) has been reviewed, for instance in "PCR protocols; A Guide to Methods and Applications", Eds. Innis *et al*, 1990, Academic Press, New York, Mullis *et al*, Cold Spring Harbor Symp; Ehrlich (ed), PCR technology, Stockton Press, NY, 1989; and Ehrlich *et al*, *Science*, 1991, **252**, 1643-1650.

A number of methods have been described for the detection of mutant forms of *PIK3CA*. The most common activating *PIK3CA* mutations found in cancer are missense mutations resulting from a single base pair change in either: exon 20, coding the helical domain; or exon 9, coding the kinase domain. Examples of common mutations in exon 20 include the following nucleotide changes (corresponding amino acid changes shown in brackets) A3140G

(H1047R), A3150T (H1047L). Examples of common mutation in exon 9 include the following nucleotide changes (corresponding amino acid changes shown in brackets) G1633A (E545K), G1624A (E542K), G1634A (E545G). A method for the detection of mutations in exons 9 and 20 using single strand conformational polymorphism (SSCP) is described in US2011/0038862. Another method that has been used for the detection of *PIK3CA* mutants is the use of allele specific PCR using primers specifically designed against common mutants (H1047L, H1047R, E542K and E545K) using the Amplification Refractory Mutation System (ARMS™, AstraZeneca) and Scopions™ (DxS), a fluorescent signalling system that detects PCR products (Board *et al.*, *Clinical Chemistry*, 2008, **54** (4), 757-760).

A number of methods have been described for the detection of mutant forms of *PTEN*. Both missense and 'nonsense' mutations (i.e. stop codon, frameshift or splicing mutations) are found in human cancers. The most common of these are nonsense mutations which often result in inactive truncated forms of the protein. A method for the detection of truncated PTEN mRNA has been described using a yeast-based assay, which relies on the incorporation of full length *PTEN* cDNA into a primer which leads to the expression of a PTEN::ADE2 (EC 4.1.1.21) protein. Colonies which lack a functional ADE2 protein appear red due to the accumulation of the ADE2 substrate (Zhang et al., *Oncogene* 2000, **19**, 4346-4353). Another method for the detection of *PTEN* deletions involves the use of FISH probes directed at the *PTEN*-locus on chromosome region 10q23 (Chang et al., *Leukemia Research*, 2006, **30** 262-265).

Alternatively, the presence of one or more variations in a component of the PI3kinase pathway may be determined by detecting, in one or more cells of a test sample, the presence of the variant component polypeptide, or the absence or reduced amount of the non-mutated component polypeptide (e.g. detection of the levels of PTEN) which is encoded by the nucleic acid sequence. A method of identifying a cancer cell in a sample from an individual as dependent on the PI3kinase pathway may include contacting a sample with a specific binding member directed against a variant (e. g. a mutant) polypeptide component of the pathway, and determining binding of the specific binding member to the sample. Another method of identifying a cancer cell in a sample from an individual as dependent on the PI3kinase pathway may include contacting a sample with a specific binding member directed against a phosphorylated polypeptide component of the pathway, and determining binding of

the specific binding member to the sample. A preferred phosphorylated polypeptide for this purpose is phospho-PDK1 (Vasudevan *et al.*, 2011).

Binding of the specific binding member to the sample may be indicative of the presence of the variant polypeptide component, or phosphorylated polypeptide component, of the pathway in a cell within the sample. Preferred specific binding molecules for use in aspects of the present invention include antibodies and fragments or derivatives thereof ('antibody molecules'). The reactivities of a binding member such as an antibody on normal and test samples may be determined by any appropriate means. Tagging with individual reporter molecules is one possibility. The reporter molecules may directly or indirectly generate detectable, and preferably measurable, signals. The linkage of reporter molecules may be directly or indirectly, covalently, e. g. via a peptide bond or non-covalently. Linkage via a peptide bond may be as a result of recombinant expression of a gene fusion encoding binding molecule (e. g. antibody) and reporter molecule.

Antibodies for PTEN are commercially available and can be used to assess the amounts of PTEN using standard techniques such as western blotting. Reverse-phase protein array (RPPA) analysis, a high throughput technique that can be used to assess multiple tissue samples, has also been used to assess levels of PTEN protein (Vasudevan *et al.*, 2011). Antibodies for phophorylated kinases such as phospho-PDK-1 or phospho-mTOR are readily available from commercial suppliers. Sotiriou *et al.* have described a signature for PI3 kinase pathway activation in breast cancer samples using microarray analysis, this or similar approaches could also be used for identifying tumours with activation of the PI3 kinase pathway (US2011/0038862).

Additionally tumours that contain a combination of mutations or transformations to members that can activate the PI3 kinase pathway may also be considered dependant on the PI3 kinase pathway. For example this could take the form of the combination of a PIK3CA mutation and the loss or low levels of PTEN. Alternatively it may be the over-expression of a growth factor receptor which can activate the PI3 kinase pathway. For example the over-expression of ErbB2 in breast cancer in combination with a reduction in the amount of PTEN, or with an activating mutation in PIK3CA. Another example would be in activating mutation in a Ras protein for example K-Ras and a mutation in PIK3CA or a reduction in the amount of PTEN.

Methods for the detecting the over expression of growth factor receptors or the presence of RAS mutations are well known in the art.

Examples:

A - Assays for activity against the IKKε and TBK-1 enzyme

Compounds of the invention (synthesised as described below) were tested for activity against the IKKε and TBK-1 enzyme as follows:

Inhibitions studies were performed using a time-resolved fluorescence-based Lanthascreen™ assay. Phosphorylation of a fluorescein-labelled substrate peptide is measured using terbium-labeled phosphospecific antibodies. Terbium is excited at 340 nm and the FRET energy transfer to fluorescein is measured at 495 and 520 nm. The emission ratio between 520 and 495 is a measure of the level of phosphorylation of the substrate by the kinase.

Kinase inhibition assays (10 μL) were performed at 20°C in 384-well plate format. Compound IC50 values were determined at the apparent Km for ATP (20 μM) based on a radiometric assay (Invitrogen) using 8 or 10 point curves in duplicate. The final reaction conditions contained 400 nM fluorescein–IkBα substrate (DRHDSGLDSMKDE), 20 μM ATP, 2 nM or 8 nM IKKε or TBK1 kinase respectively, and 3% DMSO in kinase assay buffer consisting of 50 mM HEPES (pH 7.5), 10 mM MgCl, 1 mM EGTA, 0.01% Brij-35.

Compound dilutions were prepared from 10 mM DMSO stocks by dilution into DMSO. Compound dilution series were further diluted in kinase assay buffer to give a 12% DMSO stock, the final concentration in the assay being 3% DMSO.

The kinase phosphorylation assay was initiated by the addition of the kinase and the reaction was allowed to proceed for 1 hr or 2.5 hr for IKKε and TBK-1 kinase respectively. Both conditions were within the linearity of the phosphorylation. The reaction was stopped by the addition of 10 mM EDTA, and phosphorylation was detected after a 1hr incubation with 1.5 nM terbium-labelled antibody against phosphorylation at Serine 32 on the IkBα peptide, both in TR-FRET dilution buffer (Invitrogen).

The results of the testing are show below.

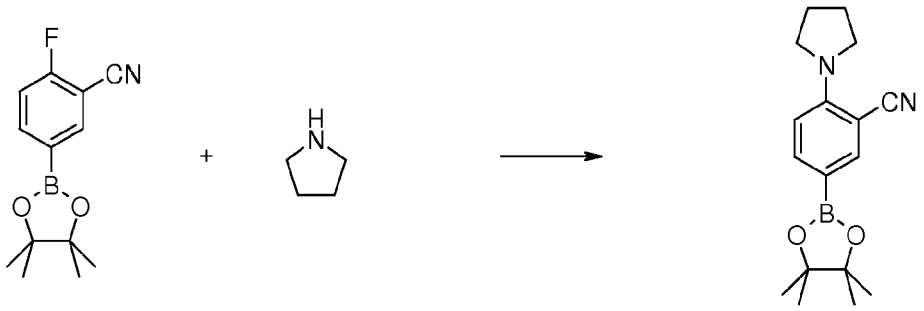
B – Synthesis of inhibitors of IKKε or TBK-1

Abbreviations Used

DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
LC-MS	Liquid chromatography-mass spectrometry
MeCN	Acetonitrile
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
NMP	*N*-Methylpyrrolidinone
THF	Tetrahydrofuran

Example DMX-A: Synthesis of 3-[4-(3-cyano-4-pyrrolidin-1-yl-phenyl)-pyrimidin-2-ylamino]-benzamide

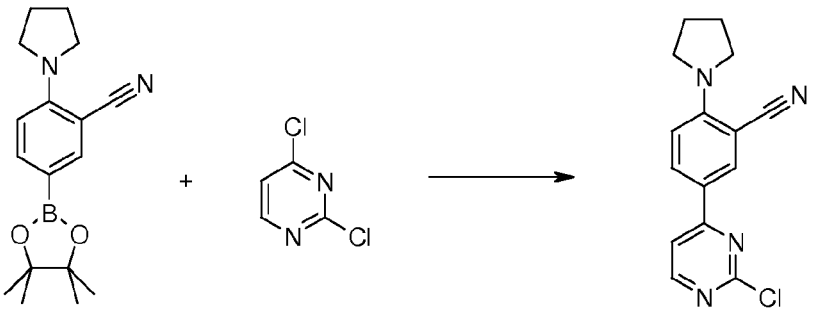
2-pyrrolidin-1-yl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile



3-Cyano-4-fluorophenyl-boronic acid pinacol ester (250 mg, 1.01 mmol) was dissolved in NMP (4 mL). Pyrrolidine (415 µL, 5.05 mmol) was added and the mixture heated at 140 °C in the microwave (300W, stirring) for 5 minutes. The reaction was repeated 14 more times. The 15 reaction mixtures were combined and the solvent evaporated *in vacuo* (*Genevac*™). The residue was dissolved in EtOAc (200 mL) and the solution washed with saturated brine solution (2 x 75 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent

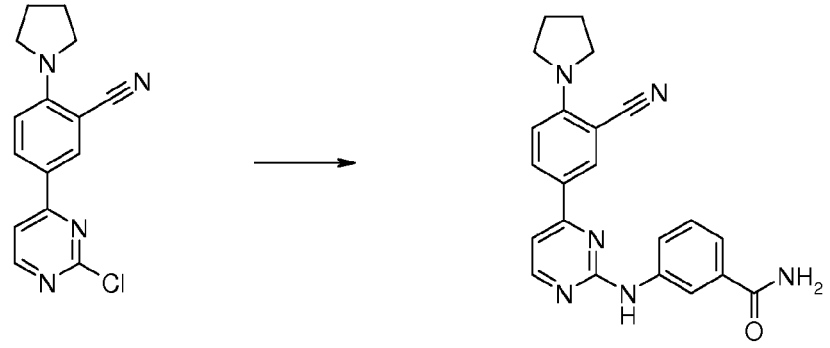
evaporated *in vacuo*. The crude product was purified by flash column chromatography (40-63 mesh silica gel, 90% isohexane-EtOAc) to provide the title compound as an off-white solid (2.84 g, 63%); LC-MS, R_t = 3.33 min (MeOH-FA method), m/z 298 (MH^+).

5-(2-chloro-pyrimidin-4-yl)-2-pyrrolidin-1-yl-benzonitrile



Pyrrolidin-1-yl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile (200 mg, 0.67 mmol), 2,4-dichloropyrimidine (120 mg, 0.81 mmol), tetrakis(triphenylphosphine)palladium(0) (78 mg, 0.07 mmol, 10 mol%) and sodium carbonate (213 mg, 2.01 mmol) were diluted with 1:1 1,4-dioxane-H_2O (4.0 mL). The mixture was then heated at 100 °C in the microwave (300W, stirring) for 10 minutes. The reaction was repeated four more times. The reaction mixtures were combined and the solvents evaporated *in vacuo (Genevac™)*. The residue was partitioned between DCM (150 mL) and H_2O (50 mL). The organic phase was washed with water (50 mL) and saturated brine solution (75 mL). The organic phase was then dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (40-63 mesh silica gel, 70% isohexane-EtOAc) to provide the title compound as a yellow solid (727 mg, 76%); LC-MS, R_t = 2.80 min (MeOH-FA method), m/z 285, 287 (MH^+).

3-[4-(3-cyano-4-pyrrolidin-1-yl-phenyl)-pyrimidin-2-ylamino]-benzamide (**DMX-A**)



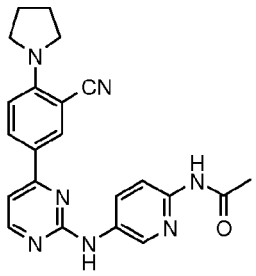
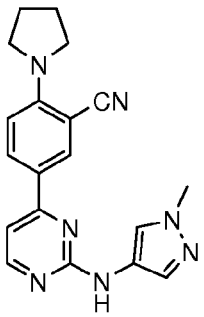
DMX-A

5-(2-Chloro-pyrimidin-4-yl)-2-pyrrolidin-1-yl-benzonitrile (50 mg, 0.18 mmol) was dissolved in NMP (1 mL). 3-Aminobenzamide (100 mg, 0.734 mmol) was added and the mixture was heated at 140 °C in the microwave (300W, stirring) for 45 minutes. The solvent was evaporated *in vacuo* (Genevac™). The residue was dissolved in DMSO (1.5 mL) and the crude product purified by reversed phase preparative LC-MS. Fractions containing desired product were combined and the solvents evaporated *in vacuo* (Genevac™). The title compound was afforded as an off-white solid (15.3 mg, 23%); LC-MS, R_t = 8.00 min (ANALpH2_MeOH_QC), m/z 400 (MH^+).

In addition to this procedure similar reactions may alternatively be accomplished by heating at 120-160°C for 15 to 360 minutes in a microwave reactor, with products purified by either reversed phase preparative LC-MS or flash chromatography on silica. Alternatively similar reactions may also be accomplished using potassium *tert*-butoxide in THF at reflux for 16 hours in a sealed tube, or potassium carbonate in DMF in a sealed tube at 125 °C for 16 hours.

The compound DMX-A had an IC_{50} for inhibition of IKKε of <30nM; and an IC_{50} for inhibition of TBK-1 of <30nM.

The following compounds were made using analogous chemistry to that described for example DMX-A:

Compound	Structure	Analytical Data	Inhibition of IKKε IC_{50}	Inhibition of TBK-1 IC_{50}
DMX-B		AnalpH2_MeOH_QC; Rt = 8.10 min; m/z 400 (MH^+); Pale brown solid.	<30nM	<30nM
DMX-C		Method X; Rt = 4.13 min; m/z 346 (MH^+); Yellow solid.	<30nM	<30nM

Analytical LC-MS Methods Used

ANALpH2_MeOH_QC: Phenomenex Luna C18 (2) 5 µm, 150 x 4.6 mm; 35°C; A = water + 0.1% formic acid; B = MeOH; 35°C; % B: 0 min 5%, 0.5 min 5%, 7.5 min 95%, 10 min 95%, 10.1 min 5%, 13 min 5%; 1.5 mL/min.

Method X: Xterra MS C18 2.5µm, 4.6 x 50 mm; A = water + 0.1% formic acid; B = MeCN + 0.1% formic acid; 25°C; % B: 0 min 10%, 4 min 90%, 7.5 min 90%, 7.6 min 10%; 1.0 mL/min.

In addition the compounds DMX-A, B and C were tested against a number of enzymes that are generally considered members of the PI3 kinase pathway. DMX-A, B and C showed high levels of selectivity for TBK1 and IKKε over the other enzymes tested: i.e. PDK-1, mTOR, PI3Kα, PI3Kβ, PI3Kγ and AKT-1.The assays were performed against IKKε and TBK-1 as described above. The counterscreening assays were performed using radiolabelled P^{33} ATP

using the Kinase Hotspot Technology (Reaction Biology Corp). Screening was carried out at the Km for ATP for IKK-ε and TBK-1 and at 10 μM ATP for the other enzymes, with the exception of screening of DMX-A against AKT-1 which was screened at 1μM ATP.

C – PTEN synthetic lethal interactions experiments

A synthetic lethality screen was performed using an isogenic model of PTEN deficiency. HCT116 human tumour cells in which both alleles of PTEN had been deactivated by gene targeting (Lee *et al.*, *Cancer Res.*, 2004, **64** (19) 6906-14) were used alongside isogenic PTEN wild type comparator HCT-116 cells. Both cell lines were screened with a siRNA library targeting ~720 kinases and kinase related genes and the affects of each siRNA on cell viability were assessed.

Cell lines were transfected with SMARTpool siRNAs using Dharmafect 3 (DF3-Dharmacon). The siRNA library (siARRAY – targeting 714 known and putative human protein kinase genes) was obtained in nine 96 well plates from Dharmacon (USA). Each well in this library contained a SMARTpool of four distinct siRNA species targeting different sequences of the target transcript. Each plate was supplemented with siCONTROL (ten wells, Dharmacon (USA)).

Cells were transfected with the SMARTpool library, where each well of the 96 well-plate contained a pool of four different siRNAs (a SMARTpool) targeting one gene. After five population doublings, cell viability in each well was estimated by use of a highly sensitive luminescent assay measuring cellular ATP levels (Cell Titre Glo, Promega). To identify loss of viability/failure to proliferate effects in each cell line, luminescence readings from each well were log transformed and then centred by the plate median, to account for plate-to-plate variation common in high-throughput screens. Well position effects were identified and eliminated and the quality of data from each plate estimated by calculating Z'-factors (Zhang *et al.*, *J. Biomol. Screen*, 1999, **4** (2), 67-73) based on positive (siRNA targeting PLK1) and negative (non-targeting siRNA) controls in each plate. The dynamic range of each screen was determined by calculating Z prime values (Zhang *et al.*; 1999); a threshold of Z prime >0.3 was used to define acceptable screens, based upon previous screens where Z prime >0.3 is predictive of reproducible data (Iorns, E., *et al.*, *Cancer Cell*, 2008, **13** (2), 91 - 104; Turner, N. C., *et al.*, *EMBO J.*, 2008, **27** (9), 1368 - 77). Analysis of the siRNA viability data

expressed as NPI scores (normalised percent inhibition) in the PTEN +/+ and PTEN -/- HCT 116 human tumour cell lines, wherein a NPI score < 1 indicates a loss of viability, identified that PTEN null cells were particularly sensitive to the knockdown of TBK-1. The NPI results of this experiment are shown in Figure 1. TBK-1 siRNAs show a selective lethality towards (PTEN-/-)-HCT116 cells.

D – PTEN matched pair TBK1/IKKε dose response experiments

Survival assays

For measurement of sensitivity to inhibitor treatment, cells were plated in 96 well plates and exposed to the drug at the indicated concentrations. For DMX-A and DMX-B, cells were dosed at 24 and 96 hours. After 7 days, cell viability was measured using CellTiter Glo Luminescent Cell Viability Assay (Promega, USA). Surviving fractions were calculated and drug sensitivity curves plotted as previously described (Farmer *et al.*, *Nature*, 2005 **434** (7035), 917-921). For DMX-C, cells were dosed every three days after initial plating. After 14 days, cell viability was measured using CellTiter Glo Luminescent Cell Viability Assay (Promega, USA). Results of these experiments are shown in Figure 2: Figure 2(a) shows the DMX-A results, Figure 2(b) shows the DMX-B results and Figure 2(c) shows the DMX-C results. A leftward shift for the (PTEN-/-) curve indicates a greater sensitivity of this cell type towards the inhibitors tested. In all cases an increased sensitivity of the PTEN null cells to TBK-1 inhibition is indicated by a leftwards shift of the curve relative to the PTEN +/+ HCT 116 line.

E – Dose response selectivity of TBK1/IKKε inhibitors on breast tumour cell lines and an ovarian tumour cell line For measurement of sensitivity to inhibitor treatment, cells were plated in 96 well plates and exposed to the drug at the indicated concentrations. Cells were dosed at 24 hours after plating and then inhibitor and media replaced 3 days later before cell viability was measured using CellTiter Glo Luminescent Cell Viability Assay (Promega, USA) at 7 days post plating. Surviving fractions were calculated and drug sensitivity curves plotted as previously described (Farmer *et al.*, 2005). See Figures 3(a) to 3(d) for results of dose response selectively in cells with PTEN mutations, and 3(e) for results of dose response selectively in cells with PTEN and PIK3CA mutations, Figures 4(a) to (c) for results of dose response selectively in cells with PIK3CA mutations, and Figures 5(a) to (e) for results of dose response selectively in cells with wild-type PTEN and PIK3CA. Figure 6(a) and (b)

show SF80 (concentration at which 80% of cells survive) and SF50 (concentration at which 50% of cells survive) results for cell lines with PTEN and/or PIKCA mutations and those with wild type PTEN and PIKCA.

DMX-C shows enhanced sensitivity towards cell lines containing either a PTEN mutation or a PIK3CA mutation compared to cell lines that contain both PTEN and PIK3CA wild-type.

All cell lines were obtained from ATCC (USA) and maintained according to the supplier instructions. STR profiling (short tandem repeat) profiling was used to verify the origin of the panel of cell lines. 8 STR loci were simultaneously amplified in a multiplex PCR reaction (Promega PowerPlex 1.2 System) and compared with the ATCC database. Where appropriate PTEN gene mutation status was determined by Sanger sequencing and western blot analysis and PIK3CA mutation status defined by Sanger sequencing. All of the cell lines used in the panel were human breast cancer cell lines with the exception of A2780 which is a human ovarian cancer cell line.

F- TBK1/IKKε sensitising to BEZ235

T47D cell line was purchased from ATCC (USA) and maintained according to the suppliers instructions. The authenticity of the cell line was verified as described above for panel of tumour cell lines. The sensitivity of this cell line to the PI3 kinase inhibitor BEZ235 was measured in the presence or absence of TBK-1 siRNA, shown in table 1 below. Cells were reverse transfected with siRNA and after 48 hours exposed to BEZ235. BEZ235 exposure was maintained for 7 days, with BEZ235 being replenished 3 days after the initial dosing. Two out of four TBK-1 siRNAs increased sensitivity to BEZ235, in a similar fashion to the positive control siRNA targeting PIK3CA.The siRNAs used were from Dharmacon siGenome® SMARTpool siRNA human protein kinase library. Results of this experiment are shown in Figure 7.

Table 1:

Pool Number	Duplex Number	Gene Symbol	Geneld	Agen Accession	GI Number	Sequence (5´-3´)	SEQ ID NO.
M-003788-02	D-003788-01	TEK1	29110	NM_013254	19743810	GAACGUAGAUUAGCUUAUA	1
M-003788-02	D-003788-02	TEK1	29110	NM_013254	19743810	UGACAGAGAUUUACUAUCA	2
M-003788-02	D-003788-06	TEK1	29110	NM_013254	19743810	UAAAGUACAUCCACGUUAU	3
M-003788-02	D-003788-07	TEK1	29110	NM_013254	19743810	GGAUAUCGACAGCAGAUUA	4

Qneg represents the negative control (i.e. no siRNA), PIK3CA represents a positive control targeting PIK3CA, and TBK_1-4 represents 4 different siRNAs targeting TBK1.

Claims:

1. A compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, for use in a method of treating a cancer that is dependent on the PI3kinase pathway.

2. A compound as claimed in claim 1 wherein the cancer is deficient in PTEN activity.

3. A compound as claimed in claim 2 wherein the level of PTEN protein is measured, or wherein the level of PTEN function is assessed by measuring the level of phospho-PDK1 present in the cancer cells.

4. A compound as claimed in any one of claim 1 to 3 wherein the cancer includes at least some cells carrying a loss of function mutation in the *PTEN* gene.

5. A compound as claimed in claim 4 wherein the presence or absence of loss of function mutations is assessed by determining the presence or absence of one or more mutations or polymorphisms in a nucleic acid sequence encoding at least a portion of the PTEN enzyme.

6. A compound as claimed in any one of claim 1 to 5 wherein the cancer has overactive PI3kinase signalling.

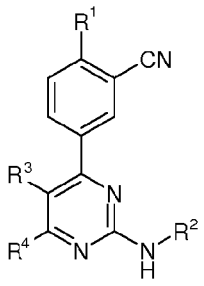
7. A compound as claimed in claim 6 wherein the level of PI3kinase signalling is assessed by measuring the level of phosphorylated PI3kinase pathways enzymes, such as-PDK1, AKT and mTOR, present in the cancer cells

8. A compound as claimed in claim 6 or 7 wherein the cancer includes at least some cells carrying an activating *PIK3CA* mutation.

9. A compound as claimed in claim 8 wherein the presence or absence of an activating *PIK3CA* mutation is assessed by determining the presence or absence of one or more mutations or polymorphisms in a nucleic acid sequence encoding at least a portion of the PI3kinase p110 catalytic subunit.

10. A compound as claimed in any one of claims 1 to 9 wherein the compound is an inhibitor of an inhibitor of one or both of TBK1 and IKKε selected from selected from the group consisting of:

(a) compounds of Formula (I):



(I)

in which:

R^1 represents an aliphatic heterocyclyl group having 4, 5, 6 or 7 ring atoms, bonded to the phenyl group shown in formula I through a ring nitrogen atom, and optionally substituted by one or more substituents selected from halogen atoms; OH; =O; C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups, each optionally substituted by one or more substituents independently selected from halogen atoms and NR^aR^b groups; NO_2; CN; NR^aR^b; COR^c; $O.CO.R^c$; CO_2R^a; $NR^a.COR^c$; $NR^aCO_2R^b$; $C(=NH)NH_2$; SO_2R^c; $NR^aSO_2R^c$; and $CH(CF_3)NH_2$;

R^2 represents a phenyl or heteroaryl group which is optionally substituted by one or more substituents independently selected from:

halogen atoms;

NR^aR^b;

C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl groups, each optionally substituted by one or more substituents independently selected from halogen atoms and NR^aR^b groups; and

$-(CH_2)_p$-R' in which p is 0, 1, 2, 3 or 4 and R' represents one of the following substituents: OH; NO_2; CN; COR^c; $O.CO.R^c$; CO_2R^b; $NR^a.COR^c$; $NR^aCO_2R^b$; $C(=NH)NH_2$; SO_2R^c; $NR^aSO_2R^c$; and $CH(CF_3)NH_2$;

and/or which is optionally substituted on adjacent ring atoms by a group $-NR^a.CO.(CH_2)_n$- or $-(CH_2)_n.CO.NR^a$- forming a fused ring;

R^a represents a hydrogen atom or a C_{1-4}alkyl group;

R^b represents a hydrogen atom, a C_{1-4}alkyl group optionally substituted by a group NR^aR^a, or a cycloalkyl group in which a CH_2 moiety may be replaced by an oxygen atom or an NR^a group;

R^c represents a hydrogen atom, a group $-NR^aR^b$, or a C_{1-4}alkyl group optionally substituted by a group NR^aR^b;

or R^a and R^b together may, when attached to the same nitrogen atom, represent a $-(CH_2)_m-$ group in which a CH_2 moiety may be replaced by an oxygen atom or an $-NR^a-$ group;

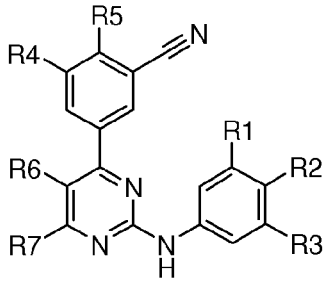
m represents 4 or 5;

n represents 1 or 2; and

each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group;

or a salt thereof;

(b) compounds of Formula (II):



(II)

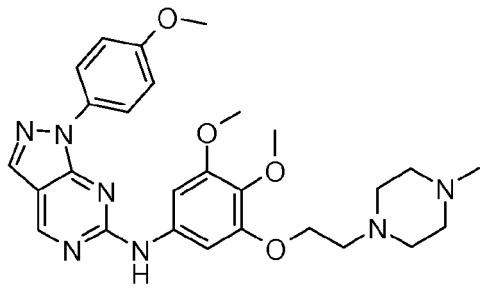
and pharmaceutically acceptable salts thereof, wherein:

R1 , R2, R3, and R5 are independently chosen from the following groups: alkyl, alkylene, alkenyl, alkenylene, alkynyl, carbocycle, cycloalkyl, cycloalkenyl, heterocycle, aryl, heteroaryl, halo, hydro, hydroxyl, alkoxy, alkynyloxy, cycloalkyloxy, heterocycloxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, mercapto, alkylthio, arylthio, cycloalkylthio, arylalkyl, heteroarylalkyl, heteroarylalkenyl, arylalkynyl, haloalkyl, aldehyde, thiocarbonyl, O-carboxy, C-carboxy, carboxylic acid, ester, C-carboxy salt, carboxyalkyl, carboxyalkenylene, carboxyalkyl salt, carboxyalkoxy, carboxyalkoxyalkanoyl, amino, aminoalkyl, nitro, O-carbamyl, N- carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, aminothiocarbonyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, cyano, nitrile, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, sulfonamide, aminosulfonyl, aminosulfonyloxy, sulfonamidecarbonyl, alkanoylaminosulfonyl, trihalomethylsulfonyl, or trihalomethylsulfonamide,

wherein any of the foregoing groups are optionally substituted at least once with alkyl, alkylene, alkenyl, alkenylene, alkynyl, carbocycle, cycloalkyl, cycloalkenyl, heterocycle, aryl, heteroaryl, halo, hydro, hydroxyl, alkoxy, alkynyloxy, cycloalkyloxy, heterocycloxy, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, mercapto, alkylthio, arylthio, cycloalkylthio, arylalkyl, heteroarylalkyl, heteroarylalkenyl, arylalkynyl, haloalkyl, aldehyde, thiocarbonyl, O-carboxy, C-carboxy, carboxylic acid, ester, C-carboxy salt, carboxyalkyl, carboxyalkenylene, carboxyalkyl salt, carboxyalkoxy, carboxyalkoxyalkanoyl, amino, aminoalkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N- thiocarbamyl, C-amido, N-amido, aminothiocarbonyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, cyano, nitrile, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, sulfonamide, aminosulfonyl, aminosulfonyloxy, sulfonamidecarbonyl, alkanoylaminosulfonyl, trihalomethylsulfonyl, or trihalomethylsulfonamide,

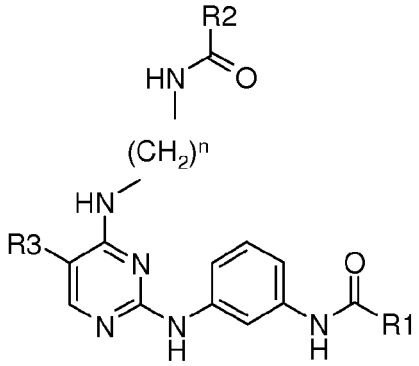
or, R2 and either Rl or R3, together with the carbon atoms to which they are bound, form an optionally-substituted cycloalkyl, heterocycle, aryl, or heteroaryl;
R4 is independently chosen from hydro, halo, and an optionally-substituted group chosen from lower alkyl, haloalkyl, alkoxy, arylalkoxy, heteroarylalkoxy, and heterocycloalkoxy;
R6 and R7 are independently chosen from hydro, halo, and lower alkyl;
or R6, taken together with R7, form an aryl or heteroaryl ring;

(c) a compound of Formula (III):



(III)

(d) compounds of Formula (IV):



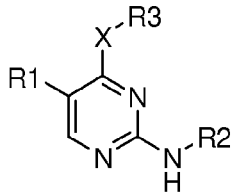
(IV)

wherein n is from 2-6;

R_1 is a 5 or 6 membered cyclic alkyl ring or aromatic cyclic ring, wherein optionally one or more carbons in the ring structure is substituted by an O, N or S;

R^2 is a 5 or 6 membered cyclic alkyl ring or arromatic cyclic ring, wherein optionally one or more carbons in the ring structure is substituted by an O, N or S, or is a linear or branched substituted or unsubstituted C_1-C_6 alkyl, C_1-C_6 alkoxy or C_2-C_6 alkenyl, wherein when substituted the substituent group may be a $C(=O)NH_2$;COOH; OH, NH_2, NO_2, and R_3 is a halo, H, CH_3, CN, NO_2;

(e) compounds of Formula (V):



(V)

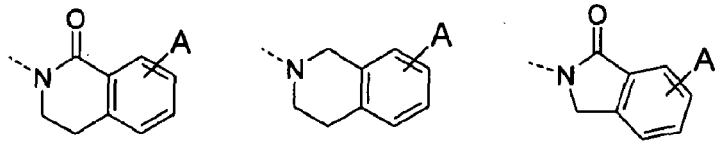
wherein: R^1 is C_{3-8}-cycloalkyl;

X is O, NR^7 or C_{3-6}-heterocycloalkyl;

R^2 is aryl, heteroaryl, fused or unfused aryl-C_{3-6}-heterocycloalkyl or fused or unfused heteroaryI-C_{3-6}- heterocycloalkyl, each of which is optionally substituted by one or more

substitutents selected from aryl, heteroaryl, C_{1-6}-alkyl, C_{3-7}-cycloalkyl and a group A, wherein said C_{1-6}-alkyl group is optionally substituted by one or more substituents selected from aryl, heteroaryl, R^{10} and a group A, said heteroaryl group is optionally substituted by one or more R<10> groups; and wherein said C_{3-6}- heterocycloalkyl group optionally contains one or more groups selected from oxygen, sulfur, nitrogen and CO;

R^3 is C_{1-6}-alkyl optionally substituted by one or more substituents selected from aryl, heteroaryl, -NR^4R^5, -OR^6, -$NR^7(CO)R^6$, -$NR^7(CO)NR^4R^5$, -NR^7SO2R^6, -NR^7COOR^7, -$CONR^4R^5$, C_{3-6}-heterocycloalkyl and



wherein said aryl, heteroaryl and C_{3-6} -heterocycloalkyl groups are each optionally substituted by one or more substituents selected from -C_{1-6}-alkyl and a group A, wherein said -C_{1-6}-alkyl group is optionally substituted by one or more substituents selected from aryl, heteroaryl and a group A;

A is selected from halogen, hydroxyl, cyano, trifluoromethyl, alkoxy, -NO_2, -NH_2, -NR^4R^5, -OR^6, -$NR^7(CO)R^6$, -$NR^7(CO)NR^4R^5$, -NR^7COOR^7, -NR^7 (SO_2)R^6, - CO_2H, -$NR^7CSO_2)NR^4R^5$, -$COOR^7$, -$CONR^4R^5$, COR^6, $SO2NR^4R^5$ and -SO_2CH_3;

each R^4 and R^5 is independently selected from hydrogen, C_{3-7}-cycloalkyl, aryl, heteroaryl, C_{1-6}-alkyl and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO and optionally substituted by one or more R^{10} groups, wherein said C_{1-6}-alkyl is optionally substituted by one or more substituents selected from halogen, cyano, hydroxyl, aryl, heteroaryl, -NR^8R^9, -NR^7 ($CO)R^6$, NR^7COOR^6, -NR^7 (SO_2)R^6, -$COOR^6$, -$CONR^8R^9$, OR^{10}, -$SO2R^6$ and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO and optionally substituted by one or more or R^{10} groups; or

R^4 and R^5 together with the N to which they are attached form a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO, wherein said C_{3-6}-heterocycloalkyl ring may be saturated or unsaturated and is optionally substituted with one or more groups selected from NR^8R^9 and R^{10} groups;

each R^6 is independently selected from C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{4-7}-heterocycloalkyl, aryl and heteroaryl, each of which may be optionally substituted by one or more substituents selected from halogen, R^{10} and $-NR^8R^9$;

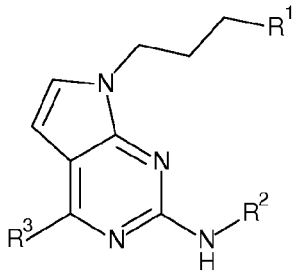
each R^7 is selected from hydrogen, C_{1-6}-alkyl and C_{3-7}-cycloalkyl, wherein said C_{1-6}-alkyl is optionally substituted by one or more halogens;

each of R^8 and R^9 is independently selected from hydrogen and C_{1-6}-alkyl, wherein said C_{1-6}-alkyl group is optionally substituted by one or more halogens; or

R^8 and R^9 together with the N to which they are attached form a C_{4-6}-heterocycloalkyl ring optionally further containing one or more heteroatoms selected from oxygen and sulfur, wherein said C_{4-6}-heterocycloalkyl ring is optionally substituted by one or more R^{10} groups; and

each R^{10} is selected from halogen, C_{3-7}-cycloalkyl and C_{1-6}-alkyl optionally substituted by one or more halogens, wherein where R^{10} is C_{1-6}-alkyl and two or more R^{10} groups are attached to the same carbon atom, the R^{10} groups may be linked to form a spiroalkyl group;

(f) compounds of Formula (VI):



(VI)

wherein: R^1 is $-NR^7(CO)R^{11}$;

R^2 is aryl, heteroaryl, fused aryl-C_{3-6} -heterocycloalkyl or fused heteroaryl-C_{3-6}-heterocycloalkyl, each of which is optionally substituted by one or more substitutents selected from aryl, heteroaryl, C_{1-6}-alkyl, C_{3-6} -heterocycloalkyl and a group A, wherein said C_{1-6}-alkyl group is in turn optionally substituted by one or more substituents selected from aryl, heteroaryl, C_{3-6}-heterocycloalkyl and a group A, said heteroaryl group is optionally substituted by one or more R^{10} groups; and wherein each C_{3-6}-heterocycloalkyl group is optionally substituted by one or more groups selected from C_{1-6}-alkyl, C_{1-6}-haloalkyl, and A, and which optionally contains one or more groups selected from oxygen, sulphur, nitrogen and CO;

R^3 is H, halogen, cyano or C_{1-6}-alkyl;

A is selected from halogen, hydroxyl, cyano, trifluoromethyl, $-NO_2$, $-NH_2$, $-NR^4R^5$, $-OR^6$, $-NR^7(CO)R^6$, $-NR^7(CO)NR^4R^5$, $-NR^7COOR^7$, $-NR^7(SO_2)R^6$, $-CO_2H$, $-NR^7(SO_2)NR^4R^5$, $-COOR^7$, $-CONR^4R^5$, COR^6 and $-SO_2CH_3$;

each R^4 and R^5 is independently selected from hydrogen, C_{3-7}-CycloalkyI, aryl, heteroaryl, C_{1-6}-alkyl and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO, and optionally substituted by one or more R^{10} groups, wherein said C_{1-6}-alkyl is optionally substituted by one or more substituents selected from halogen, cyano, hydroxyl, aryl, heteroaryl, $-NR^8R^9$, $-NR^7(CO)R^6$, $-NR^7COOR^6$, $-NR^7(SO_2)R^6$, $-COOR^6$, $-CONR^8R^9$, OR^{10}, $-SO_2R^6$ and a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO and optionally substituted by one or more or R^{10} groups; or

R^4 and R^5 together with the N to which they are attached form a C_{3-6}-heterocycloalkyl ring optionally further containing one or more groups selected from oxygen, sulfur, nitrogen and CO, wherein said C_{3-6}-heterocycloalkyl ring may be saturated or unsaturated and is optionally substituted with one or more groups selected from NR^8R^9 and R^{10};

each R^6 is independently selected from C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{4-7}-heterocycloalkyl, aryl and heteroaryl, each of which may be optionally substituted by one or more substituents selected from halogen, R^{10} and $-NR^8R^9$;

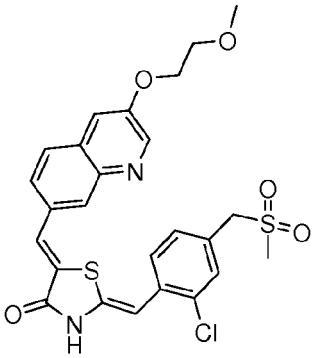
each R^7 is selected from hydrogen, C_{1-6}-alkyl and C_{3-6}-cycloalkyl, wherein said C_{1-6}-alkyl is optionally substituted by one or more halogens;

each of R^8 and R^9 is independently selected from hydrogen and C_{1-6}-alkyl, wherein said C_{1-6}-alkyl group is optionally substituted by one or more halogens; or

R^8 and R^9 together with the N to which they are attached form a C_{4-6}-heterocycloalkyl ring optionally further containing one or more heteroatoms selected from oxygen and sulfur, wherein said C_{4-6}-heterocycloalkyl ring is optionally substituted by one or more R^{10} groups; and

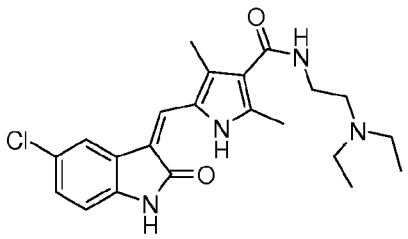
each R^{10} is selected from C_{3-7}-cycloalkyl and C_{1-6}-alkyl optionally substituted by one or more halogens, wherein where R^{10} is C_{1-6}-alkyl and two or more R^{10} groups are attached to the same carbon atom, the R^{10} groups may be linked to form a spiroalkyl group; and each R^{11} is independently selected from C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl-C_{3-7}-cycloalkyl, C_{4-7}-heterocycloalkyl, aryl and heteroaryl, each of which may be optionally substituted by one or more substituents selected from A;

(g) compound of Formula (VII)



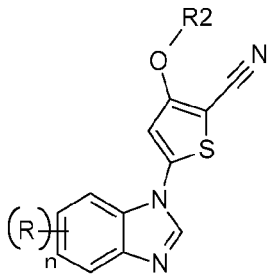
(VII)

(h) compound of Formula (VIII)



(VIII)

(i) compounds of Formula (X):



(X)

wherein: n is 0, 1,2, 3, or 4 ;

each R^1 which may be the same or different, independently represents H, halogen or a group $(X)_a(Y)_bZ$;

X represents -O- or -CONH-;

a is 0 or 1;

Y represents C_{1-6}alkylene-;

b is 0 or 1;

Z represents hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{5-7} heterocyclyl, C_{1-6} alkoxyalkyl, C_{1-6} haloalkoxyalkyl;

R^2 represents a group $-(X^1)_c(Y^1)_dZ^1$;

wherein X^1 represents $-C_{1-12}$ alkylene-;

c is 0 or 1;

Y^1 represents -O-;

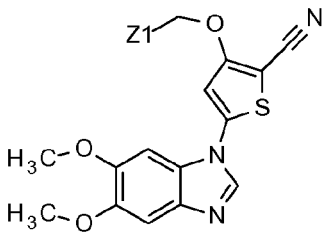
d is 0 or 1;

Z^1 represents H, aryl or heteroaryl each of which contains 5-14 ring atoms, C_{5-7} heterocyclyl, C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, (each of which aryl, heteroaryl, heterocyclyl, cycloalkyl,

cycloalkenyl may be optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S0_2R^3$, C_{1-6} hydroxyalkyl);

R^3 represents H or C_{1-6} alkyl;

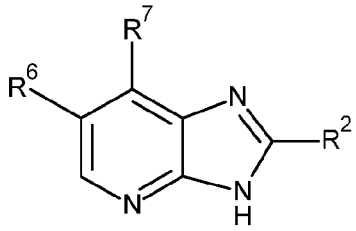
or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof



(Xa)

where Z^1 is aryl or heteroaryl each of which is optionally substituted by one of more substituents independently selected from halogen, CF_3, CH_2OH, SO_2CH_3, CH_3, OCH_3;

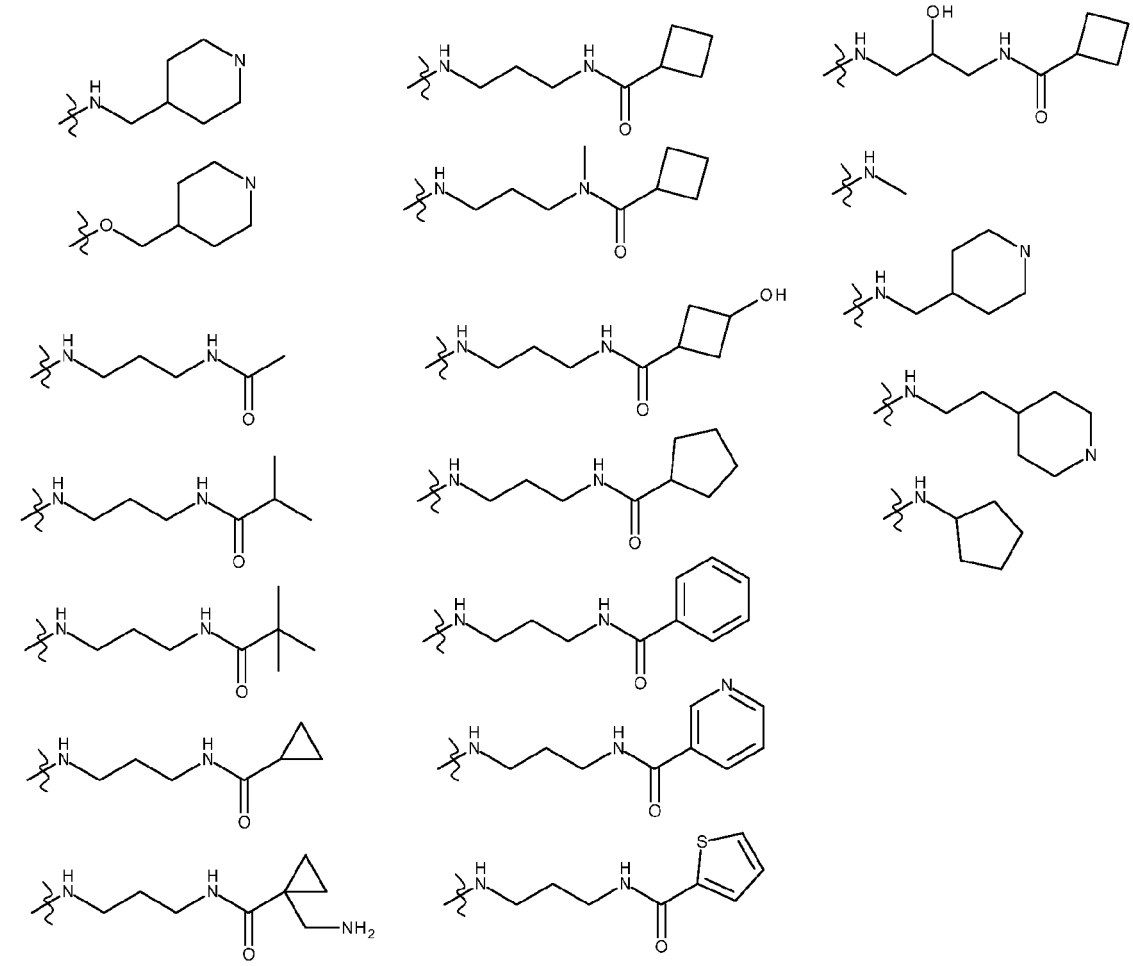
(j) a compound of formula (XI)



(XI)

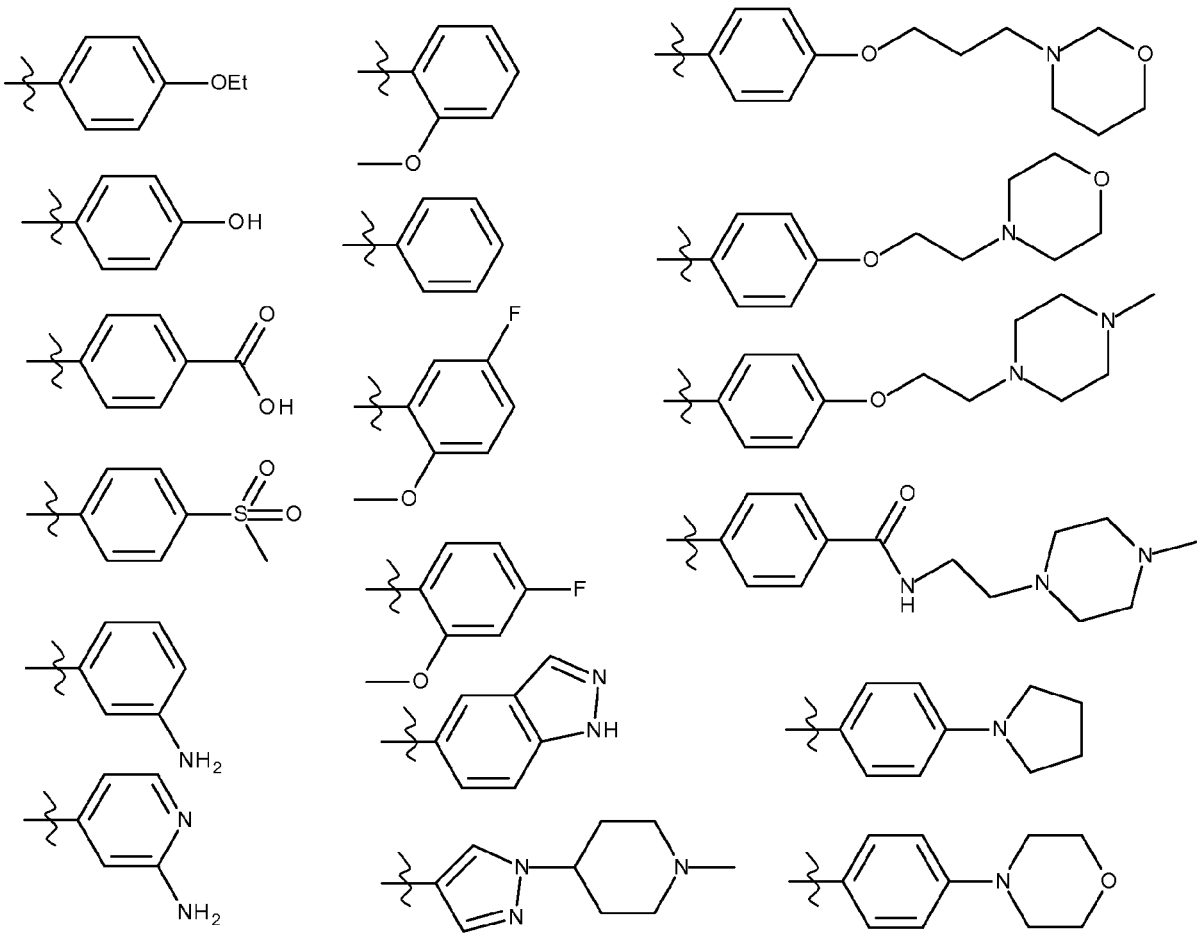
wherein R^6 is Br, CN, $CONH_2$ or Cl;

wherein R^7 represents



;

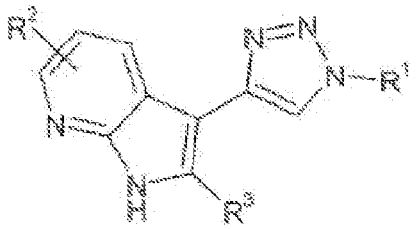
and wherein R^2 represents



;

or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof; and

(k) compounds of the formula (XII)



(XII)

in which R^1 denotes A, -[C(R^3)(R^4)]$_n$Ar, --[C(R^3)(R^4)] $_n$Het or --[C(R^3)(R^4)] $_n$Cyc,

R^2 denotes H, A, Hal, CN, -[C(R^3) $_2$]$_n$-Ar', -[C(R^3) $_2$] $_n$-Het', --[C(R^3) $_2$]$_n$-Cyc, OR^3 or N(R^3) $_2$,

R^3 denotes H or A,

R^4 denotes H, A, -[C(R^3) $_2$]$_n$$OR^3$, -[C($R^3$) $_2$]$_n$$COOR^3$, -[C($R^3$) $_2$]$_n$N(R^3) $_2$ or -[C(R^3) $_2$]$_n$Het,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which one or two CH_2 groups may be replaced by O, N and/or S atoms and/or by --CH=CH-- groups and/or, in addition, 1-7 H atoms may be replaced by F,

Cyc denotes cycloalkyl having 3, 4, 5, 6 or 7 C atoms,

Ar denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, -[C(R^3) $_2$]$_n$$OR^3$, N($R^3$)$_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$ and/or S(O)$_n$A,

Ar' denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^3, N(R^3) $_2$, SR^3, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, $SO_2N(R^3)_2$, S(O)$_n$A, CO-Het_1, Het_1, [C(R^3) $_2$] $_n$N(R^3)$_2$, [C(R^3)$_2$]$_n$$Het_1$, O[C($R^3$)$_2$]$_n$N($R^3$) $_2$, O[C(R^3)$_2$]$_n$$Het_1$, NHCOOA, $NHCON(R^3)_2$, NHCOO[C(R^3)$_2$]$_n$N(R^3) $_2$, NHCOO[C(R^3)$_2$]$_n$$Het_1$, NHCONH[C($R^3$)$_2$]$_n$N($R^3$) $_2$, NHCONH[C(R^3)$_2$]$_n$$Het_1$, OCONH[C($R^3$)$_2$]$_n$N($R^3$) $_2$, OCONH[C(R^3) $_2$]$_n$$Het_1$, CO-$Het_1$, CHO and/or COA,

Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, and/or O and/or S atoms which is unsubstituted or mono- or disubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^S, SO_2NR^3 and/or S(O)$_n$A,

Het' denotes a mono-, bi- or tricyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms which is unsubstituted or may be mono- or disubstituted by Hal, A, OR^3, N(R^3)$_2$, SR^3, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, $SO_2N(R^3)_2$, S(O) $_n$ A, CO-Het_1, Het_1, [C(R^3) $_2$] $_n$N(R^3) $_2$, [C(R^3) $_2$]$_n$$Het_1$, O[C($R^3$)$_2$]$_n$N($R^3$) $_2$, O[C(R^3)$_2$]$_n$$Het_1$, NHCOOA, $NHCON(R^3)_2$, NHCOO[C(R^3)$_2$]$_n$N(R^3) $_2$, NHCOO[C(R^3)$_2$]$_n$Het.sup.1, NHCONH[C(R^3)$_2$]$_n$N(R^3) $_2$, NHCONH[C(R^3)$_2$]$_n$$Het_1$, OCONH[C($R^3$)$_2$]$_n$N($R^3$) $_2$, OCONH[C(R^3)$_2$]$_n$$Het_1$, CO-$Het_1$, CHO, COA, =S, =NH, =NA and/or =O (carbonyl oxygen),

Het_1 denotes a monocyclic saturated heterocycle having 1 to 2 N and/or O atoms, which may be mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),

Hal denotes F, Cl, Br or I,

N denotes 0, 1 or 2,

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

11. A compound as claimed in any one of claims 1 to 9 wherein the compound is a down-regulator of the expression of one or both of TBK1 and IKKε, selected from the group consisting of siRNA reagents with the target sequence:

5′-GAACGUAGAUUAGCUUAUA-3′ (TBK1) [SEQ ID NO. 1],
5-UGACAGAGAUUUACUAUCA-3′ (TBK1) [SEQ ID NO. 2],
5′-UAAAGUACAUCCACGUUAU-3′ (TBK1) [SEQ ID NO.3],
5′-GGAUAUCGACAGCAGAUUA-3′ (TBK1) [SEQ ID NO. 4];
5′-ACAAACAGUUCAAGAAGUC-3′ (IKKε) [SEQ ID NO. 5],
5′-GGACCUGCUUCUCCACAUG-3′ (IKKε) [SEQ ID NO. 6],
5′-GAAGGCGGCUGCAGAACUG-3′ (IKKε) [SEQ ID NO. 7],
5′-GGCAGGAGCUAAUGUUUCG-3′ (IKKε) [SEQ ID NO. 8].

12. A compound as claimed in any one of claims 1 to 11 that is used in combination with one or more further therapeutic agents.

13. A compound as claimed in claim 12 wherein a further therapeutic agent is selected from the group consisting of inhibitors of mTOR, inhibitors of PI3kinase, inhibitors of both mTOR and PI3kinase, inhibitors of AKT, and inhibitors of PDK1.

14. A compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, for use in a method of treating a cancer that is dependent on the PI3kinase pathway comprising:
- identifying a cancer in the individual as being dependent on the PI3kinase pathway, and
- administering the compound to the individual.

15. A compound as claimed in claim 14 wherein the cancer is as described in any one of claims 2 to 9, or the compound is as described in any one of claims 10 to 13.

16. A method of treating cancer in an individual in whom the cancer is dependent on the PI3kinase pathway, comprising administering to the individual a compound that is an

inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε.

17. A method as claimed in claim 16 wherein the cancer is as described in any one of claims 2 to 9, or the compound is as described in any one of claims 10 to 13.

18. A method of treating cancer in an individual comprising:
- identifying the cancer as dependent on the PI3kinase pathway, and
- administering to the individual a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε.

19. A method as claimed in claim 18 wherein the cancer is as described in any one of claims 2 to 9, or the compound is as described in any one of claims 10 to 13.

20. A method of determining the susceptibility of a cancer in an individual to treatment with a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, comprising determining whether the cancer is dependent on the PI3kinase pathway, whereby a dependence on the PI3kinase pathway indicates that the cancer in the individual has an increased susceptibility to treatment with a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε.

21. A method as claimed in claim 20 wherein the cancer is as described in any one of claims 2 to 9, or the compound is as described in any one of claims 10 to 13.

22. A method of determining a suitable treatment for an individual with a cancer comprising:

(i) determining whether the cancer is dependent on the PI3kinase pathway; and

(ii) determining a suitable treatment, whereby a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε is suitable in the treatment of an individual with a cancer that is dependent on the PI3kinase pathway.

23. A method as claimed in claim 22 wherein the cancer is as described in any one of claims 2 to 9, or the compound is as described in any one of claims 10 to 13.

24. A method of predicting the response of a cancer condition in an individual to a treatment with a compound that is an inhibitor of one or both of TBK1 and IKKε, or a down-regulator of the expression of one or both of TBK1 and IKKε, comprising:

- determining whether the cancer is dependent on the PI3kinase pathway.

25. A method as claimed in claim 24 wherein the cancer is as described in any one of claims 2 to 9, or the compound is as described in any one of claims 10 to 13.

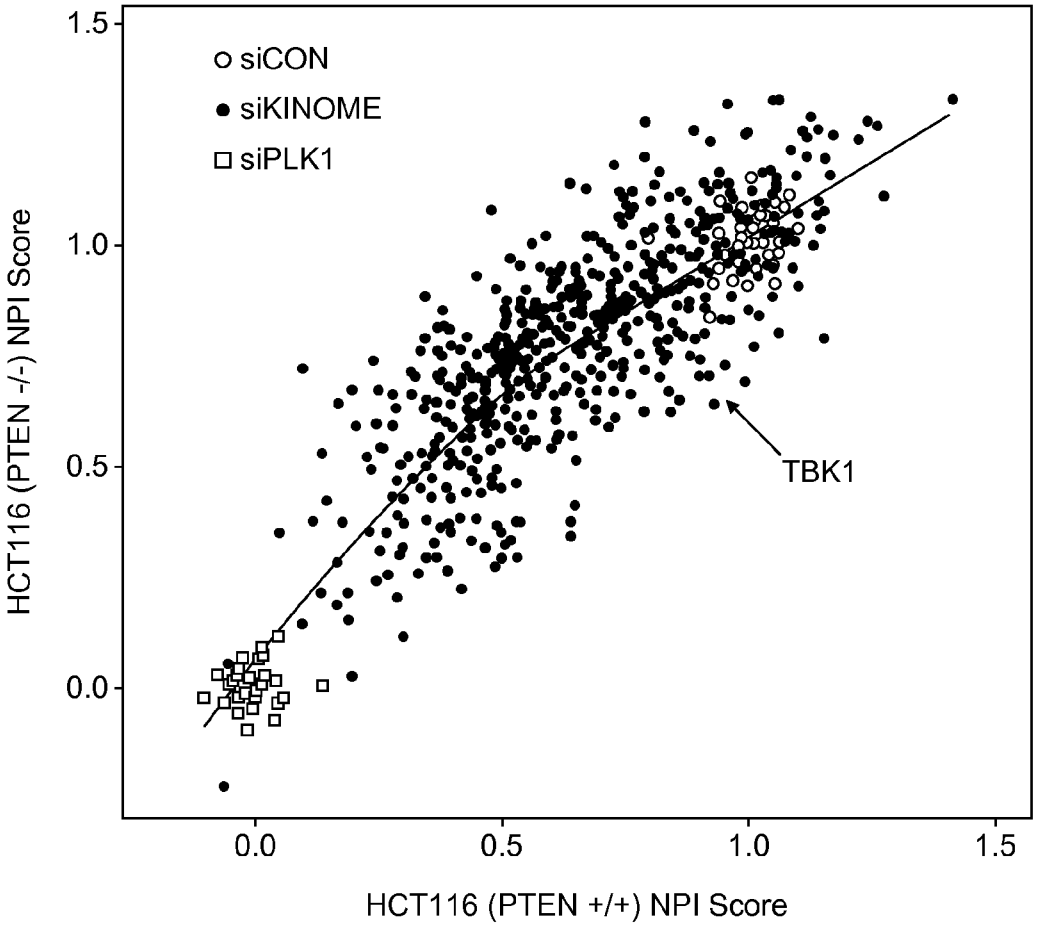

siCON
siKINOME
siPLK1
TBK1
HCT116 (PTEN -/-) NPI Score
HCT116 (PTEN +/+) NPI Score
0.0
0.5
1.0
1.5

FIG. 1

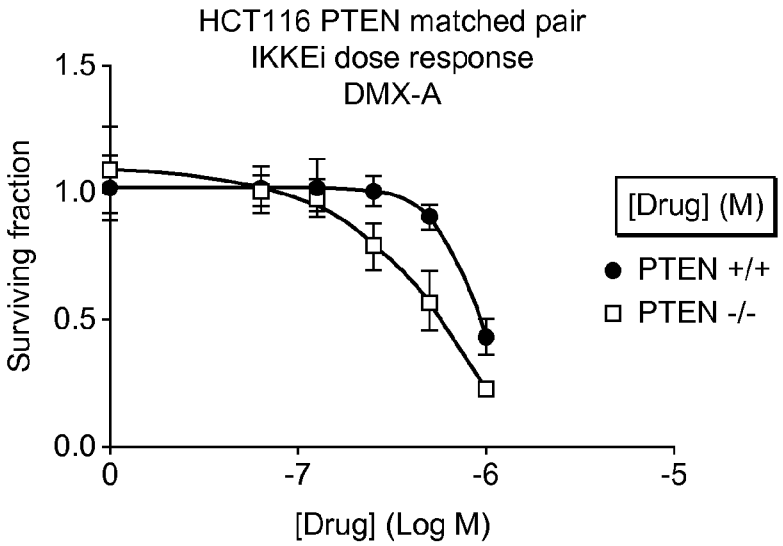

HCT116 PTEN matched pair
IKKEi dose response
DMX-A
Surviving fraction
1.5
1.0
0.5
0.0
0
-7
-6
-5
[Drug] (Log M)
[Drug] (M)
PTEN +/+
PTEN -/-

FIG. 2(a)

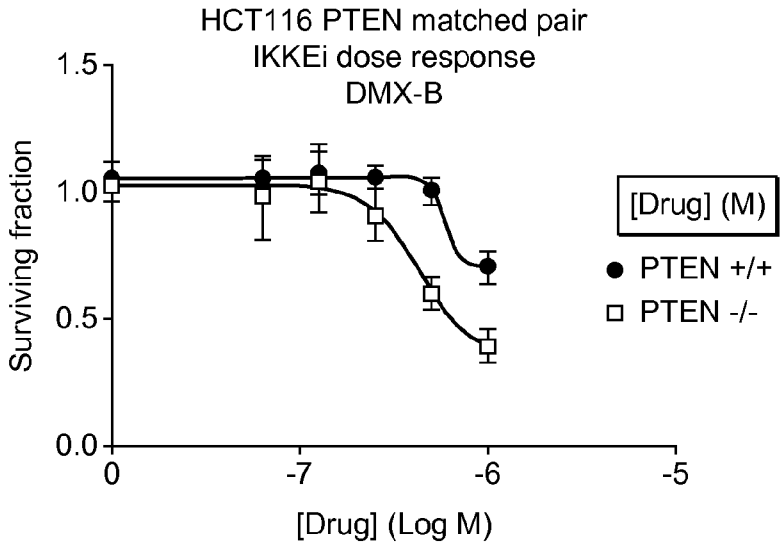

HCT116 PTEN matched pair
IKKEi dose response
DMX-B
Surviving fraction
1.5
1.0
0.5
0.0
0
-7
-6
-5
[Drug] (Log M)
[Drug] (M)
PTEN +/+
PTEN -/-

FIG. 2(b)

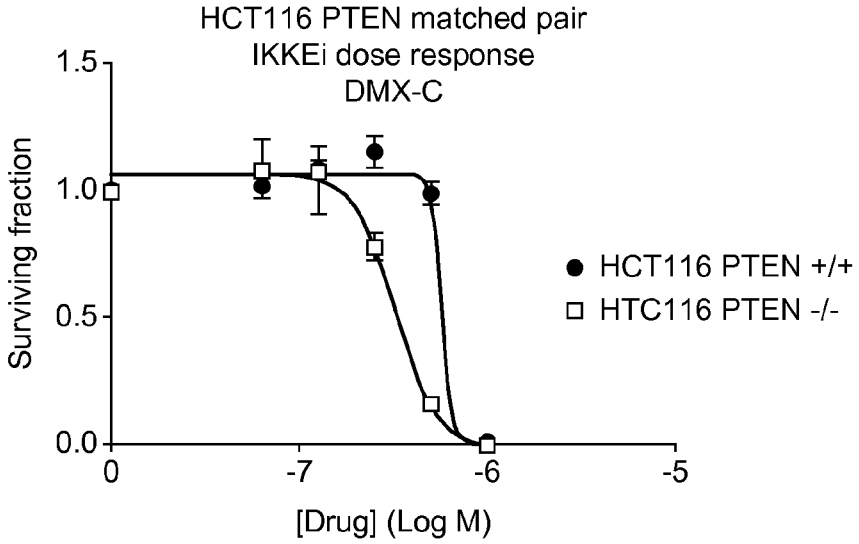

HCT116 PTEN matched pair
IKKEi dose response
DMX-C
Surviving fraction
1.5
1.0
0.5
0.0
0
-7
-6
-5
[Drug] (Log M)
HCT116 PTEN +/+
HTC116 PTEN -/-

FIG. 2(c)

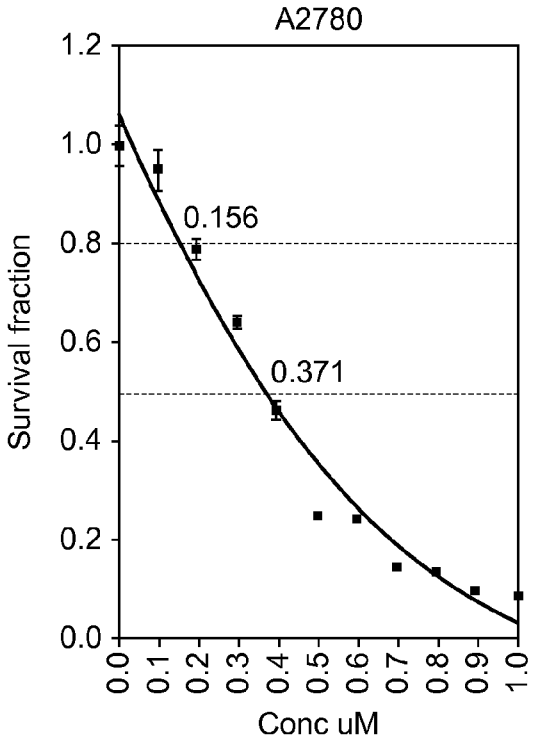

A2780
Survival fraction
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.156
0.371
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Conc uM

FIG. 3(a)

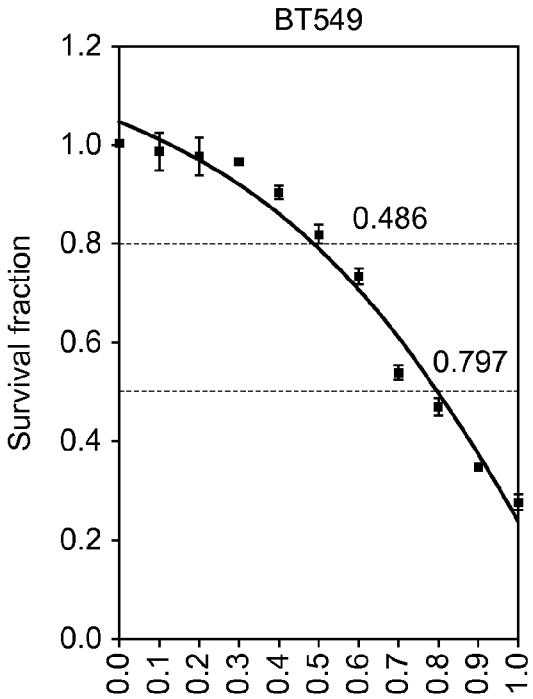

BT549
Survival fraction
0.486
0.797
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

FIG. 3(b)

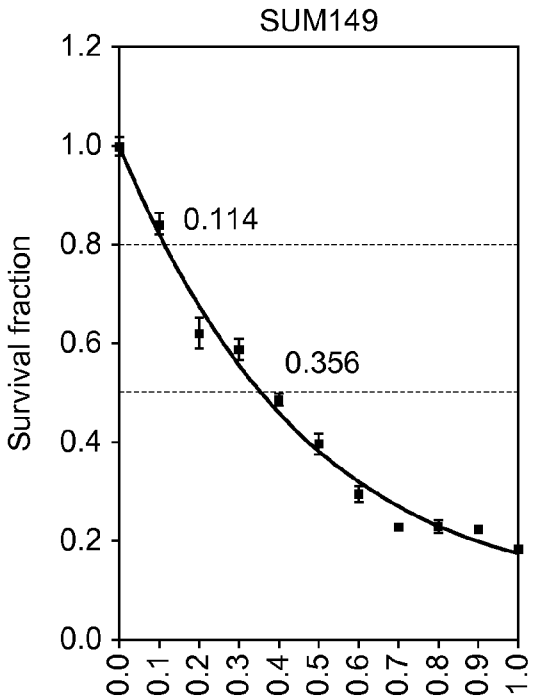

SUM149
Survival fraction
0.114
0.356
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

FIG. 3(c)

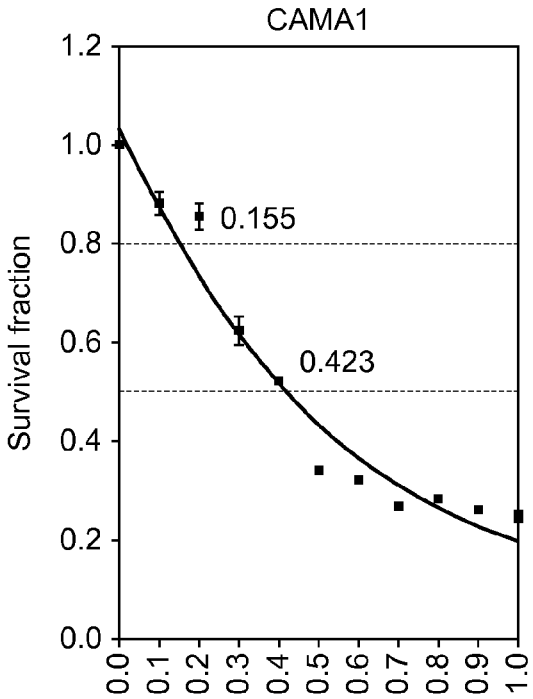

CAMA1
Survival fraction
0.155
0.423
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 3(d)

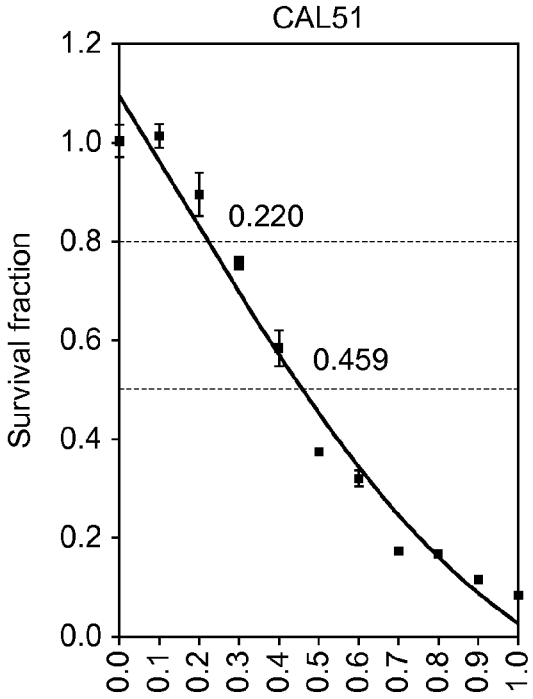

CAL51
Survival fraction
0.220
0.459
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 3(e)

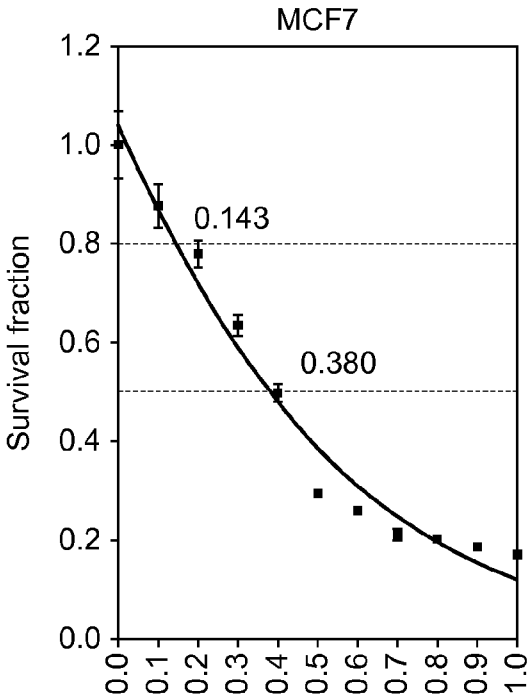

MCF7
Survival fraction
0.143
0.380
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 4(a)

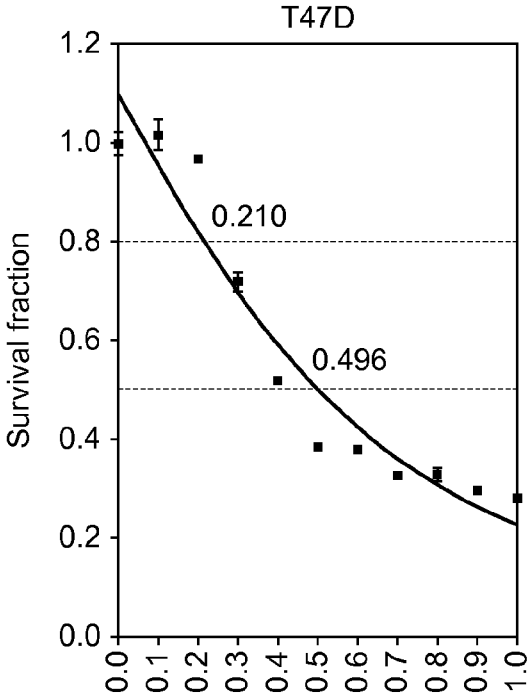

T47D
Survival fraction
0.210
0.496
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 4(b)

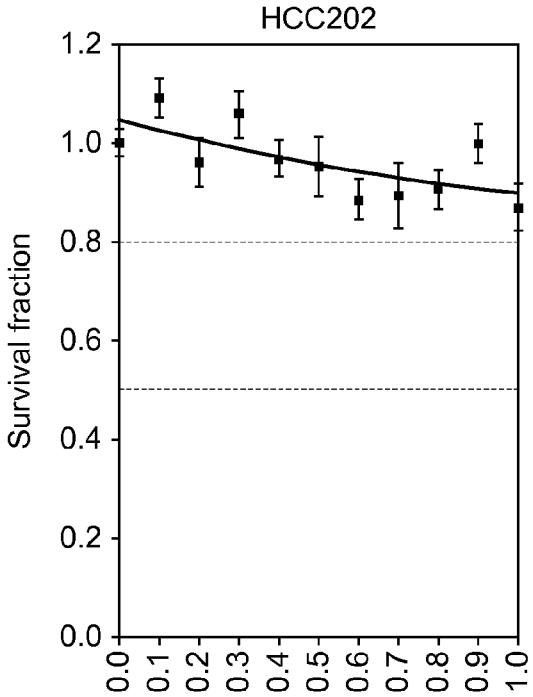

HCC202
Survival fraction
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

FIG. 4(c)

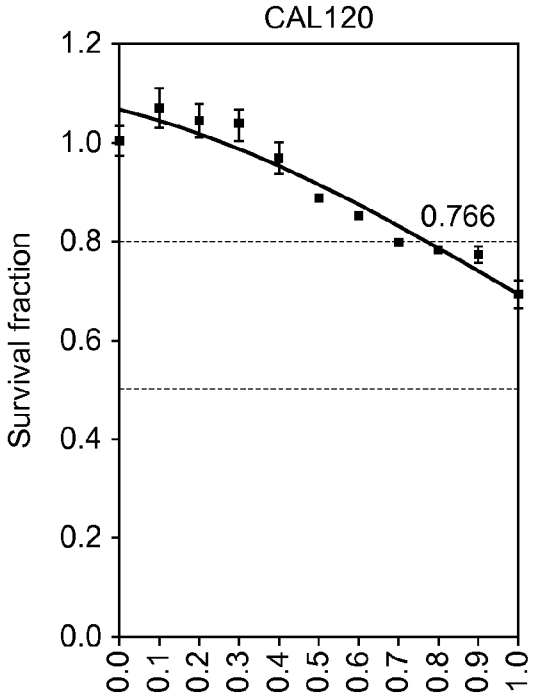

CAL120
Survival fraction
0.766
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

FIG. 5(a)

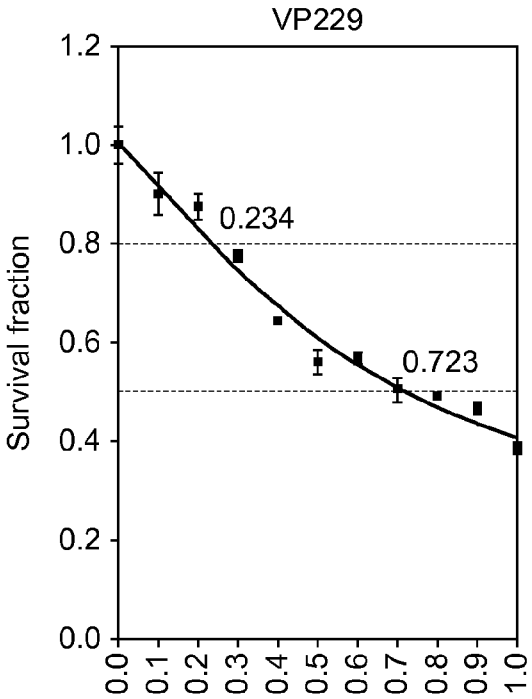

VP229
Survival fraction
0.234
0.723
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 5(b)

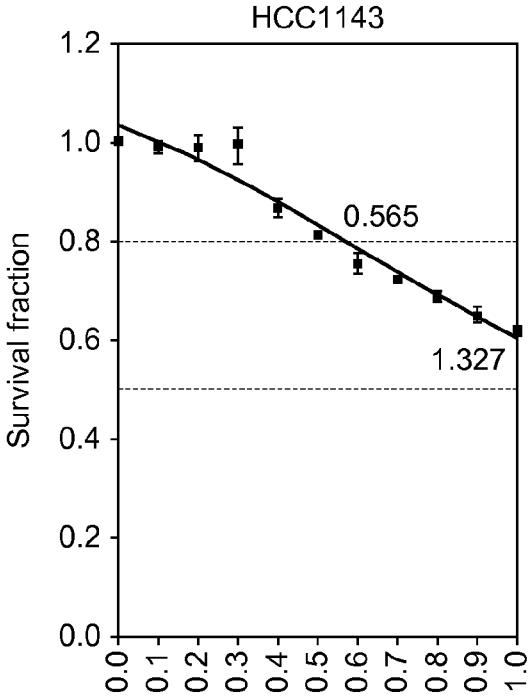

HCC1143
Survival fraction
0.565
1.327
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 5(c)

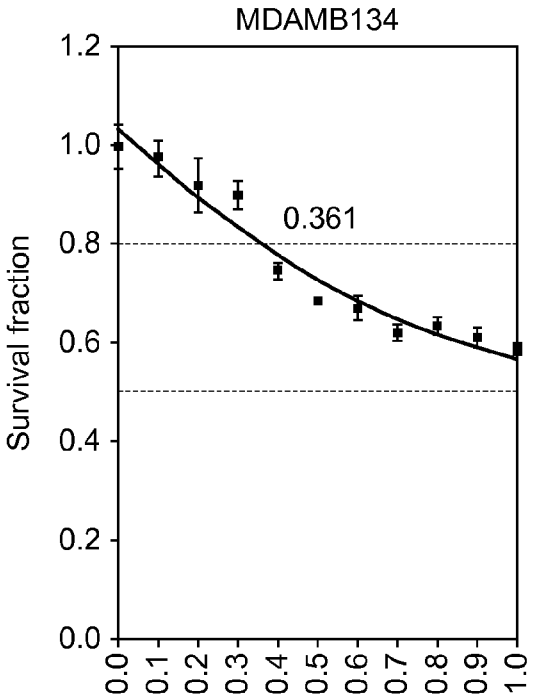

MDAMB134
Survival fraction
0.361
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 5(d)

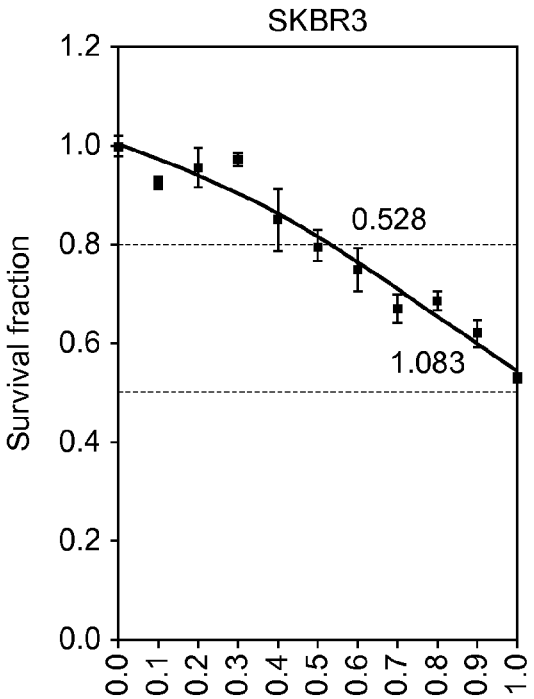

SKBR3
Survival fraction
0.528
1.083
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

FIG. 5(e)

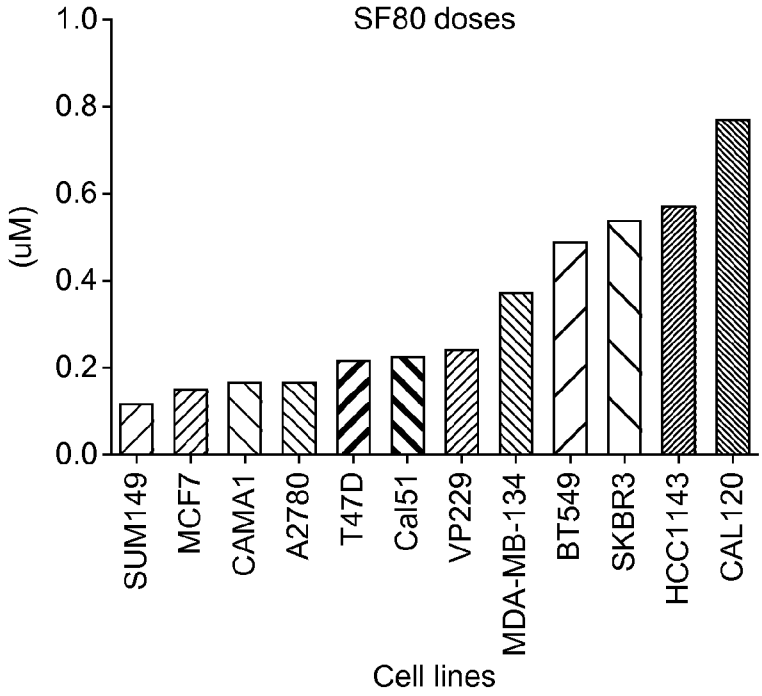

SF80 doses
1.0
0.8
0.6
0.4
0.2
0.0
(uM)
SUM149
MCF7
CAMA1
A2780
T47D
Cal51
VP229
MDA-MB-134
BT549
SKBR3
HCC1143
CAL120
Cell lines

FIG. 6(a)

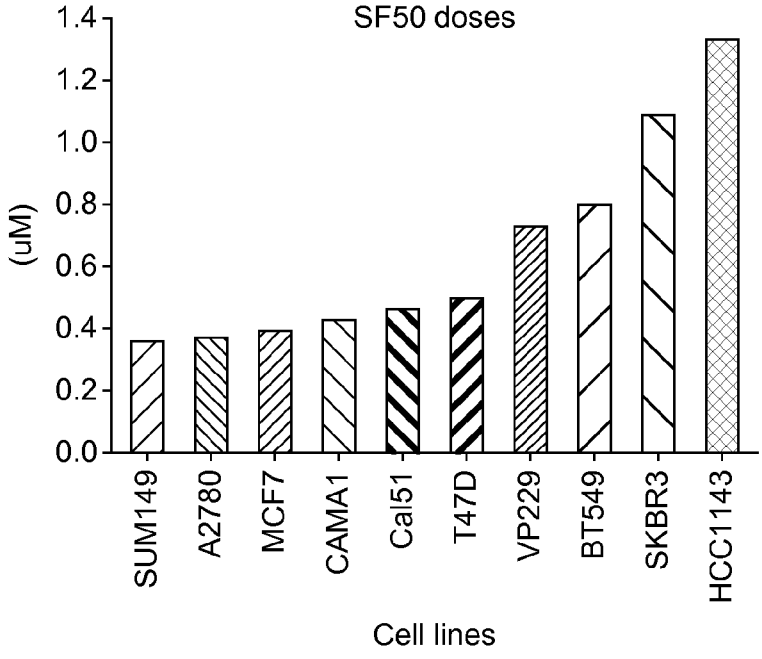

SF50 doses
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
(uM)
SUM149
A2780
MCF7
CAMA1
Cal51
T47D
VP229
BT549
SKBR3
HCC1143
Cell lines

FIG. 6(b)

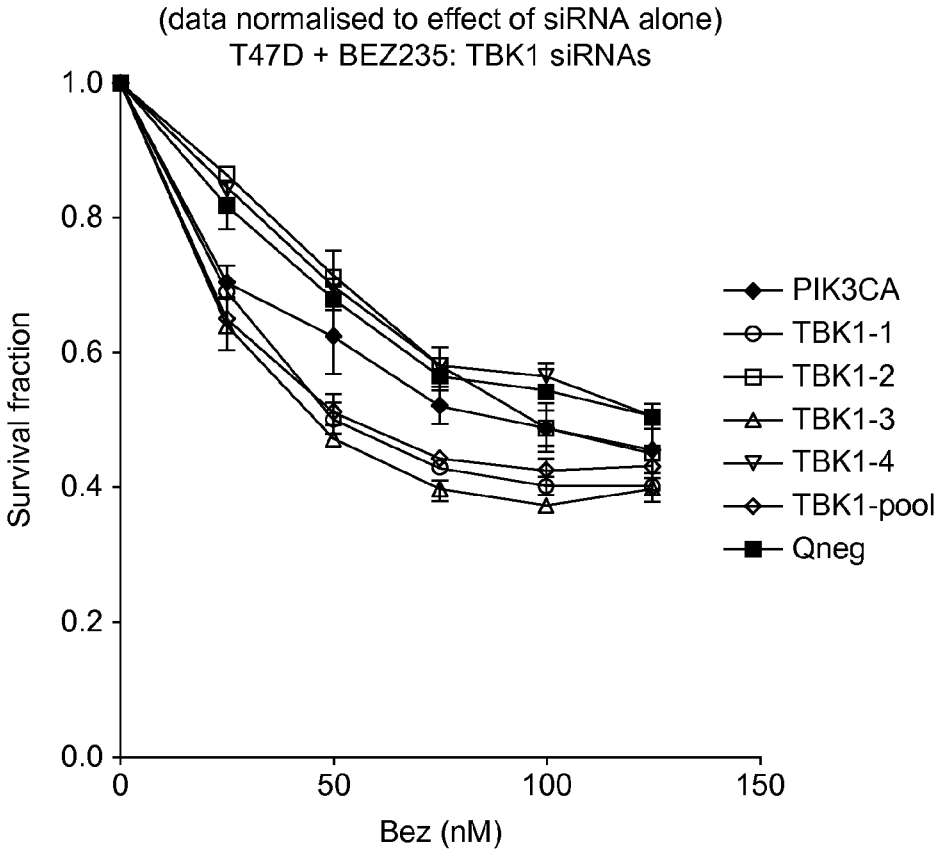

(data normalised to effect of siRNA alone)
T47D + BEZ235: TBK1 siRNAs
Survival fraction
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
Bez (nM)
PIK3CA
TBK1-1
TBK1-2
TBK1-3
TBK1-4
TBK1-pool
Qneg

FIG. 7