(54) Title: IMIDAZO [2,1-B] [1,3,4] THIADIAZOLES AS PROTEIN OR LIPID KINASE INHIBITORS

(57) Abstract: There is provided compounds of formula (I): wherein R¹, R² and R³ have meanings given in the description, and pharmaceutically-acceptable esters, amides, solvates or salts thereof, which compounds are useful in the treatment of diseases in which inhibition of a protein or lipid kinase (e.g. PI3-K, particularly class I PI3K, mTOR and/or Flt3) is desired and/or required, and particularly in the treatment of cancer. The invention also relates to combinations containing such compounds.
FIELD OF THE INVENTION

This invention relates to novel pharmaceutically-useful compounds, which compounds are useful as inhibitors of protein or lipid kinases (such as inhibitors of the phosphoinositide 3-OH kinase (PI3 kinase) family, particularly the PI3K class I sub-type. The compounds may also be useful as inhibitors of the mammalian target of rapamycin (mTOR) and/or compounds may be useful as inhibitors of Flt3. The compounds are of potential utility in the treatment of diseases such as cancer. The invention also relates to the use of such compounds as medicaments, to the use of such compounds for in vitro, in situ and in vivo diagnosis or treatment of mammalian cells (or associated pathological conditions), to pharmaceutical compositions containing them, and to synthetic routes for their production.

BACKGROUND OF THE INVENTION

The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases. A large share of the oncogenes and proto-oncogenes involved in human cancers code for PKs. The enhanced activities of PKs are also implicated in many non-malignant diseases, such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. PKs are also implicated in inflammatory conditions and in the multiplication of viruses and parasites. PKs may also play a major role in the pathogenesis and development of neurodegenerative disorders.

For a general reference to PKs malfunctioning or disregulation see, for instance, Current Opinion in Chemical Biology 1999, 3, 459 - 465.

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid and serine/threonine kinases that catalyze the phosphorylation of the membrane lipid phosphatidylinositol (PI) on the 3'-OH of the inositol ring to produce...

Multiple PI3K isoforms categorized by their catalytic subunits, their regulation by corresponding regulatory subunits, expression patterns and signalling specific functions ($p^{110}\alpha$, $\beta$, $\delta$, $\gamma$) perform this enzymatic reaction (Exp. Cell. Res. 25 (1), 239-54 (1999) by Vanhaesebroeck and Katso et al., 2001, above).

The closely related isoforms $p^{110}\alpha$ and $\beta$ are ubiquitously expressed, while $\delta$ and $\gamma$ are more specifically expressed in the haematopoietic cell system, smooth muscle cells, myocytes and endothelial cells (see e.g. Trends Biochem. Sci. 22 (7), 267-72 (1997) by Vanhaesebroeck et al). Their expression might also be regulated in an inducible manner depending on the cellular, tissue type and stimuli as well as disease context. Inductibility of protein expression includes synthesis of protein as well as protein stabilization that is in part regulated by association with regulatory subunits.

Eight mammalian PI3Ks have been identified so far, including four class I PI3Ks. Class Ia includes $PI3K\alpha$, $PI3K\beta$ and $PI3K\delta$. All of the class Ia enzymes are heterodimeric complexes comprising a catalytic subunit ($p^{110}\alpha$, $p^{110}\beta$ or $p^{110}\delta$) associated with an SH2 domain containing p85 adapter subunit. Class Ia PI3Ks are activated through tyrosine kinase signalling and are involved in cell proliferation and survival. $PI3K\alpha$ and $PI3K\beta$ have also been implicated in tumorigenesis in a variety of human cancers. Thus, pharmacological inhibitors of $PI3K\alpha$ and $PI3K\beta$ are useful for treating various types of cancer.

$PI3K\gamma$, the only member of the Class Ib PI3Ks, consists of a catalytic subunit $p^{110}\gamma$, which is associated with a $p^{110}$ regulatory subunit. $PI3K\gamma$ is regulated by...
G protein coupled receptors (GPCRs) via association with βγ subunits of heterotrimeric G proteins. ΡΙ3Κγ is expressed primarily in hematopoietic cells and cardiomyocytes and is involved in inflammation and mast cell function. Thus, pharmacological inhibitors of ΡΙ3Κγ are useful for treating a variety of inflammatory diseases, allergies and cardiovascular diseases.

These observations show that deregulation of phosphoinositol-3-kinase and the upstream and downstream components of this signalling pathway is one of the most common deregulations associated with human cancers and proliferative diseases (see e.g. Parsons et al., Nature 436:792 (2005); Hennessey et al., Nature Rev. Drug Discovery 4: 988-1004 (2005).

The mammalian target of rapamycin (mTOR) also known as FK506 binding protein 12-rapamycin associated protein 1 (FRAP1) is a protein which in humans is encoded by the FRAP1 gene. mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. The inhibition of mTORs are believed to be useful for treating various diseases/conditions, such as cancer (for example, as described in Easton et al. (2006). "mTOR and cancer therapy". Oncogene 25 (48): 6436-46).

Flt3 kinase (FMS-like tyrosine kinase 3) is a useful target for certain cancers, including leukemia. Flt3 is prevalent in acute myelogenous leukemia (AML) patients, so inhibitors of Flt3 may be useful to treat such patients. Smith et al reported an alkaloid that is a potent inhibitor of Flt3 and provided clinical responses in tested subjects with minimal dose-related toxicity (Blood, vol 103(10), 3669-76 (2004)).

Flt3 inhibitors may also be useful in the treatment of inflammation, as they have been shown to be effective in treating airway inflammation in mice, using a murine asthma model (Edwan et al., J. Immunology, 5016-23 (2004)).

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.
For the treatment of cancer, targeted therapies are becoming more important. That is, therapy that has the effect of interfering with specific target molecules that are linked to tumor growth and/or carcinogenesis. Such therapy may be more effective than current treatments (e.g. chemotherapy) and less harmful to normal cells (e.g. because chemotherapy has the potential to kill normal cells as well as cancerous cells). This, and also the fact that targeted therapies may be selective (i.e. it may inhibit a certain targeted molecule more selectively as compared to other molecular targets, e.g. as described hereinafter), may have the benefit of reducing side effects and may also have the benefit that certain specific cancers can be treated (also selectively). The latter may in turn also reduce side effects.

Hence, it is a clear goal of current oncologists to develop targeted therapies (e.g. ones that are selective). In this respect, it should be pointed out that several different molecular targets may exist that are linked to certain diseases (e.g. cancer). However, one simply cannot predict if a therapy (e.g. a small molecule as a therapeutic) that interferes with or inhibits one target molecule could inhibit a different molecular target (be it one that will ultimately have the effect of treating the same disease or a different one).

International patent applications WO 2009/055418 and WO 2010/108074 both disclose various compounds for use as kinase inhibitors. However, neither document discloses imidazolothiadiazoles.

International patent application WO 2009/040552 discloses various imidazolothiadiazole compounds for use as kinase inhibitors. However, this document does not predominantly relate to imidazolothiadiazoles directly substituted at the 2- and 5-position with an aromatic group. Nor does this document disclose any aromatic substituents on the imidazolothiadiazole, which are further substituted with a sulfonamido moiety.

Unpublished European patent application 09380069.6 and international patent application WO 2010/112874 also disclose various imidazolothiadiazoles for use as kinase inhibitors.
Disclosure of the Invention

According to the invention, there is provided a compound of formula I.

\[
\begin{align*}
R^1 & \quad \text{represents:} \\
R^2 & \quad \text{in which the squiggly line represents the point of attachment to the requisite imidazothiadiazole core of formula I:} \\
\text{each } X^1 & \quad \text{independently represents } -N=, -C(H)= \text{ or } -C(A^1)= \\
\text{each } X^2 & \quad \text{independently represents } -C(H)= \text{ or } -C(A^2)=; \\
R^3 & \quad \text{represents hydrogen, halo, } -CN \text{ or } C_{1-3} \text{ alkyl optionally substituted by one or more fluoro atoms;} \\
R^4 & \quad \text{represents hydrogen, } Q^1 \text{ (e.g. halo), } C_{1-6} \text{ alkyl (optionally substituted by one or more substituents selected from } =0 \text{ and } A^5), \text{ heterocycloalkyl (optionally substituted by one or more substituents selected from } =0 \text{ and } A^6), \text{ aryl (optionally substituted by one or more substituents selected from } A^3) \text{ or heteroaryl (optionally substituted by one or more substituents selected from } A^4); \\
R^5 & \quad \text{each } A^1, A^2, A^3, A^4, A^5 \text{ and } A^6 \text{ independently represents, on each occasion when used herein:
(i) } Q^1; \\
(ii) \text{Cl}_{1-2} \text{ alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from } =0, =S, =N(R^{10b}) \text{ and } Q^2;
\end{align*}
\]
(iii) aryl or heteroaryl, both of which are optionally substituted by one or more substituents selected from Q³;

each Q¹a, Q¹, Q² and Q³ independently represents, on each occasion when used herein:

case, -CN, -NO₂, -N(R₁₀a)R₁¹a, -OR₁₀a, -C(=Y)-R₁₀a, -C(=Y)-OR₁₀a,
    -C(=Y)N(R₁₀a)R₁¹a, -OC(=Y)-R₁₀a, -OC(=Y)-OR₁₀a, -OC(=Y)N(R₁₀a)R₁¹a,
    -OS(O)₁₂aOR₁⁰a, -OP(=Y)(OR₁⁰a)(OR₁¹a), -OP(OR₁⁰a)(OR₁¹a), -N(R₁⁰a)C(=Y)R₁¹a,
    -N(R₁²a)C(=Y)OR₁¹a, -N(R₁²a)C(=Y)N(R₁⁰a)R₁¹a, -NR₁²aS(O)₂R₁⁰a,
    -NR₁²aS(O)₂N(R₁⁰a)R₁¹a, -S(O)₂N(R₁⁰a)R₁¹a, -SC(=Y)R₁₀a, -SC(=Y)OR₁⁰a,
    -SC(=Y)N(R₁⁰a)R₁¹a, -S(O)₂R₁⁰a, -SR₁⁰a, -S(O)₁₂aR₁⁰a, -S(O)₂OR₁⁰a, C₁₋₁₂ alkyl,
    heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =0, =S, =N(R₂⁰) and E¹), aryl or heteroaryl
    (which latter two groups are optionally substituted by one or more substituents selected from E²);

each R₁⁰a independently represents, on each occasion when used herein, hydrogen, -N(R¹¹)(R¹²), C₁₋₁₂ alkyl, heterocycloalkyl (which latter two groups are
    optionally substituted by one or more substituents selected from =0, =S, =N(R₂⁰)
    and E³), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E⁴);

each R¹¹, R¹², R₁⁰a, R¹¹a and R¹₂a independently represents, on each occasion
    when used herein, hydrogen, C₁₋₁₂ alkyl, heterocycloalkyl (which latter two groups
    are optionally substituted by one or more substituents selected from =0, =S,
    =N(R₂⁰) and E³), aryl or heteroaryl (which latter two groups are optionally
    substituted by one or more substituents selected from E⁴); or

any relevant pair of R¹¹, R¹², R₁⁰a, R¹¹a and R¹₂a may (for example, when attached
to the same atom, adjacent atom (i.e. 1,2-relationship) or to atoms that are two
atom atoms apart, i.e. in a 1,3-relationship) be linked together to form (e.g. along
with the requisite nitrogen atom to which they may be attached) a 4- to 20- (e.g.
4- to 12-) membered ring, optionally containing one or more heteroatoms (for
example, in addition to those that may already be present, e.g. (a) heteroatom(s)
selected from oxygen, nitrogen and sulfur), optionally containing one or more
unsaturations (e.g. triple or, preferably, double bonds), and which ring is
optionally substituted by one or more substituents selected from =0, =S, =N(R^{20})
and E^5;

5 each E^1, E^2, E^3, E^4 and E^5 independently represents, on each occasion when
used herein:
(i) Q^4;
(ii) C_{1-12} alkyl or heterocycloalkyl, both of which are optionally substituted by one
or more substituents selected from =0 and Q^5;
10 (iii) aryl or heteroaryl, both of which are optionally substituted by one or more
substituents selected from Q^6;

each Q^4, Q^5 and Q^6 independently represents, on each occasion when used
herein:
15 halo, -CN, -N0_2, -N(R^{20})_2, -OR^{20}, -C(=Y)-R^{20}, -C(=Y)-OR^{20},
-C(=Y)N(R^{20})_R^{21}, -OC(=Y)-R^{20}, -OC(=Y)-OR^{20}, -OC(=Y)N(R^{20})_R^{21}, -OS(0)_2OR^{20},
-OP(=Y)(OR^{20})(OR^{21}), -OP(OR^{20})(OR^{21}), -N(R^{22})C(=Y)R^{21}, -N(R^{22})C(=Y)OR^{21},
-N(R^{22})C(=Y)N(R^{20})_R^{21}, -NR^{22}S(0)_2R^{20}, -NR^{22}S(O)_2N(R^{20})_R^{21}, -S(O)_2N(R^{20})_R^{21},
-SC(=Y)R^{20}, -SC(=Y)OR^{20}, -SC(=Y)N(R^{20})_R^{21}, -S(0)_2R^{20}, -SR^{20}, -S(0)R^{20},
20 -S(0)_2OR^{20}, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally
substituted by one or more substituents selected from =0 and J^1), aryl or
heteroaryl (which latter two groups are optionally substituted by one or more
substituents selected from J^2);

25 each Y independently represents, on each occasion when used herein, =0, =S or
=NR^{23};

each R^{20}, R^{21}, R^{22} and R^{23} independently represents, on each occasion when
used herein, hydrogen, C_{1-8} alkyl, heterocycloalkyl (which latter two groups are
optionally substituted by one or more substituents selected from J^3 and =0), aryl
or heteroaryl (which latter two groups are optionally substituted by one or more
substituents selected from J^4); or

30 any relevant pair of R^{20}, R^{21} and R^{22}, may (for example, when attached to the
same atom, adjacent atom (i.e. 1,2-relationship) or to atoms that are two atom
atoms apart, i.e. in a 1,3-relationship) be linked together to form (e.g. along with
the requisite nitrogen atom to which they may be attached) a 4- to 20- (e.g. 4- to
12-) membered ring, optionally containing one or more heteroatoms (for example,
in addition to those that may already be present, e.g. (a) heteroatom(s) selected
from oxygen, nitrogen and sulfur), optionally containing one or more
unsaturations (e.g. triple or, preferably, double bonds), and which ring is
optionally substituted by one or more substituents selected from J5 and =0;

each J1, J2, J3, J4 and J5 independently represents, on each occasion when used
herein:
(i) Q7;
(ii) C16 alkyl or heterocycloalkyl, both of which are optionally substituted by one or
more substituents selected from =0 and Q8;
(iii) aryl or heteroaryl, both of which are optionally substituted by one or more
substituents selected from Q9;

each Q7, Q8 and Q9 independently represents, on each occasion when used
herein:
-CN or, more preferably, halo, -N(R50)R51, -OR50, -C(=Y5)-R50, -C(=Y5)-OR50,
-C(=Y5)N(R50)R51, -N(R52)C(=Y5)R51, -NR50S(0)2R50, -S(0)2R50, -SR50, -S(0)R50 or
C16 alkyl optionally substituted by one or more fluoro atoms;

each Y5 independently represents, on each occasion when used herein, =0, =S
or =NR53;

each R50, R51, R52 and R53 independently represents, on each occasion when
used herein, hydrogen or C1-alkyl optionally substituted by one or more
substituents selected from fluoro, -OR50 and -N(R51)R52; or
any relevant pair of R50, R51 and R52 may (for example when attached to the same
or adjacent atoms) be linked together to form, a 3- to 8-membered ring, optionally
containing one or more heteroatoms (for example, in addition to those that may
already be present, heteroatoms selected from oxygen, nitrogen and sulfur),
optionally containing one or more unsaturations (e.g. triple or, preferably, double
bonds), and which ring is optionally substituted by one or more substituents
selected from =0 and C1,3 alkyl;
R^80, R^81 and R^82 independently represent hydrogen or C_1-6 alkyl optionally substituted by one or more fluoro atoms;

or a pharmaceutically acceptable ester, amide, solvate or salt thereof,

which compounds, esters, amides, solvates and salts are referred to hereinafter as "the compounds of the invention".

Pharmaceutically acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

By "pharmaceutically acceptable ester, amide, solvate or salt thereof, we include salts of such an ester or amide, and solvates of such an ester, amide or salt. For instance, pharmaceutically acceptable esters and amides such as those defined herein may be mentioned, as well as pharmaceutically acceptable solvates or salts.

Pharmaceutically acceptable esters and amides of the compounds of the invention are also included within the scope of the invention. Pharmaceutically acceptable esters and amides of compounds of formula I may have an appropriate group, for example an acid group, converted to the appropriate ester or amide. For example, pharmaceutically acceptable esters (of carboxylic acids) that may be mentioned include optionally substituted C_1-6 alkyl, C_5-10 aryl and/or C_5-10 aryl-C_1-6 alkyl- esters. Pharmaceutically acceptable amides (of carboxylic acids) that may be mentioned include those of the formula -C(O)N(R^{31})R^{32}, in which R^{31} and R^{32} independently represent optionally substituted C_1-6 alkyl, C_5-10 aryl, or C_5-10 aryl-C_1-6 alkyne-. Preferably, C_1-6 alkyl
groups that may be mentioned in the context of such pharmaceutically acceptable esters and amides are not cyclic, e.g. linear and/or branched.

Preferably, specific esters and amides of compounds of the invention that may be mentioned include those esters and amides those mentioned herein in respect of compounds of formula I (or compounds of the invention).

Further compounds of the invention that may be mentioned include carbamate, carboxamido or ureido derivatives, e.g. such derivatives of existing amino functional groups.

For the purposes of this invention, therefore, prodrugs of compounds of the invention are also included within the scope of the invention.

The term "prodrug" of a relevant compound of the invention includes any compound that, following oral or parenteral administration, is metabolised in vivo to form that compound in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration.

Prodrugs of compounds of the invention may be prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, in vivo when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesising the parent compound with a prodrug substituent. Prodrugs include compounds of the invention wherein a hydroxyl, amino, sulphhydryl, carboxy or carbonyl group in a compound of the invention is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, sulphhydryl, carboxy or carbonyl group, respectively.

Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, N-acyl derivatives and N-Mannich bases. General information on prodrugs may be found e.g. in Bundegaard, H. "Design of Prodrugs" p. 1-92, Elesevier, New York-Oxford (1985).
Compounds of the invention may contain double bonds and may thus exist as E (entgegen) and Z (zusammen) geometric isomers about each individual double bond. Positional isomers may also be embraced by the compounds of the invention. All such isomers (e.g. if a compound of the invention incorporates a double bond or a fused ring, the cis- and trans- forms, are embraced) and mixtures thereof are included within the scope of the invention (e.g. single positional isomers and mixtures of positional isomers may be included within the scope of the invention).

Compounds of the invention may also exhibit tautomerism. All tautomeric forms (or tautomers) and mixtures thereof are included within the scope of the invention. The term "tautomer" or "tautomer form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerisations. Valence tautomers include interconversions by reorganisation of some of the bonding electrons.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person.
All stereoisomers (including but not limited to diastereoisomers, enantiomers and atropisomers) and mixtures thereof (e.g. racemic mixtures) are included within the scope of the invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as $^2$H, $^3$H, $^{11}$C, $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{2}$H, $^{33}$P, $^{35}$S, $^{18}$F, $^{15}$Cl, $^{125}$I, and $^{125}$I. Certain isotopically-labeled compounds of the present invention (e.g., those labeled with $^3$H and $^{14}$C) are useful in compound and for substrate tissue distribution assays. Tritiated ($^3$H) and carbon-14 ($^{14}$C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as $^{15}$O, $^{13}$N, $^{1}$C and $^{18}$F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following...
procedures analogous to those disclosed in the Scheme 1 and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Unless otherwise stated, the terms \( \text{Ci}_{-q} \) alkyl, and \( \text{Ci}_{-q} \) alkylene, groups (where \( q \) is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number of carbon atoms, be branched-chain, saturated or unsaturated (so forming, for example, an alkenyl or alkynyl group).

\( \text{C}_{2-q} \) cycloalkyl groups (where \( q \) is the upper limit of the range) that may be mentioned may be monocyclic or bicyclic alkyl groups, which cycloalkyl groups may further be bridged (so forming, for example, fused ring systems such as three fused cycloalkyl groups). Such cycloalkyl groups may be saturated or unsaturated containing one or more double or triple bonds (forming for example a cycloalkenyl or cycloalkynyl group). Substituents may be attached at any point on the cycloalkyl group. Further, where there is a sufficient number (i.e. a minimum of four) such cycloalkyl groups may also be part cyclic. For the avoidance of doubt, optional substituents may also be other cyclic groups, which may be attached via a single carbon atom common to both rings, so forming a spiro-cycle.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Heterocycloalkyi groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyi groups in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between five and ten. Such heterocycloalkyi groups may also be bridged. Further, such heterocycloalkyi groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a \( \text{C}_{2-q} \) heterocycloalkenyl (where \( q \) is the upper limit of the range) or a \( \text{C}_{7-q} \) heterocycloalkynyl group. \( \text{C}_{2-q} \) heterocycloalkyi groups that may be mentioned include 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidinyl, dihydropyranyl, dihydropritydyl, dihydroprrolyl (including 2,5-dihydropyrrolyl), dioxolany (including 1,3-dioxolany), dioxanyl
(including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl),
dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, 7-
oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]octanyl, oxetanyl, oxiranyl,
piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl,
pyrroline, quinuclidinyl, sulfolanly, 3-sulfolenyl, tetrahydropyranylyl,
tetrahydrofuranylyl, tetrahydropiridyl (such as 1,2,3,4-tetrahydropiridyl and
1,2,3,6-tetrahydropiridyl), thietanyl, thiranyl, thiolanyl, thiomorpholinyl, trithiayl
(including 1,3,5-trithiayl), tropanyl and the like. Substituents on heterocycloalkylyl
groups may, where appropriate, be located on any atom in the ring system
including a heteroatom. The point of attachment of heterocycloalkylyl groups may
be via any atom in the ring system including (where appropriate) a heteroatom
(such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be
present as part of the ring system. Heterocycloalkylyl groups may also be in the N-
or S-oxidised form (i.e. those heteroatoms may be substituted with one or two
=0 substituents, as appropriate). As stated herein other carbon atoms of the
heterocycloalkylyl groups mentioned herein may also be substituted by one or
more =0 substituents. For the avoidance of doubt, optional substituents may
also be other cyclic groups, which may be attached via a single carbon atom
common to both rings (so forming a spiro cycle).

For the avoidance of doubt, the term "bicyclic" (e.g. when employed in the context
of heterocycloalkylyl groups) refers to groups in which the second ring of a two-ring
system is formed between two adjacent atoms of the first ring. The term
"bridged" (e.g. when employed in the context of cycloalkyl or heterocycloalkylyl
groups) refers to monocyclic or bicyclic groups in which two non-adjacent atoms
are linked by either an alkylene or heteroalkylene chain (as appropriate).

Aryl groups that may be mentioned include C₆₋₁₀ aryl groups. Such groups may
be monocyclic, bicyclic or tricyclic and have between 6 and 10 ring carbon atoms,
in which at least one ring is aromatic. C₆₋₁₀ aryl groups include phenyl, naphthyl
and the like, such as 1,2,3,4-tetrahydronaphthyl. The point of attachment of aryl
groups may be via any atom of the ring system. However, when aryl groups are
bicyclic or tricyclic, they are linked to the rest of the molecule via an aromatic ring.
For the avoidance of doubt, optional substituents include those defined herein
and also include =0 substituents that may be attached to any non-aromatic rings
of a polycyclic (e.g. bicyclic) aryl group (however, in an embodiment, =0 substituents are not included). For the avoidance of doubt, optional substituents may also be other cyclic groups, which may be, when attached to a non-aromatic ring of an aryl group, attached via a single carbon atom common to both rings (so forming a spiro-cycle).

Unless otherwise specified, the term "heteroaryl" when used herein refers to an aromatic group containing one or more heteroatom(s) (e.g. one to four heteroatoms) preferably selected from N, O and S. Heteroaryl groups include those which have between 5 and 10 members and may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic (so forming, for example, a mono-, bi- or tricyclic heteroaromatic group). However, when heteroaryl groups are bicyclic or tricyclic, they are linked to the rest of the molecule via an aromatic ring. Heteroaryl groups that may be mentioned include acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), benzothiazolyl, benzoazolyl (including 3,4-dihydro-2/-/-1,4-benzoazinyl), benzoazoxyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-a]pyridyl, indazolyl, indolyl, indoly1, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiochromanyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thiphenethyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. For the avoidance of doubt, optional substituents include those
defined herein and also include =0 substituents that may be attached to any non-aromatic rings of a polycyclic (e.g. bicyclic) heteroaryl group (but, in an embodiment, =0 substituents are not included). For the avoidance of doubt, optional substituents may also be other cyclic groups, which may be, when attached to a non-aromatic ring of a heteroaryl group, attached via a single carbon atom common to both rings (so forming a spiro-cycle). The point of attachment of heteroaryl groups may be via any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heteroaryl groups may also be in the N- or S- oxidised form.

It may be specifically stated that the heteroaryl group is monocyclic or bicyclic. In the case where it is specified that the heteroaryl is bicyclic, then it may be consist of a five-, six- or seven-membered monocyclic ring (e.g. a monocyclic heteroaryl ring) fused with another a five-, six- or seven-membered ring (e.g. a monocyclic aryl or heteroaryl ring).

Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulphur.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which there is more than one A¹ substituent present, then those A¹ substituents may be the same or different. Further, in the case where there are two A¹ substituents present, in which one represents -OR¹⁰a and the other represents -C(O)-R¹⁰a, then those R¹⁰a groups are not to be regarded as being interdependent.

For the avoidance of doubt, in the instance where cyclic substituents (e.g. cycloalkyi or heterocycloalkyi groups) are present on groups (such as alkyl groups), then those cyclic substituents may be attached to the same carbon atom, so forming for example a spiro-cyclic group.
All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred feature) mentioned herein (hence, preferred features may be taken in conjunction with other preferred features, or independently of them).

The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

For the avoidance of doubt, when a term such as "R^{10a} to R^{12a}" is employed herein, this will be understood by the skilled person to mean R^{10a}, R^{11a} and R^{12a}, inclusively. Likewise, a term such as "A^1 to A^6n" when employed herein, will be understood by the skilled person to mean A^1, A^2, A^3, A^4, A^5 and A^6, inclusively.

In an embodiment of the invention, there is provided compounds of the invention as hereinbefore defined but in which R^2 represents hydrogen. In another embodiment of the invention, there is provided compounds of the invention as hereinbefore defined but in which R^2 represents C_{1-3} alkyl (e.g. methyl) optionally substituted by one or more fluoro atoms (e.g. especially those in which R^2 represents unsubstituted methyl).

Preferred compounds of the invention include those in which:

each R^{10x} independently represents, on each occasion when used herein, hydrogen, C_{1,12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =0, =S, =N(R^{20}) and E^3),

aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^4);

each R^1 and R^2 independently represents, on each occasion when used herein, hydrogen or C_{1,12} alkyl optionally substituted by one or more substituents selected from =S, =N(R^{20}), and preferably, =0 and E^3;

at least one of R^4 and R^2 represents C_{1,12} alkyl optionally substituted as defined herein and the other represents hydrogen or, preferably C_{1,12} alkyl optionally substituted as defined herein;
when \( R^{x_1} \) and \( R^{t_2} \) represent \( C_{1:12} \) alkyl, then preferred groups include \( C_{1:6} \) (e.g. \( C_{1:3} \)) alkyl groups, which are preferably unsubstituted.

Further preferred compounds of the invention include those in which:

5. \( R^i \) may represent (in situations in which \( R^3 \) represents aryl or heteroaryl, both of which are optionally substituted as defined herein and, preferably, \( R^{10x} \) represents optionally substituted aryl or heteroaryl) heteroaryl (e.g. 3-pyridyl) substituted (e.g. at the position \textit{meta} to the point of attachment to the imidazothiadiazole, i.e. in the case of 3-pyridyl, at the 5-position) with -NR\(^{12a}\)S(O)\(_2\)R\(^{10x} \) (and which heteroaryl group is optionally substituted with one or more (e.g. one to three, when \( R^i \) represents pyridyl) further substituents selected from \( A^2 \);

\[
\begin{align*}
\text{A}^2 & \text{N} \\
\text{R}^{12a} & \text{SO}_2 \\
\text{R}^{10x} & 
\end{align*}
\]

in which the squiggly line represents the point of attachment to the requisite imidazothiadiazole core of formula \( i \). \( X^1 \) represents -N= or, preferably, -C(H)= (and the other substituents, i.e. \( A^2, R^{10x} \) and \( R^{12a} \) are as defined herein). Preferred embodiments include those in which \( X^1 \) represents -C(H)= (i.e. forming a 3-pyridyl group).

20. Preferred compounds of the invention that may be mentioned include those in which:

- \( R^2 \) represents hydrogen or \( C_{1:3} \) alkyl optionally substituted by one or more fluoro atoms;
- \( R^3 \) represents aryl or heteroaryl, each of which is optionally substituted by one or more substituents selected from \( A^3 \) and \( A^4 \), respectively;
- each \( Q^7, Q^8 \) and \( Q^9 \) independently represents, on each occasion when used herein:
  - -CN or, more preferably, halo, -N(R\(^{50}\))R\(^{1}\), -OR\(^{50}\), -C(=Y\(^a\))-R\(^{50}\), -C(=Y\(^a\))-OR\(^{50}\), -C(=Y\(^a\))N(R\(^{50}\))R\(^{51}\), -N(R\(^{52}\))C(=Y\(^a\))R\(^{51}\), -NR\(^{52}\)S(0)\(_2\)R\(^{50}\), -S(0)\(_2\)R\(^{50}\), -SR\(^{50}\), -SR\(^{50}\) or \( C_{1:6} \) alkyl optionally substituted by one or more fluoro atoms.
Preferred compounds of the invention also include those in which:

- \( R^{10a} \) (that is a part of the requisite \(-\text{NR}^{12a}S(O)_{2}R^{10a}\) moiety, represents \( C_{3-12} \) cycloalkyl (optionally substituted by one or more substituents selected from \( =0 \) and, preferably, \( E^{3} \)), heterocycloalkyl (optionally substituted by one or more substituents selected from \( =0 \) and, preferably, \( E^{3} \)), aryl (optionally substituted by one or more substituents selected from \( E^{4} \)) or heteroaryl (optionally substituted by one or more substituents selected from \( E^{4} \)). More preferably such \( R^{10a} \) groups represent optionally substituted heterocycloalkyl (e.g. a 9- or 10-membered bicyclic group or, preferably, a 5- or 6-membered monocyclic group), particularly, heteroaryl (e.g. a 9- or 10-membered bicyclic group or, preferably, a 5- or 6-membered monocyclic group) and, especially, aryl (e.g. phenyl).

Further preferred compounds of the invention that may be mentioned include those in which:

- when \( R^{1} \) represents pyridyl (e.g. 3-pyridyl) substituted at the 5-position with \(-\text{NR}^{12a}S(O)_{2}R^{10a}\), then the 2- and 4-positions are preferably unsubstituted and the 6-position is optionally (but preferably) substituted by \( A^{1} \) or \( A^{2} \) (as appropriate; e.g. \( A^{2} \));
- when \( R^{1} \) represents phenyl substituted at the 3-position with \(-\text{NR}^{12a}S(O)_{2}R^{10a}\), then the 2, 5 and 6 positions are preferably unsubstituted and the 4-position is optionally (but preferably) substituted by \( A^{1} \) or \( A^{2} \) (as appropriate; e.g. \( A^{2} \));
- \( R^{12a} \) represents \( C_{1-3} \) alkyl or, preferably, hydrogen;
- \( R^{10a} \) (e.g. as a part of the above-mentioned \(-\text{NR}^{12a}S(O)_{2}R^{10a}\) group) represents aryl or heteroaryl (preferably aryl, such as phenyl) optionally substituted by one or more substituents selected from \( E^{4} \) (preferably when it represents phenyl, then that group is preferably substituted e.g. with two \( E^{4} \) substituents located at the \( \text{ortho and para} \) position; in which each \( E^{4} \) preferably represents fluoro);
- \( A^{1} \) and \( A^{2} \) independently represent \( Q^{1} \);
- each \( A^{2} \) independently represents \( Q^{1} \);
- \( Q^{1} \) represents \(-\text{OR}^{10a} \) (in which \( R^{10a} \) is preferably \( C_{1-3} \) alkyl optionally substituted by one or more fluoro atoms; preferably \( R^{10a} \) in this instance represents unsubstituted methyl);
- \( E^{4} \) represents \( Q^{4} \);
- \( Q^{4} \) represents halo (especially fluoro);
R\(^2\) represents hydrogen or C\(_{1-3}\) alkyl (e.g. methyl) (preferably hydrogen);
R\(^3\) represents a 6-membered monocyclic heteroaryl group (in which there are one
or two heteroatoms preferably selected from nitrogen; so forming e.g. a
pyridazinyl (e.g. 4-pyridazinyl) group; preferably unsubstituted), which may be
substituted with one or more A\(^4\) substituents, but which is preferably
unsubstituted.

Other preferred compounds of the invention that may be mentioned include those
in which:

R\(^1\) represents aryl, or, preferably, heteroaryl (e.g. 3-pyridyl) substituted (e.g. at the
position meta to the point of attachment to the imidazothiadiazole, i.e. in the case
of 3-pyridyl, at the 5-position) with \(-\text{NR}^{12a}\text{S(O)}_2\text{R}^{10x}\), and optionally substituted with
one or more (e.g. one to three, when R\(^1\) represents pyridyl) further substituents
selected from A\(^1\) or A\(^2\) (as appropriate).

Preferred compounds of the invention that may be mentioned include those in
which:
the point of attachment of heteroaryl groups that R\(^1\) and R\(^3\) may represent is via a
heterocyclic ring (e.g. heteroaromatic ring) of that heteroaryl group (for example,
if/when the heteroaryl ring is bicyclic in which there is benzene ring fused to a
heterocyclic ring, then the point of attachment is via the heterocyclic ring, rather
than the benzene ring, e.g. an indolyl group is preferably linked via the 2- or 3-
position);
when any relevant pair of R\(^{10a}\), R\(^{11a}\) and R\(^{12a}\) and/or R\(^{20}\), R\(^{21}\) and R\(^{22}\) are linked
together, then they may be linked when those substituents are attached to the
same atom (i.e. the same nitrogen atom to which they are necessarily attached);
when either of R\(^1\) and/or R\(^3\) (as/if appropriate) represent a heteroaryl group, then
it may be a:
(i) monocyclic 5- or 6-membered ring, containing between one and four
heteroatoms (e.g. between one and three, preferably one or two), in which the
heteroatoms are preferably selected from oxygen, sulfur and, especially, nitrogen,
and which ring is optionally substituted as defined herein;
(ii) a bicyclic 8-, 9- or 10-membered heteroaryl group, containing between one
and four heteroatoms (e.g. between one and three, preferably one or two), and in
which the bicycle consists of a 5- or 6-membered ring fused with another 5- or 6-
membered ring. Preferably, it consists of a benzene ring fused to a monocyclic heteroaryl group as defined herein (e.g. a 5- or 6-membered ring as defined above).

Preferred compounds of the invention include those in which: A¹, A², A³, A⁴, A⁵ and A⁶ independently represent, on each occasion when used herein, Q¹ or C₁₆ (e.g. C₄₃) alkyl substituted by one or more substituents selected from Q²; each Q¹, Q² and Q³ independently represent, on each occasion when used herein halo, -CN, -N⁰₂, -N(R¹⁰a)R¹¹a, -OR¹⁰a, -C(=Y)-R¹⁰a, -C(=Y)-OR¹⁰a, -C(=Y)N⁰(R¹⁰a)R¹¹a, -N(R¹²a)C(=Y)R¹¹a, -N(R¹²a)C(=Y)OR¹¹a, -NR¹²aS(O)₂R¹⁰a, -S(O)₂N(R¹⁰a)R¹¹a, -S(O)₂R¹⁰a, -SR¹⁰a, -S(O)R¹⁰a or C₁₃₋₁₂ (e.g. C₅) alkyl (optionally substituted by one or more substituents selected from =0 and, preferably, E¹); each R¹⁰a, R¹¹a and R¹²a independently represent, on each occasion when used herein, hydrogen or C₁₃₋₁₂ alkyl optionally substituted by one or more substituents selected from =0 and, preferably, E³; or any relevant pair of R¹⁰a, R¹¹a and R¹²a (e.g. R¹⁰a and R¹¹a) may be linked together to form (e.g. when attached to the same nitrogen atom, along with the requisite nitrogen atom to which they are attached) a 4- to 8-membered ring, optionally containing one or more double bonds (e.g. one or two), and which ring may contain a further two or, preferably, one heteroatom (preferably selected from nitrogen and, especially, oxygen), and which ring is optionally substituted by one or more substituents selected from E⁵ and =0; E¹, E², E³, E⁴ and E⁵ (e.g. E¹, E² and E³) independently represent, on each occasion when used herein, Q⁴ or C₁₆ (e.g. C₄₃) alkyl optionally substituted by one or more substituents selected from =0 and, preferably, Q⁵ (most preferably such E¹ to E⁵ groups represent Q⁴); each Q⁴, Q⁵ and Q⁶ (e.g. Q⁴) independently represents, on each occasion when used herein halo, -CN, -N⁰₂, -N(R²⁰)R²¹, -OR²⁰, -C(=Y)-R²⁰, -C(=Y)-OR²⁰, -C(=Y)N(R²⁰)R²¹, -N(R²²)C(=Y)R²¹, -N(R²²)C(=Y)OR²¹, -NR²²S(O)₂R²², -S(O)₂N(R²⁰)R²¹, -S(O)₂R²², -SR²⁰, -S(O)R²⁰, or C₁₆ alkyl optionally substituted by one or more substituents selected from fluoro; each Y independently represents, on each occasion when used herein, =0;
each R\(^{20}\), R\(^{21}\), R\(^{22}\) and R\(^{23}\) independently represent, on each occasion when used herein, hydrogen or C\(_{1-3}\) alkyl optionally substituted by one or more substituents selected from J\(^{3}\) and =0; or any pair of R\(^{20}\), R\(^{21}\) and R\(^{22}\) (e.g. R\(^{20}\) and R\(^{21}\)) may be linked together to form (e.g. when attached to the same nitrogen atom, along with the requisite nitrogen atom to which they are attached) a 4- to 8-membered ring, optionally containing one or more double bonds (e.g. one or two), and which ring may contain a further two or, preferably, one heteroatom (preferably selected from nitrogen and, especially, oxygen), and which ring is optionally substituted by one or more substituents selected from J\(^{5}\) and =0;
each J\(^{1}\), J\(^{2}\), J\(^{3}\), J\(^{4}\) and J\(^{5}\) independently represents, on each occasion when used herein: (i) Q\(^{7}\); or (ii) C\(_{1-6}\) alkyl optionally substituted by one or more substituents selected from =0 and Q\(^{8}\) (more preferably, each J\(^{1}\), J\(^{2}\), J\(^{3}\), J\(^{4}\) and J\(^{5}\) (e.g. each J\(^{1}\) and J\(^{2}\)) independently represents Q\(^{7}\);
each Q\(^{7}\), Q\(^{8}\) and Q\(^{9}\) (e.g. Q\(^{7}\)) independently represents -N(R\(^{59}\))R\(^{61}\), -OR\(^{60}\) or, preferably, halo (e.g. fluoro) or C\(_{1-3}\) alkyl (e.g. methyl) optionally substituted by one or more fluoro atoms;
each Y\(^{8}\) independently represents =0;
each R\(^{60}\), R\(^{61}\), R\(^{65}\) and R\(^{66}\) substituent independently represents, on each occasion when used herein, hydrogen or C\(_{1-6}\) (e.g. C\(_{1-3}\)) alkyl optionally substituted by one or more substituents selected from fluoro; R\(^{60}\), R\(^{61}\) and R\(^{62}\) independently represent methyl or hydrogen.

Preferred aryl and heteroaryl groups that R\(^{1}\) (if appropriate), R\(^{3}\) and (when aromatic) R\(^{10x}\) may independently represent include optionally substituted phenyl, naphthyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, pyridyl, indazolyl, indolyl, indoliny1, isoindoliny1, quinoliny1, isoquinoliny1, quinoliziny1, benzoazolyl, benzofurany1, isobenzofurany1, chromany1, benzothienyl, pyridaziny1, pyrimidiny1, pyraziny1, indazolyl, benzimidazolyl, quinazoliny1, quinoxaliny1, 1,3-benzodioxolyl, tetrazolyl, benzothiazolyl, and/or benzodioxany1. Particularly preferred groups that R\(^{3}\) may independently represent include optionally substituted phenyl, pyridyl (e.g. 3- or 4-pyridyl), quinolinyl (e.g. 3-quinolinyl), pyrazolyl (e.g. 4-pyrazolyl). Preferred groups that R\(^{1}\) may represent include pyridyl (e.g. 3-pyridyl) (substituted with the -NR\(^{12}\)S(O)\(^{2}\)R\(^{10x}\)
substituent as defined and further optionally substituted as defined herein). Preferred groups that $R^{10x}$ may represent include optionally substituted phenyl.

Preferred substituents on aryl or heteroaryl groups that $R^1$, $R^3$ and (when aromatic) $R^{10x}$ may represent include (as appropriate):

$=0$ (e.g. in the case of cycloalkyl or, preferably, heterocycloalkyl groups);

-CN;

halo (e.g. fluoro, chloro or bromo);

$C_1-4$ alkyl, which alkyl group may be cyclic, part-cyclic, unsaturated or, preferably, linear or branched (e.g. $C_{1-4}$ alkyl (such as ethyl, n-propyl, isopropyl, i-butyl or, preferably, n-butyl or methyl), all of which are optionally substituted with one or more substituents selected from -OR, -N(R$_z$)$_2$ and -C($O$)$_2$N(R$_z$)$_2$, so forming, for example, fluormethyl, difluormethyl or, preferably, trifluoromethyl);

aryl (e.g. phenyl), if appropriate (e.g. when a substituent on an alkyl group, thereby forming e.g. a benzyl group);

-OR;

-N(R$_z$)$_2$;

-CONH$_2$;

wherein $R^{z1}$ to $R^{z10}$ independently represent, on each occasion when used herein, H or $C_{1-4}$ alkyl (e.g. ethyl, n-propyl, i-butyl or, preferably, n-butyl, methyl or isopropyl) optionally substituted by one or more substituents selected from halo (e.g. fluoro), -N(R$_{z11}$)C($O$)$_2$ and -C($O$)$_2$N(R$_{z12}$)R$_{z14}$, in which $R^{z11}$ to $R^{z14}$ independently represent H or $C_{1-4}$ alkyl (e.g. methyl or i-butyl), or $R^{z13}$ and $R^{z14}$ are linked together to form a 5- or 6-membered ring (optionally containing a further heteroatom, so forming e.g. a morpholinyl group).

Preferred compounds of the invention include those in which:

$R^1$ represents aryl (e.g. phenyl) substituted as defined herein, or, a certain heteroaryl group as defined herein (e.g. pyridyl, such as 3-pyridyl) substituted as defined herein;
when \( R^1 \) represents a certain optionally substituted heteroaryl defined herein, then it preferably represents an optionally substituted 6-membered monocyclic heteroaryl group containing two or, preferably, one nitrogen atom(s); 

\( R^2 \) represents hydrogen or methyl;

\( R^3 \) represents aryl (e.g. phenyl) optionally substituted by one or more substituents selected from \( A^3 \), or, heteroaryl (e.g. a 5- or 6-membered group) optionally substituted by one or more substituents selected from \( A^4 \);

when \( R^3 \) represents optionally substituted heteroaryl, then it preferably represents an optionally substituted monocyclic heteroaryl group (e.g. a 5- or, preferably, 6-membered monocyclic heteroaryl group), preferably containing one or two heteroatoms (preferably selected from oxygen, sulfur or, especially, nitrogen);

\( A^1, A^2, A^3, A^4, A^5 \) and \( A^6 \) independently represent \( Q^1 \) or may alternatively represent \( C_{1-6} \) alkyl (e.g. methyl or ethyl) or heterocycloalkyi (e.g. a 6-membered heterocycloalkyi group; which may be linked \( \text{via} \) a single carbon atom common to the heterocycloalkyi group and the non-aromatic cyclic ring of an aryl or heteroaryl group to which that heterocycloalkyi group is attached), both of which are optionally substituted by one or more \( Q^2 \) substituents;

each \( Q^1 \), \( Q^2 \) and \( Q^3 \) independently represents \( C_{1-6} \) alkyl (optionally substituted by one or more fluoro atoms), a 5- or 6-membered heterocycloalkyi group (optionally substituted by one or more substituents selected from \( E^1 \); which preferably contains one or two heteroatoms), -SR\(^{10a} \), -S(O)R\(^{10a} \), -NR\(^{12a} \)S(O)\(^2 \)R\(^{10a} \), -C(=Y)-N(R\(^{10a} \))R\(^{11a} \), -S(O)\(^2 \)N(R\(^{10a} \))R\(^{11a} \) or, more preferably, halo (e.g. chloro or, preferably, fluoro), -CN, -OR\(^{10a} \), -N(R\(^{10a} \))R\(^{11a} \), -C(=Y)-R\(^{10a} \), -N(R\(^{10a} \))C(=Y)R\(^{11a} \), -C(=Y)OR\(^{10a} \) or -S(O)\(^2 \)R\(^{10a} \);

\( Q^2 \) represents halo (e.g. fluoro) or \( C_{1-6} \) alkyl (e.g. methyl; which alkyl group is optionally substituted by one or more fluoro atoms);

each \( R^{10a} \), \( R^{11a} \) and \( R^{12a} \) (e.g. \( R^{10a} \)) independently represents hydrogen, \( C_{1-3} \) alkyl (e.g. methyl or ethyl) or heterocycloalkyi (e.g. piperidinyl), which latter two groups are optionally substituted by one or more substituents selected from \( E^3 \) (preferably each \( R^{10a} \), \( R^{11a} \) and \( R^{12a} \) independently represent hydrogen or \( C_{1-3} \) alkyl optionally substituted by one or more substituents selected from \( E^3 \); in which \( E^3 \) may be fluoro or another substituent as defined herein such as -N(R\(^{20g} \))R\(^{21} \); or \( R^{10a} \) and \( R^{11a} \) may be linked together to form a 5- or preferably 6-membered ring optionally containing one further heteroatom (e.g. nitrogen or, preferably,
oxygen), so forming for example a morpholinyl group (which ring may be substituted by one or more E⁵ substituents (but is preferably unsubstituted); R¹²a represents C₁₃ alkyl or, preferably, hydrogen;
each E¹, E², E³, E⁴ and E⁵ (e.g. E³) independently represent C₁₋₄ alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =0 and, preferably, Q⁵) or E¹ to E⁵ (e.g. E³) independently (and more preferably) represent Q⁴ (in which E⁴ is preferably halo (e.g. fluoro));
each Q⁴, Q⁵ and Q⁶ (e.g. Q⁴) independently represent halo (e.g. fluoro), C(=Y)-OR²₀ or, more preferably, -N(R²₀)R²₁, -C(=Y)N(R²₀)R²₁ or -N(R²₂)C(=Y)OR²₁;
each Y independently represents =S or, preferably, =0;
R²₀, R²¹ and R²² (e.g. R²₀ and R²¹) independently represent hydrogen or, preferably, C₁₋₄ alkyl (e.g. methyl or f-butyl); or
R²₀ and R²¹, when attached to the same nitrogen atom are linked together to form a 5- or 6-membered ring, optionally containing a further heteroatom (e.g. nitrogen, or, preferably, oxygen) so forming, e.g. a morpholinyl group;
R²² represents hydrogen.

Particularly preferred compounds of the invention that may be mentioned include those in which:
R¹ represents pyridyl (e.g. 3-pyridyl) substituted (e.g. at the position meta to the point of attachment to the imidazothiadiazole, i.e. in the case of 3-pyridyl, at the 5-position) with -NR¹²aS(O)₂R¹⁰a (and which R¹ group is optionally substituted with one or more (e.g. one to three, when R¹ represents pyridyl) further substituents selected from A¹ and/or A² (as appropriate);
when R¹ represents pyridyl, it preferably contains (in addition to the requisite -NR¹²aS(O)₂R¹⁰a substituent) no further substituents or one further substituent selected from A¹ and/or A² (as appropriate; e.g. A³);
R¹ more preferably represents:
in which the squiggly line represents the point of attachment to the requisite imidazothiadiazole core of formula I (and the other substituents, i.e. $A^2$, $R^{10x}$ and $R^{12a}$ are as defined herein);

5 $R^2$ represents hydrogen or $C_{1-2}$ alkyl (e.g. methyl) (most preferably $R^2$ represents hydrogen);

$R^3$ represents hydrogen, $Q^{1a}$, $C_{1-6}$ alkyl (optionally substituted as defined herein; which group is preferably cyclic or bears a cyclic group), heterocycloalkyl (optionally substituted as defined herein) or, preferably, aryl or heteroaryl (both of which latter two substituents are optionally substituted by one or more substituents selected from $A^3$ and $A^4$, respectively);

$R^3$ preferably represents a cyclic aromatic or non-aromatic group (or may bear a cyclic group);

$Q^{1a}$ preferably represents $-C(=Y)-R^{10a}$ or $-N(R^{10a})C(=Y)R^{11a}$;

15 when $R^3$ represents $C_{1-6}$ alkyl, it is preferably acyclic $C_{1-3}$ alkyl (e.g. methyl, optionally substituted by one or more (e.g. one) $A^5$ group) or $C_{3-6}$ cycloalkyl (optionally containing two or preferably one double bond, e.g. cyclohexenyl);

when $R^3$ represents heterocycloalkyl, it is preferably a 5- or 6-membered heterocycloalkyl group (containing one or two heteroatoms, preferably selected from oxygen and, especially, nitrogen, and optionally containing two or preferably one double bond; e.g. a piperidinyl group optionally containing one double bond); $A^5$ and $A^6$ independently represent $Q^1$;

when $A^6$ represents $Q^1$, then $Q^1$ preferably represents $-C(=Y)-OR^{10a}$, $-N(R^{10a})C(=Y)R^{11a}$ (in which $R^{10a}$ and $R^{11a}$ may be linked together to form a 5- or 6-membered heterocycloalkyl group optionally containing a further heteroatom, so forming e.g. a morpholinyl group) or heterocycloalkyl (e.g. a 5- or 6-membered group containing one or two heteroatoms);

when $A^6$ represents $Q^1$, then $Q^1$ preferably represents $-C(=Y)-OR^{10a}$;

$A^3$ and $A^4$ independently represent optionally substituted heterocycloalkyl or, preferably, $Q^1$, $C_{1-4}$ alkyl (e.g. methyl or ethyl; which alkyl group is optionally
substituted by one or more substituents selected from \( Q^2 \), in which \( Q^2 \) is preferably fluoro, so forming e.g. a \( -CF_3 \) group;
when \( A^3 \) and \( A^4 \) represent heterocycloalkyi, then it is preferably a 5- or 6-membered group containing one or two heteroatoms preferably selected from nitrogen and oxygen;
when \( A^3 \) and \( A^4 \) represent \( Q^1 \), then \( Q^1 \) represents halo (e.g. chloro), \(-\text{OR}^{10a}\) or \(-\text{N}(\text{R}^{10a})\text{R}^{11a}\) (e.g. in which \( R^{10a} \) and \( R^{11a} \) are linked together to form a 5- or 6-membered heterocycloalkyi group optionally containing a further heteroatom (e.g. nitrogen or oxygen));
\( Q^2 \) represents halo (e.g. fluoro);
\( A^1 \) and \( A^2 \) independently represent \( Q^1 \);
when \( A^2 \) (or \( A^1 \)) represents \( Q^1 \), it is preferably \(-\text{OR}^{10a}\) (in which \( R^{10a} \) is preferably \( \text{Cl} \)-2 alkyl, such as methyl);
\( R^{10a} \) represents optionally substituted heteroaryl or, preferably, aryl optionally substituted by one or more (e.g. one to three) substituents selected from \( E^4 \);
\( E^3 \) and \( E^4 \) independently represent \( Q^4 \);
when \( E^3 \) or \( E^4 \) represents \( Q^4 \), then \( Q^4 \) preferably represents halo (e.g. fluoro);
\( R^{10a} \) represents hydrogen or \( C_{14} \) (e.g. \( \text{C}_{1-2} \)) alkyl (e.g. tert-butyl or methyl);
\( R^{12a} \) represents hydrogen;
\( R^{11a} \) represents \( C_{13} \) (e.g. \( C_{1-2} \)) alkyl (e.g. methyl);
or \( R^{10a} \) and \( R^{11a} \) may be linked together to form a 5- or 6-membered heterocycloalkyi group optionally containing a further heteroatom (e.g. nitrogen or oxygen);
\( Y \) represents \( =0 \).

Most preferred compounds of the invention include those in which:
\( R^2 \) represents hydrogen or methyl (especially hydrogen);
\( R^3 \) represents hydrogen, iodo, methyl, \(-\text{C}(0)\text{H}, \ -\text{N}(\text{H})\text{-C}(0)\text{CH}_3 \), preferably, cyclohexenyl, piperidinyl (e.g. 3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester), \(-\text{CH}_2\text{-[4-morpholiny]}\) or, more preferably, phenyl (e.g. unsubstituted phenyl, hydroxyphenyl or methoxyphenyl), pyridyl (e.g. 3- or 4-pyridyl, such as 3-chloro-4-pyridyl, 2-CF\(_3\)-4-pyridyl, 2-methyl-4-pyridyl or 2-(4-morpholiny1)-4-pyridyl), quinolinyl (e.g. 3-quinolinyl), pyrazolyl (e.g. 4-pyrazolyl, such as 1-ethyl-4-pyrazolyl) or, especially, pyridazinyl (e.g. 4-pyridazinyl);
\( R^{10a} \) groups represent difluorophenyl (e.g. 2,4-difluorophenyl).
Particularly preferred compounds of the invention include those of the examples described hereinafter.

Compounds of the invention may be made in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I which process comprises:

(i) for compounds of formula I in which R³ is other than hydrogen or halo, reaction of a corresponding compound of formula II,

\[
\begin{align*}
  & R^1 \quad \text{II} \\
  & \quad L^1 \quad R^2
\end{align*}
\]

wherein \( L^1 \) represents a suitable leaving group, such as iodo, bromo, chloro or a sulfonate group (e.g. \(-\text{OS}(0)\_2\text{CF}_3\), \(-\text{OS}(0)\_2\text{CH}_3\) or \(-\text{OS}(0)\_2\text{PhMe}\)) (most preferably \( L^1 \) represents iodo), and \( R^1 \) and \( R^2 \) are as hereinbefore defined, with a compound of formula III,

\[
\begin{align*}
  & L^2\text{-}R^3^a \\
  & \quad \text{III}
\end{align*}
\]

wherein \( L^2 \) represents a suitable group such as \(-\text{B(OH)}\_2\), \(-\text{B(OR)}\_2\) or \(-\text{Sn(OR)}\_3\), in which each \( R^\text{™} \) independently represents a \( C\_\text{nH}_\text{m} \) alkyl group, or, in the case of \(-\text{B(OR)}\_2\), the respective \( R^\text{™} \) groups may be linked together to form a 4- to 6-membered cyclic group (such as a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group), and \( R^3^a \) represents \( R^3 \) as hereinbefore defined provided that it does not represent hydrogen or halo (most preferably \( L^2 \) represents \(-\text{BiOR}^\text{™} \)). This reaction may be performed, for example in the presence of a suitable catalyst system, e.g. a metal (or a salt or complex thereof) such as Cul, Pd/C, PdCl₂, Pd(OAc)₂, Pd(Ph₃P)₂Cl₂, Pd(Ph₃P)₄ (i.e. palladium tetrakistriphenylphosphine), Pd₃(dba)₃ or NiCl₂ and a ligand such as f-Bu₃P, \((C\_6\text{H}_\text{n})_3\text{P}\), \( \text{Ph}_3\text{P}\), AsPh₃, P(o-Tol)₃, 1,2-bis(diphenylphosphino)ethane, \( \text{2,2'}\text{-bis(di-feri-butylphosphino)-1, r} \)-
biphenyl, 2,2'-bis(diphenylphosphino)-1,1'-bi-naphthyl, 1,1'-bis(diphenylphosphino-ferrocene), 1,3-bis(diphenylphosphino)propane, xantphos, or a mixture thereof, together with a suitable base such as, Na$_2$CO$_3$, K$_2$PO$_4$, Cs$_2$CO$_3$, NaOH, KOH, K$_2$C$_7$O$_3$, CsF, Et$_3$N, (/-Pr)$_2$NEt, f-BuONa or f-BuOK (or mixtures thereof) in a suitable solvent such as dioxane, toluene, ethanol, dimethylformamide, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, N-methylpyrrolidone, tetrahydrofuran, dimethoxyethane (DME) or mixtures thereof (preferably a polar aprotic solvent is employed, e.g. dioxane or DME). The reaction may also be carried out for example at room temperature or above (e.g. at a high temperature such as the reflux temperature of the solvent system). The reaction may also be carried out under microwave irradiation reaction conditions, for example at elevated temperature (e.g. at above 100°C, such as at about 135 to 140°C). Alternative L$^2$ groups that may be mentioned include alkali metal groups (e.g. lithium) and halo groups, which may be converted to a magnesium halide (i.e. a Grignard reagent), in which the magnesium may undergo a 'trans-metallation' reaction, thereby being exchanged with, for example, zinc;

(ii) reaction of a compound of formula IV,

\[
\begin{array}{c}
\text{L}^3 \\
\text{S} \\
\text{N} \\
\text{N} \\
\text{R}^2 \\
\end{array}
\]

IV

wherein L$^3$ represents a suitable leaving group, such as one hereinbefore defined in respect of L$^1$ (e.g. iodo), and R$^2$ and R$^3$ are as hereinbefore defined, with a compound of formula V,

\[
\begin{array}{c}
\text{R}^1 \cdot \text{L}^4 \\
\end{array}
\]

V

wherein L$^4$ represents a suitable leaving group, such as one hereinbefore defined in respect of L$^2$ (e.g. a boronic acid), and R$^1$ is as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of process step (i) above. Alternatively, steps (i) and (ii) may be
performed in the same pot, i.e. the L₁ and L₃ moieties may be replaced with R³ and R¹ in the same pot;

(iii) for compounds of formula I in which there is a Q¹ to Q⁹ substituent present (i.e. Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, Q⁸ and/or Q⁹ substituent present), in which such groups represent -OR₁⁰, -OR₂⁰ or -OR₅⁰, as appropriate, in which R₁⁰, R₂⁰ and R₅⁰ do not represent hydrogen (and most preferably represent optionally substituted alkyl as defined herein, e.g. C₁₁₂ or C₁₆ alkyl optionally substituted as defined herein), reaction of a corresponding compound of formula I in which there is a Q¹ to Q⁹ present, which represents -OR₁⁰, -OR₂⁰ and -OR₅⁰ (as appropriate), in which R₁⁰, R₂⁰ and R₅⁰ do represent hydrogen, with a compound of formula VI,

\[ R^*-L^5 \quad VI \]

wherein L⁵ represents a suitable leaving group, such as one hereinbefore defined in respect of the L¹ definition (e.g. chloro or, preferably, bromo), and R* represents R₁⁰, R₂⁰ or R₅⁰ (as appropriate), provided that they do not represent hydrogen (and preferably represent C₁₁₂ or C₁₆ alkyl optionally substituted as defined herein), under reaction conditions known to those skilled in the art, the reaction may be performed at around room temperature or above (e.g. up to 40-180°C), optionally in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, /V-ethyldiisopropylamine, /V-(methylpolystyrene)-4-(methylamino)pyridine, potassium bis(trimethylsilyl)-amide, sodium bis(trimethylsilyl)amide, potassium ferb-butoxide, lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidine or mixtures thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, trifluoromethylbenzene, dioxane, triethylamine, water or mixtures thereof);

(iv) compounds of formula I may be prepared by reaction of a compound corresponding to a compound of formula I but in which R¹ represents the relevant
aryl or heteroaryl group substituted (at the appropriate position) by -NH$_2$, by reaction with a compound of formula VIA,

$$L^6\text{-S(O)}_2\text{-R}^{10x} \quad \text{VIA}$$

wherein L$^6$ represents a suitable leaving group such as one hereinbefore defined in respect of the L$^1$ definition (e.g. chloro), and R$^{10x}$ is as hereinbefore defined, for example in the presence of a suitable solvent and base (for instance under reaction conditions such as those described in respect of process step (iii) above).

Compounds of formula II in which L$^1$ represents halo, may be prepared by reaction of a compound of formula VII,

$$R^1\equiv\text{S}(\equiv\text{N}) \equiv \text{N} \equiv \text{R}^2 \quad \text{VII}$$

or, compounds of formula IV may be prepared by reaction of a compound of formula VIIA,

$$L^3\equiv\text{S}(\equiv\text{N}) \equiv \text{N} \equiv \text{R}^2 \quad \text{VIIA}$$

wherein, in the above instances, L$^3$, R$^1$ and R$^2$ are as hereinbefore defined, with a source of halide ions, for instance an electrophile that provides a source of iodide ions includes iodine, diiodoethane, diiodotetrachloroethane or, preferably, $N$-iodosuccinimide, a source of bromide ions includes $\text{N}$-bromosuccinimide and bromine, and a source of chloride ions includes $\text{N}$-chlorosuccinimide, chlorine and iodine monochloride.

Other compounds of formula II may also be prepared under standard conditions, for instance such as those described herein. For example, for synthesis of compounds of formula II in which L$^1$ represents a sulfonate group, reaction of a compound corresponding to a compound of formula II but in which L$^1$ represents -OH with an appropriate sulfonyl halide, under standard reaction conditions, such
as in the presence of a base (e.g. as hereinbefore described in respect of preparation of compounds of formula I (process step (iii)).

Compounds of formula VII (e.g. those in which R² represents hydrogen or methyl) may be prepared by reaction of a compound of formula VII,

\[
\begin{array}{c}
\text{VIII} \\
\text{R}^1 - \text{S} - \text{NH}_2 \\
\end{array}
\]

wherein R¹ is as hereinbefore defined, with a compound of formula IX,

\[
\begin{array}{c}
\text{IX} \\
\text{Cl-CH}_2\text{C(0)-R'}^2 \\
\end{array}
\]

wherein R² represents hydrogen or C₁₃ alkyl optionally substituted by one or more halo (e.g. fluoro) atoms (most preferably R² represents hydrogen or methyl), under standard conditions known to those skilled in the art. For example, the compound of formula IX may already be present in water, and hence, the reaction may be performed in the presence of water as a solvent, optionally in the presence of a further solvent, such as an alcohol (e.g. n-butanol), for example at room temperature or, preferably, elevated temperature such as at reflux.

Compounds of formula VIII may be prepared by reaction of a corresponding compound of formula X,

\[
\begin{array}{c}
\text{X} \\
\text{L}^1 - \text{S} - \text{NH}_2 \\
\end{array}
\]

wherein L¹ is as hereinbefore defined, with a compound of formula V as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of preparation of compounds of formula I (process step (ii)).
Compounds of formula $X$ in which $L^1$ represents halo, may be prepared by reaction of a corresponding compound of formula XI,

\[
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{S}
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{NH}_2
\end{array}
\]

in the presence of a source of halide ions (e.g. in the case of bromide ions, bromine), such as those described hereinbefore in respect of preparation of compounds of formula II, for instance, in the presence of a suitable solvent, such as an alcohol (e.g. methanol) optionally in the presence of a suitable base, such as a weak inorganic base, e.g. sodium bicarbonate.

Compounds of formulae III, V, VI, VIA, VIIA, IX and XI (as well as certain other intermediate compounds) are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions. Further, the skilled person will appreciate that where reactions to introduce the "-R" moiety of compounds of formula I is described, similar reactions may be performed to introduce the "-R-$^3$" (or "-R-$^2$") moiety in compounds of formula I and vice versa. Further, processes to prepare compounds of formula I may be described in the literature, for example in:

Werber, G. et al.; J. Heterocycl. Chem.; EN; 14; 1977; 823-827;
Asuncion Marin et al. Farmaco 1992, 47 (1), 63-75;
M. Kuwahara et al., Chem. Pharm Bull., 1996, 44, 122;
J. Kobe et al., Tetrahedron, 1968, 24, 239 ;
M. Kuwahara et al., Chem. Pharm Bull., 1996, 44, 122;
L. Wengwei et al., Tetrahedron Lett., 2006, 47, 1941 ;
Seyden-Penne, J. Reductions by the Alumino and Borohydrides, VCH, NY, 1991;
O. C. Dermer, Chem. Rev., 1934, 14, 385;
S.J. Gregson et al., J. Med. Chem., 2004, 47, 1161;
E. Abignente et al., Il Farmaco, 1990, 45, 1075;
J. A. H. Lainton et al., J. Comb. Chem., 2003, 5, 400; or

Other specific transformation steps (including those that may be employed in order to form compounds of formula i) that may be mentioned include:

(i) reductions, for example of a carboxylic acid (or ester) to either an aldehyde or an alcohol, using appropriate reducing conditions (e.g. -C(0)OH (or an ester thereof), may be converted to a -C(0)H or -CH₂OH group, using DIBAL and LiAlH₄, respectively (or similar chemoselective reducing agents));

(ii) reductions of an aldehyde (-C(0)H) group to an alcohol group (-CH₂OH), using appropriate reduction conditions such as those mentioned at point (i) above;
(iii) oxidations, for example of a moiety containing an alcohol group (e.g. -CH₂OH) to an aldehyde (e.g. -C(O)H) or of a -S- moiety to a -S(O)₂- or -S(O)₃- moiety (or the reverse reduction reaction), for example in the presence of a suitable oxidising agent, e.g. MnO₂ or mcpba or the like;

(iv) reductive amination of an aldehyde and an amine, under appropriate reaction conditions, for example in "one-pot" procedure in the presence of an appropriate reducing agent, such as a chemoselective reducing agent such as sodium cyanoborohydride or, preferably, sodium triacetoxoborohydride, or the like. Alternatively, such reactions may be performed in two steps, for example a condensation step (in the presence of e.g. a dehydrating agent such as trimethyl orthoformate or MgSO₄ or molecular sieves, etc) followed by a reduction step (e.g. by reaction in the presence of a reducing agent such as a chemoselective one mentioned above or NaBH₄, AlH₃, or the like), for instance the conversion of -NH₂ to -N(H)-isopropyl by condensation in the presence of acetone (H₃C-C(0)-CH₃) followed by reduction in the presence of a reducing agent such as sodium cyanaoborohydride (i.e. overall a reductive amination);

(v) formation of an amide or sulfonamide, for example by reaction of a sulfonyl chloride with an amine or by an amide coupling reaction, i.e. the formation of an amide from a carboxylic acid (or ester thereof), for example -C(0)OH (or an ester thereof), may be converted to -C(O)N(R¹⁰a)R¹¹a group (in which R¹⁰a and R¹¹a are as hereinbefore defined, and may be linked together, e.g. as defined above), and which reaction may (e.g. for -COOH) be performed in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldimidazole, /V,AT-dicyclohexylcarbodiimide, or the like) or, in the case of an ester (e.g. -C(0)OCH₃ or -C(0)OCH₂CH₃), be performed in the presence of e.g. trimethylaluminium, or, alternatively the -C(0)OH group may first be activated to the corresponding acyl halide (e.g. -C(0)Cl, by treatment with oxalyl chloride, thionyl chloride, phosphorous pentachloride, phosphorous oxychloride, or the like), and, in all cases, the relevant compound is reacted with a compound of formula HN(R¹⁰a)R¹¹a (in which R¹⁰a and R¹¹a are as hereinbefore defined), under standard conditions known to those skilled in the art (e.g. optionally in the presence of a suitable solvent, suitable base and/or in an inert atmosphere);

(vi) conversion of a primary amide to a nitrile functional group, for example under dehydration reaction conditions, e.g. in the presence of POCl₃, or the like;
(vii) nucleophilic substitution (e.g. aromatic nucleophilic substitution) reactions, where any nucleophile replaces a leaving group, e.g. an amine may replace a \(-\text{S}(\text{O})\text{CH}_3\) leaving group;
(viii) transformation of a methoxy group to a hydroxy group, by reaction in the presence of an appropriate reagent, such as boron fluoride-dimethyl sulfide complex or BBr$_3$ (e.g. in the presence of a suitable solvent such as dichloromethane);
(ix) alkylation, acylation or sulfonylation reactions, which may be performed in the presence of base and solvent (such as those described hereinbefore);
(x) specific deprotection steps, such as deprotection of an A'-Boc protecting group by reaction in the presence of an acid, or, a hydroxy group protected as a silyl ether (e.g. a ferf-butyl-dimethylsilyl protecting group) may be deprotected by reaction with a source of fluoride ions, e.g. by employing the reagent tetrabutylammonium fluoride (TBAF);
(xi) aromatic nitration reactions (for instance which may be performed on compounds of formulae VII or V IIA; e.g. by reaction in the presence of nitric acid at low temperature, followed by addition of cone. H$_2$SO$_4$);
(xii) reductions of nitro groups to amino groups under standard conditions, e.g. iron-based reduction), which may be followed by an acylation reaction (see (ix) above) or a reductive amination (see (iv) above).

The substituents \(R^1\), \(R^2\) and \(R^3\) (or substituents thereon, e.g. defined by \(A^1\), \(A^2\), \(A^3\), \(A^4\), \(A^5\), \(A^6\) or, \(Q^1\), \(Q^2\), \(Q^3\), \(Q^4\), \(Q^5\), \(Q^6\), \(Q^7\), \(Q^8\) and/or \(Q^9\) in final compounds of the invention or relevant intermediates may be modified one or more times, after or during the processes described above by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions, oxidations, alkylation, acylations, hydrolyses, esterifications, etherifications, halogenations or nitration. Such reactions may result in the formation of a symmetric or asymmetric final compound of the invention or intermediate. The precursor groups can be changed to a different such group, or to the groups defined in formula I, at any time during the reaction sequence. For example, in cases in which there is a \(-\text{CO}_2\text{H}\) present, the skilled person will appreciate that at any stage during the synthesis (e.g. the final step), the relevant ester group may be hydrolysed to form a carboxylic acid functional group.

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Compounds of the invention bearing a carboxyester functional group may be converted into a variety of derivatives according to methods well known in the art to convert carboxyester groups into carboxamides, N-substituted carboxamides, N,N-disubstituted carboxamides, carboxylic acids, and the like. The operative conditions are those widely known in the art and may comprise, for instance in the conversion of a carboxyester group into a carboxamide group, the reaction with ammonia or ammonium hydroxide in the presence of a suitable solvent such as a lower alcohol, dimethylformamide or a mixture thereof; preferably the reaction is carried out with ammonium hydroxide in a methanol/dimethylformamide mixture, at a temperature ranging from about 50°C to about 100°C. Analogous operative conditions apply in the preparation of N-substituted or N,N-disubstituted carboxamides wherein a suitable primary or secondary amine is used in place of ammonia or ammonium hydroxide. Likewise, carboxyester groups may be converted into carboxylic acid derivatives through basic or acidic hydrolysis conditions, widely known in the art. Further, amino derivatives of compounds of the invention may easily be converted into the corresponding carbamate, carboxamido or ureido derivatives.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques (e.g. recrystallisations).

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

Medical and Pharmaceutical Uses

Compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention, for use as a pharmaceutical.

For the avoidance of doubt, although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the "active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

A "prodrug of a compound of the invention" is as hereinbefore defined, including compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time (e.g. about 1 hour), following oral or parenteral administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or
parenteral administration to form compounds which possess pharmacological activity.

Compounds of the invention may inhibit protein or lipid kinases, such as a PI3 kinase (especially a class I PI3K), for example as may be shown in the tests described below (for example, the test for PI3Koc inhibition described below) and/or in tests known to the skilled person. The compounds of the invention may also inhibit mTOR and/or Flt-3. Thus, the compounds of the invention may be useful in the treatment of those disorders in an individual in which the inhibition of such protein or lipid kinases (e.g. PI3K, particularly class I PI3K, mTOR and/or Flt3) is desired and/or required (for instance compounds of the invention may inhibit PI3K, particularly class I PI3K and, optionally, may also inhibit mTOR). Further, certain compounds of the invention may also further inhibit (in addition to inhibiting PI3K and, optionally, mTOR) Flt-3. Hence, certain compounds of the invention may be "dual" (e.g. PI3K and mTOR or PI3K and Flt3) or even "triple" inhibitors (i.e. inhibitors of PI3K, mTOR and Flt3).

The term "inhibit" may refer to any measurable reduction and/or prevention of catalytic kinase (e.g. PI3K, particularly class I PI3K, mTOR and/or Flt3) activity. The reduction and/or prevention of kinase activity may be measured by comparing the kinase activity in a sample containing a compound of the invention and an equivalent sample of kinase (e.g. PI3K, particularly class I PI3K, mTOR and/or Flt3) in the absence of a compound of the invention, as would be apparent to those skilled in the art. The measurable change may be objective (e.g. measurable by some test or marker, for example in an in vitro or in vivo assay or test, such as one described hereinafter, or otherwise another suitable assay or test known to those skilled in the art) or subjective (e.g. the subject gives an indication of or feels an effect).

Compounds of the invention may be found to exhibit 50% inhibition of a protein or lipid kinase (e.g. PI3K, such as class I PI3K, mTOR and/or Flt3) at a concentration of 100 µM or below (for example at a concentration of below 50 µM, or even below 10 µM, such as below 1 µM), when tested in an assay (or other test), for example as described hereinafter, or otherwise another suitable assay or test known to the skilled person.
Compounds of the invention are thus expected to be useful in the treatment of a disorder in which a protein or lipid kinase (e.g. PI3K, such as class I PI3K, mTOR and/or Flt3) is known to play a role and which are characterised by or associated with an overall elevated activity of that kinase (due to, for example, increased amount of the kinase or increased catalytic activity of the kinase). Hence, compounds of the invention are expected to be useful in the treatment of a disease/disorder arising from abnormal cell growth, function or behaviour associated with the protein or lipid kinase (e.g. PI3K, such as class I PI3K, mTOR and/or Flt3). Such conditions/disorders include cancer, immune disorders, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders.

Compounds of the invention (alone or in combination with another active) may be shown to be active e.g. in the biochemical assays described herein, may be shown to have predictive activity based on e.g. the phosphorylation assay described herein, and/or may reduce the rate of cell proliferation e.g. as may be shown in the cell proliferation assays described herein (for instance using cancer cell lines (e.g. known commercially available ones), such as those described herein).

The disorders/conditions that the compounds of the invention may be useful in treating hence includes cancer (such as lymphomas, solid tumours or a cancer as described hereinafter), obstructive airways diseases, allergic diseases, inflammatory diseases (such as asthma, allergy and Chrohn’s disease), immunosuppression (such as transplantation rejection and autoimmune diseases), disorders commonly connected with organ transplantation, AIDS-related diseases and other associated diseases. Other associated diseases that may be mentioned (particularly due to the key role of kinases in the regulation of cellular proliferation) include other cell proliferative disorders and/or non-malignant diseases, such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, bone disorders, atherosclerosis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

Other disease states that may be mentioned include cardiovascular disease,
stroke, diabetes, hepatomegaly, Alzheimer's disease, cystic fibrosis, hormone-related diseases, immunodeficiency disorders, destructive bone disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukaemia, liver disease, pathologic immune conditions involving T cell activation and CNS disorders.

As stated above, the compounds of the invention may be useful in the treatment of cancer. More, specifically, the compounds of the invention may therefore be useful in the treatment of a variety of cancer including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including non-small cell cancer and small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, skin, squamous cell carcinoma, testis, genitourinary tract, larynx, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma, small cell lung carcinoma, lung adenocarcinoma, bone, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukaemia; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocyte leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Further, the protein or lipid kinases (e.g. PI3K, such as class I PI3K, mTOR and/or Flt3) may also be implicated in the multiplication of viruses and parasites. They may also play a major role in the pathogenesis and development of
neurodegenerative disorders. Hence, compounds of the invention may also be useful in the treatment of viral conditions, parasitic conditions, as well as neurodegenerative disorders.

Compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a disease (e.g. cancer or another disease as mentioned herein) which is associated with the inhibition of protein or lipid kinase (e.g. PI3K, such as class I PI3K, mTOR and/or Flt3) is desired and/or required (for example, a method of treatment of a disease/disorder arising from abnormal cell growth, function or behaviour associated with protein or lipid kinases, e.g. PI3K, such as class I PI3K, mTOR and/or Flt3), which method comprises administration of a therapeutically effective amount of a compound of the invention, as hereinbefore defined, to a patient suffering from, or susceptible to, such a condition.

"Patients" include mammalian (including human) patients. Hence, the method of treatment discussed above may include the treatment of a human or animal body.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (e.g. measurable by some test or marker) or subjective (e.g. the subject gives an indication of or feels an effect).

Compounds of the invention may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, by any other parenteral route or via inhalation, in a pharmaceutically acceptable dosage form.

Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The type of pharmaceutical formulation may be selected with due
regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutically acceptable carriers may be chemically inert to the active compounds and may have no detrimental side effects or toxicity under the conditions of use.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques and/or in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

Depending on e.g. potency and physical characteristics of the compound of the invention (i.e. active ingredient), pharmaceutical formulations that may be mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%) by weight. That is, the ratio of active ingredient to the other components (i.e. the addition of adjuvant, diluent and carrier) of the pharmaceutical composition is at least 1:99 (or at least 10:90, at least 30:70 or at least 50:50) by weight.

The amount of compound of the invention in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

The invention further provides a process for the preparation of a pharmaceutical formulation, as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier.
Compounds of the invention may also be combined with other therapeutic agents that are inhibitors of protein or lipid kinases (e.g. PI3K (such as class I PI3K), mTOR, Flt3, a PIM family kinase (e.g. PIM-1, PIM-2 or PIM-3), EGFR and/or MEK) and/or useful in the treatment of a cancer and/or a proliferative disease.

Compounds of the invention may also be combined with other therapies (e.g. radiation).

For instance, compounds of the invention may be combined with one or more treatments independently selected from surgery, one or more anti-cancer/anti-neoplastic/anti-tumoral agent, one or more hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation.

More specifically, compounds of the invention may be combined with an agent that modulates the Ras/Raf/Mek pathway (e.g. an inhibitor of MEK), the Jak/Stat pathway (e.g. an inhibitor of Jak), the PI3K/Akt pathway (e.g. an inhibitor of Akt), the DNA damage response mechanism (e.g. an inhibitor of ATM or ATR) or the stress signaling pathway (an inhibitor of p38 or NF-KB).

For instance, compounds of the invention may be combined with:

(i) a targeted kinase inhibitor;
(ii) a receptor tyrosine kinase (RTK) inhibitor;
(iii) a PIM family kinase inhibitor, such as SGI-1776;
(iv) an Flt-3 inhibitor;
(v) an EGFR or HER2 inhibitor, such as lapatanib;
(vi) a therapeutic monoclonal antibody, such as the HER2 inhibitor trastuzumab;
(vii) a MEK inhibitor, such as PD-0325901;
(vii) a BRaf inhibitor, such as GDC-0879;
(viii) an anthracyclin, such as doxorubicin;
(ix) a taxane, such as paclitaxel or, particularly, docetaxel;
(x) a platin, such as carboplatin or, particularly, cisplatin;
(xi) a nucleotide analog, such as 5-fluorouracil (5-FU) or gemcitabine);
(xii) an alkylating agent, such as temozolomide;
(xiii) a hormone therapeutic agent, such as an estrogen receptor antagonist e.g. tamoxifen;
(xiv) an anti-tumour compound that has potential radiosensitising and/or chemosensitising effects, such as chloroquine;
(xv) an mTOR inhibitor, such as rapamycin;
(xvi) an Akt or PI3-K inhibitor, such as GDC-0941;
(xvii) a JAK inhibitor; and/or
(xviii) an agent that modulates the DNA damage response mechanism and/or the stress signaling pathway, e.g. an inhibitor of ATM or ATR, an inhibitor of p38 and/or NF-κB.

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention, as hereinbefore defined; and
(B) another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:
(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

In a particularly preferred aspect of the invention, compounds of the invention may be combined with other therapeutic agents (e.g. chemotherapeutic agents) for use as medicaments (e.g. for use in the treatment of a disease or condition as mentioned herein, such as one in which the inhibition of growth of cancer cells are required and/or desired e.g. for treating hyperproliferative disorders such as cancer (e.g. specific cancers that may be mentioned herein, e.g. in the examples) in mammals, especially humans). Such active ingredients in combinations may act in synergy.

In particular, compounds of the invention may be combined with known chemotherapeutic agents (as may be demonstrated by the examples, for instance where a compound of the examples is employed in combination and inhibits cellular proliferation \textit{in vitro}; in particular such combinations may be useful in treating lung and/or ovarian cancer), for instance:

(i) a MEK inhibitor, such as PD-0325901;

(ii) an EGFR inhibitor, such as Lapatinib; and/or

(iii) docetaxel (Taxotere®, Sanofi-Aventis).

The MEK inhibitor PD-0325901 (CAS RN 391210-10-9, Pfizer) is a second-generation, non-ATP competitive, allosteric MEK inhibitor for the potential oral tablet treatment of cancer (US6960614; US 6972298; US 2004/147478; US 2005/085550). Phase II clinical trials have been conducted for the potential treatment of breast tumors, colon tumors, and melanoma. PD-0325901 is named (R)-N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide, and has the structure:

Lapatinib (TYKERB®, GW572016, Glaxo SmithKline) has been approved for use in combination with capecitabine (XELODA®, Roche) for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane and trastuzumab. Lapatinib is an ATP-competitive epidermal growth factor (EGFR) and HER2/neu (ErbB-2) dual tyrosine kinase inhibitor (US 6727256; US 6713485; US 7109333; US 6933299; US 7084147; US 7157466; US 7141576) which inhibits receptor autophosphorylation and activation by binding to the ATPbinding pocket of the EGFR/HER2 protein kinase domain. Lapatinib is named as N-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-6-(5-((2-(methylsulfonyl)ethylamino)-methyl)furan-2-yl)quinazolin-4-amine (or alternatively named as /V-[3-chloro-4-[(3-
fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonylethylamino)methyl]-2-fu
quinazolin-4-amine), and has the structure:

The invention further provides a process for the preparation of a combination product as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with the other therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.

For instance, compounds of the invention may be combined with a chemotherapeutic agent. A "chemotherapeutic agent" is a biological (large molecule) or chemical (small molecule) compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, proteins, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in "targeted therapy" and non-targeted, conventional chemotherapy.

Examples of chemotherapeutic agents include those mentioned in e.g. WO 2010/105008, for instance: dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine.

Examples of chemotherapeutic agents also include: erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine,
dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology), temozolomide (4-methyl-5-oxo-2,3,4,6,8-pentazabicyclo [4.3.0]nona-2,7,9-triene-9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((Z)-2-[4-(1,2-diphenylbut-1-ethyl)phenoxo]-N,N-dimethyl-ethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, rapamycin, and lapatinib (TYKERB®, Glaxo SmithKline).

More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU1 1248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (MEK inhibitor, Exelixis, WO 2007/044515), ARRY 886 (MEK inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafere Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), ABT-869 (multi-targeted inhibitor of VEGF and PDGF family receptor tyrosine kinases, Abbott Laboratories and Genentech), ABT-263 (Bc1-2/Bcl-xL inhibitor, Abbott Laboratories and Genentech), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), lonafamib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), capecitabine (XELODA®, Roche), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, 11), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thioTepa and cyclophosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, imposulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramid, triethylenethiophosphoramid and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin;
duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chloronaphazine, chlorophosphamide, estramustine, ifosfamide, mechloretamine, mechloretamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gamma II, calicheamicin omega II, dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carubicin, carminomycin, carzinophilin, chromomycinis, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfomycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimethoprim; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmustine, cytarabine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostane, testolactone; antiadrenals such as aminogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestramucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; anepothione; etoglocid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitaerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; tiaziquone; 2,2',2"-trichlorotriethylamine; trichotheccenes (especially T-2 toxin, verrucarin A, roridin A
and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thioTepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are: (i) antihormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY1 17018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminogluthethimide, MEGASE® (megestrol acetate), AROMASN® ( exemestane; Pfizer), formestane, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, for example, PKC-alpha, Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.
Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Iidee), pertuzumab (OMNITARG™, rhuMab 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

Humanised monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the PI3K inhibitors of the invention include: alemtuzumab, apolizumab, aselizumab, atilizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, rolizumab, sibrotuzumab, siplizumab, sonaltuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, and visilizumab.

By "bringing into association", we mean that the two components are rendered suitable for administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit of parts as hereinbefore defined, by bringing the two components "into association with" each other, we include that the two components of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.
Depending on the disorder, and the patient, to be treated, as well as the route of administration, compounds of the invention may be administered at varying therapeutically effective doses to a patient in need thereof. However, the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the mammal over a reasonable timeframe. One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by *inter alia* the pharmacological properties of the formulation, the nature and severity of the condition being treated, and the physical condition and mental acuity of the recipient, as well as the potency of the specific compound, the age, condition, body weight, sex and response of the patient to be treated, and the stage/severity of the disease.

Administration may be continuous or intermittent (e.g. by bolus injection). The dosage may also be determined by the timing and frequency of administration. In the case of oral or parenteral administration the dosage can vary from about 0.01 mg to about 1000 mg per day of a compound of the invention.

In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention may have the advantage that they are effective inhibitors of protein or lipid kinases (e.g. PI3K, such as class I PI3K, mTOR and/or Flt3). In an embodiment, compounds of the invention may have the advantage that they are both PI3K (e.g. class I PI3K, such as PI3Ka) inhibitors and mTOR inhibitors (or they are both PI3K (e.g. class I PI3K, such as PI3Ka) inhibitors and Flt3 inhibitors), i.e. they may exhibit dual kinase inhibition. Further, certain compounds of the invention may have the advantage that they are PI3K (e.g. class I PI3K, such as PI3Ka) inhibitors, mTOR inhibitors and Flt3 inhibitor, i.e. they may exhibit triple kinase inhibition.
Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise.

As stated hereinbefore, compounds of the invention may have the advantage that they may exhibit dual or triple kinase inhibitory activity (e.g. may act as inhibitors of PI3K (such PI3Koc), mTOR and Flt3). In this respect, advantageously, compounds of the invention may be considered as multi-targeted kinase inhibitors. Compounds of the invention that exhibit single selectivity for a kinase may have the additional benefit that they exhibit less side effects, whereas compounds of the invention that exhibit multiple kinase selectivity may have the additional benefit that they exhibit better potency and/or efficacy.

To date, clinical development of PI3K and dual PI3K/mTOR inhibitors have shown moderate activities, suggesting that either more potent/efficacious inhibitors are required or that inhibition of multiple targets or even pathways might be required for effective treatments (see e.g. Bunney, Tom D., Katan, Matilda, Phosphoinositide signalling in cancer: beyond PI3K and PTEN, Nature Reviews Cancer (2010), 10(5), 342-352; Cleary, James M. and Shapiro, Geoffrey I., Development of phosphoinositol-3 kinase pathway inhibitors for advanced cancer, Current Oncology Report (2010), 12, 87-94; and van der Heijden, Michiel S. and Bernards, Rene; Inhibition of the PI3K Pathway: Hope We Can Believe in? Clinical Cancer Research (2010),16, 3094-3099).

Advantageously, the compounds of the invention may have the benefit that they inhibit multiple targets (or even multiple pathways). For instance, in addition to being inhibitors of PI3K (e.g PI3Ka) and mTOR, they may also be effective inhibitors of other protein or lipid kinases such as: Flt3, BRafV600E, Kit, FGFR1, PDGFRα and/or VEGFR (as may be demonstrated by known tests; see e.g. the examples hereinafter). In this respect, compounds of the invention may be considered to have an improved kinase inhibition cross-reactivity profile, e.g. by
being selective against multiple kinases of therapeutic interest, for instance compared to compounds known in the prior art. For instance, they may have a favorable activity profile against RAF, Kit, FGFR, PDGFR, VEGFR and Flt3, and therefore have advantages in the clinic.

Synergistic effects have been reported for inhibitors of the PI3K/Akt/mTOR signaling pathway in combination with inhibitors of the RAF/MEK pathway (see "The future of targeted therapy approaches in melanoma", L.P.Cantini et al., Expert Opin Drug Discov 2009, 4, 445). Targeted inhibition of receptor tyrosine kinases (RTK) often leads to drug resistance (see "FLT3 inhibition and mechanisms of drug resistance in mutant FLT3-positive AML", E. Weisberg et al., Drug Resistance Updates 2009, 12, 81-89). Spontaneous mutations of Flt3 (and Kit) and other RTK (like VEGFR and PDGFR) have been shown to activate the PI3K/Akt/mTOR pathway, and combination studies of PI3K and/or mTOR inhibitors with RTK inhibitors like sorafenib, sunitinib, gefitinib, erlotinib and others have led to synergistic effects (see "Efficacy and mechanisms of apoptosis induction by simultaneous inhibition of PI3K with GDC-0941 and blockade of Bcl-2 (ABT-737) or Flt3 (sorafenib) in AML cells in the hypoxic bone marrow microenvironment", L. Jin et al., 52nd Ash annual meeting, 2010 and "Activation of PI3K/Akt signaling pathway mediates acquired resistance to sorafenib in hepatocellular carcinoma cells", K.-F. Chen et al., Journal of Pharmacology and Experimental Therapeutics 2010 (online); see also Fan, Qi-Wen and Weiss, William A., Targeting the RTK-PI3K-mTOR Axis in Malignant Glioma: Overcoming Resistance; Curr Top Microbiol Immunol. (2010), 347, 279-296; Agarval, Roshan et al, PI3K pathway-directed therapeutic strategies in cancer, Current Opinion in Investigational Drugs (2010), 11 (6), 615-628, as well as the Weisberg et al reference above). Wu and Hu, PI3K/Akt/mTOR Pathway Inhibitors in Cancer: A Perspective on Clinical Progress, Current Medicinal Chemistry, 2010, 17, 4326-4341 also provides a review on this topic.

Compounds of the invention may therefore combine dual PI3K/mTOR activity with activity on other key kinases (indeed, combination products covering this spectrum of kinases are currently being evaluated as mentioned above), thereby allowing single-agent administration (or, potentially, combination products with
reduced dosages) and providing the associated benefits, e.g. reducing the risk of drug-drug interactions, etc.

Compounds of the invention may be beneficial as they are medicaments with targeted therapy, i.e. which target a particular molecular entity by inferring or inhibiting it (e.g. in this case by inhibiting one or more protein or lipid kinases as hereinbefore described). Compounds of the invention may therefore also have the benefit that they have a new effect (for instance as compared to known compounds in the prior art), for instance, the new effect may be a particular mode of action or another effect resultant of the targeted therapy. Targeted therapies may be beneficial as they may have the desired effect (e.g. reduce cancer, by reducing tumor growth or carcinogenisis) but may also have the advantage of reducing side effects (e.g. by preventing the killing of normal cells, as may occur using e.g. chemotherapy).

Furthermore, compounds of the invention may selectively target particular protein or lipid kinases (e.g. the ones described herein) compared to other known protein or lipid kinases (as may be shown experimentally hereinafter; see Table 4 for example). Accordingly, compounds of the invention may have the advantage that certain, specific, cancers may be treated selectively, which selective treatment may also have the effect of reducing side effects.

Examples/Biological Tests

Determination of PI3 kinase activity of compounds of the invention (such as those exemplified) is possible by a number of direct and indirect detection methods. Certain exemplary compounds described herein were prepared, characterized, and assayed for their PI3Ka, mTOR and Flt3 enzymatic activities using the methods described herein. The compounds may also be tested in cell-based assays.

PI3K activity assay
The kinase activity was measured by using the commercial ADP Hunter™ Plus assay available from DiscoveR x (#33-016), which is a homogeneous assay to measure the accumulation of ADP, a universal product of kinase activity. The
enzyme, PI3K (p10a/p85α) was purchased from Carna Biosciences (#07CBS-0402A). The assay was done following the manufacturer recommendations with slight modifications: Mainly the kinase buffer was replace by 50 mM HEPES, pH 7.5, 3 mM MgCl₂, 100 mM NaCl, 1 mM EGTA, 0.04% CHAPS, 2 mM TCEP and 0.01 mg/ml BGG. The PI3K was assayed in a titration experiment to determine the optimal protein concentration for the inhibition assay. To calculate the IC₅₀ of the ETP-compounds, serial 1:5 dilutions of the compounds were added to the enzyme at a fixed concentration (2.5 µg/ml). The enzyme was preincubated with the inhibitor and 30 µM PIP₂ substrate (P9763, Sigma) for 5 min and then ATP was added to a final 50 µM concentration. Reaction was carried out for 1 hour at 25°C. Reagent A and B were sequentially added to the wells and plates were incubated for 30 min at 37 °C. Fluorescence counts were read in a Victor instrument (Perkin Elmer) with the recommended settings (544 and 580 nm as excitation and emission wavelengths, respectively). Values were normalized against the control activity included for each enzyme (i.e., 100 % PI3 kinase activity, without compound). These values were plotted against the inhibitor concentration and were fit to a sigmoid dose-response curve by using the Graphad software.

20 **Cellular Mode of Action**

**Cell culture:** The cell lines are obtained from the American Type Culture Collection (ATCC). U2OS (human osteosarcoma) is cultured in Dulbecco's modified Eagle's medium (DMEM). PC3 (human prostate carcinoma), MCF7 (human breast carinoma), HCT116 (human colon carcinoma), 768-0 (human neuroblastoma), U251 (human glioblastoma) are grown in RPMI. All media are supplemented with 10% fetal bovine serum (FBS) (Sigma) and antibiotics-antimycotics. Cells are maintained in a humidified incubator at 37°C with 5% CO₂ and passaged when confluent using trypsin/EDTA.

**U2foxRELOC and U2nesRELOC assay:** The U2nesRELOC assay and the U2foxRELOC assay have been described. Briefly, cells are seeded at a density of 1.0x10⁵ cells/ml into black-wall clear-bottom 96-well microplates (BD Biosciences). After incubation at 37°C with 5% CO₂ for 12 hours, 2µl of each test compound are transferred from the mother plates to the assay plates. Cells are
incubated in the presence of the compounds for one hour. Then cells are fixed and the nucleus stained with DAPI (Invitrogen). Finally the plates are washed with 1X PBS twice and stored at 4°C before analysis.

**Image acquisition and processing:** Assay plates are read on the BD Pathway™ 855 Bioimager equipped with a 488/10 nm EGFP excitation filter, a 380/10 nm DAPI excitation filter, a 515LP nm EGFP emission filter and a 435LP nm DAPI emission filter. Images are acquired in the DAPI and GFP channels of each well using 10x dry objective. The plates are exposed 0.066 ms (Gain 31) to acquire DAPI images and 0.55 ms (Gain 30) for GFP images.

**Data analysis:** The BD Pathway Bioimager outputs its data in standard text files. Data are imported into the data analysis software BD Image Data Explorer. The nuclear/cytoplasmic (Nuc/Cyt) ratios of fluorescence intensity are determined by dividing the fluorescence intensity of the nucleus by the cytoplasmic. A threshold ratio of greater than 1.8 is employed to define nuclear accumulation of fluorescent signal for each cell. Based on this procedure we calculate the percentage of cells per well displaying nuclear translocation or inhibition of nuclear export. Compounds that induce a nuclear accumulation of the fluorescent signal greater than 60% of that obtained from wells treated with 4nM LMB are considered as hits. In order to estimate the quality of the HCS assay, the Z factor is calculated by the equation: 

\[ Z = 1 - \left( \frac{3 \times \text{std. dev. of positive controls}}{\text{mean of positive controls}} + \frac{3 \times \text{std. dev. of negative controls}}{\text{mean of negative controls}} \right) \]

**PI3K signalling**

**AKT phosphorylation Inhibition Western Blot Analysis:** Subconfluent cells are incubated under different conditions and are washed twice with TBS prior to lysis. Lysis buffer is added containing 50 mM Tris HCl, 150 mM NaCl, 1% NP-40, 2mM Na$_3$VO$_4$, 100 mM NaF, 20 mM Na$_4$P$_2$O$_7$ and protease inhibitor cocktail (Roche Molecular Biochemicals). The proteins are resolved on 10% SDS-PAGE and are transferred to nitrocellulose membrane (Schleicher & Schuell, Dassel, Germany). The membranes are incubated overnight at 4°C with antibodies specific for Akt, phospho-Ser-473-Akt (Cell Signaling Technology) and a-tubulin (Sigma), they are washed and then incubated with IRDye800 conjugated anti-
mouse and Alexa Fluor 680 goat anti-rabbit IgG secondary antibodies. The bands
are visualized using an Odyssey infrared imaging system (Li-Cor Biosciences).

**Cytotoxicity assessment**

The compounds are tested on 96-well trays. Cells growing in a flask are
harvested just before they became confluent, counted using a haemocytometer
and are diluted down with media adjusting the concentration to the required
number of cells per 0.2 ml (volume for each well). Cells are then seeded in 96-
well trays at a density between 1000 and 4000 cells/well, depending of the cell
size. Cells are left to plate down and grow for 24 hours before adding the drugs.

Drugs are weighed out and diluted with DMSO to get them into solution to a
concentration of 10mM. From here a "mother plate" with serial dilutions is
prepared at 200X the final concentration in the culture. The final concentration of
DMSO in the tissue culture media should not exceed 0.5%. The appropriate
volume of the compound solution (usually 2 microlitres) is added automatically
(Beckman FX 96 tip) to media to make it up to the final concentration for each
drug. The medium is removed from the cells and replaced with 0.2 ml of medium
dosed with drug. Each concentration is assayed in triplicate. Two sets of control
wells are left on each plate, containing either medium without drug or medium
with the same concentration of DMSO. A third control set is obtained with the
cells untreated just before adding the drugs (seeding control, number of cells
starting the culture). Cells are exposed to the drugs for 72 hours and then
processed for MTT colorimetric read-out.

**mTOR assay**

The enzymatic mTOR activity was measured using a Lanthascreen™ kinase
activity assay (Invitrogen). The enzyme was purchased from Invitrogen (PV4754),
as well as the GFP-labeled substrate (4EBP1-GFP; PV4759) and the Tb-anti-
p4EBP1(pThr46) antibody (PV4757). The assay was performed in 50 mM
HEPES buffer, pH 7.5, containing 1.5 mM MnCl₂, 10 mM MgCl₂, 1 mM EGTA, 2.5
mM DTT and 0.01% Tween-20. The concentration of the assay components were
the following: 0.24 nM mTOR kinase, 400 nM 4EBP1-GFP, 10 mM ATP and
serial dilutions of the compound (inhibitor) to be evaluated. After 1 h incubation at
room temperature, 20 mM EDTA was used to stop the reaction and terbium-
labeled antibody (4 nM) added to detect phosphorylated product. The antibody
associates with the phosphorylated product resulting in an increased TR-FRET value. The TR-FRET value (a dimensionless number) was calculated as the ratio of the acceptor signal (GFP, emission at 520 nm) to the donor signal (terbium, emission at 495 nm). Values were plotted against the inhibitor concentration and fitted to a sigmoid dose-response curve using GraphPad software.

**FLT3 biochemical assay**

The biochemical assay to measure FLT3 activity relies on the ADP Hunter assay kit (DiscoveRx Corp., Cat. # 90-0077), that determines the amount of ADP as direct product of the kinase enzyme activity. Assay conditions were as indicated by the kit manufacturers with the following adaptations for the kinase activity step:

- Kinase assay buffer and assay volume stay as recommended (15 mM HEPES, pH 7.4, 20 mM NaCl, 1 mM EGTA, 0.02% Tween 20, 10 mM MgCl2 and 0.1 mg/ml bovine gamma-globulins/25 µL assay volume)
- Incubation time and temperature: 60 min at 37°C
- FLT3 final concentration: 0.4 µg/ml (0.6 µg/ml; 12 nM)
- ATP final concentration: 100 µM
- ABLtide substrate peptide: EAIYAAPFAKKK
- Peptide final concentration: 100 µM
- Positive control for kinase activity inhibition: 1 µM Staurosporine
- DMSO concentration below 2% during the kinase reaction

Assays were performed in either 96 or 384-well plates (corning 3575 or 3573). The final outcome of the coupled reactions provided by the kit is the release of the fluorescent product Resorufin and has been measured with a multilabel HTS counter VICTOR V or ENVISION (PerkinElmer) using an excitation filter at 544 nm and an emission filter at 580 nm.

**PI3K cellular activity (Elisa assay):** Activity was measured as endogenous levels of phospho-Akt1 (Ser473) protein. Osteosarcoma U20S cells are plated in 96 Poly-D-Lysine coating tissue culture plates (18.000 cells/well). After the treatment with serial dilutions of the compound during 3h, the cells are fixed directly in the wells with 4% paraformaldehyde.
After fixing, individual wells go through the same series of steps used for a conventional immunoblot: including blocking with 5% BSA, incubation with 1/1000 of primary antibody-AKT (Ser 74) in PBS containing 5% BSA at 4°C overnight (Cell Signalling), washing and incubation with second antibody HRP-anti-mouse IgG for 1h at RT (Amersham). After the addition of SuperStignal ELISA Femto maximum sensitivity chemiluminescent substrate (Pierce) the results are read using a luminescence plate reader (Victor).

**Cell viability assays and combination assays:** Cells were seeded at 10,000-50,000 cells/well in 96-well plates for 16h. On day two, nine serial 1:3 compound dilutions were made in DMSO using 96-well plates. The compounds were added in duplicate to the cell plates using a FX BECKMAN robot (Beckman Coulter) and incubated at 37°C in C0₂ atmosphere. After 3 days, relative numbers of viable cells were measured by MTT (Sigma) according to the manufacturer's instructions and read on EndVision (Perkin Elmer). EC₅₀ values were calculated using ActivityBase (IDBS). Drugs used in the combination assays were dosed starting at 4xEC₅₀ concentrations and continuing with serial 1:2 dilutions. PI3K inhibitors and chemotherapeutic agents were added simultaneously. An additional exemplary *in vitro* cell proliferation assay includes the following steps:

1. An aliquot of 200 µl of cell culture containing optimal density (between 10⁴ -5x1 0⁴ cells (see cell lines and tumour types in Example 26, Tables A and B hereinafter) in medium was deposited in each well of a 96-well flat bottom plate.

2. Control wells were prepared containing medium without cells.

3. The compound was added to the experimental wells and incubated for 3 days.

4. One quarter volume of MTT reagent with respect to the volume of cell culture medium present in each well was added and incubated at 37°C for 24h at 5% C0₂.

5. One quarter volume of solubilisation buffer with respect to the volume of cell culture medium present in each well was added and incubated at 37°C for 24h at 5% C0₂.
6. Formazan salt formed was recorded and reported in graphs as relative growth vs. cells treated only with DMSO.

For each cell type, the EC₅₀ values of the exemplary compound alone and of the chemotherapeutic agent alone, each measured individually, were compared with the EC₅₀ value of the combined treatment. The combination index (CI) score was calculated using the method of Chou and Talalay (CalcuSyn software, Biosoft). A CI less than 0.8 indicates synergy. A CI between 0.8 and 1.2 indicates additivity. A CI greater than 1.2 indicates antagonism.

Synergy was expressed semi-quantitatively, where (++++) represents a combination index less than 0.1, (+++) represents a combination index greater than 0.1 but less than 0.3, (+++) represents a combination index greater than 0.3 but less than 0.7, (+) represents a combination index greater than 0.7 but less than 1.2, (-) represents a combination index greater than 1.2.

Tables A and B (of Example 26) In vitro cell proliferation assays of combination of the compound of Example 7 or Example 8 and various chemotherapeutics agents.

Inhibitory Activity for other Kinases

Inhibitory activity for other kinases was measured using known procedures/protocols. In the case of Example 27 below, the inhibitory activity was measured at ProQinase GmbH, Freiburg, Germany. The following protocol may be employed:

FlashPlate-based Protein Kinase Assay Protocol (33PanQinase® Assay)

BRaf-V660E, Kit, PDGFRalpha and VEGFR2 activity were measured at ProQinase (Freiburg, Germany). The assay was performed in a 96-well MTP-FlashPlate format at single-point compound concentration (1 µM) measuring incorporation of ³²P in the specific substrate.

Reactions were carried out in a 50 µl reaction cocktail containing 70 mM HEPES-NaOH, pH7.5, 3 mM MgCl₂, 3 mM MnCl₂, 3 µM Na-orthovanadate, 1.2 mM DTT,
50 μg/ml PEG20000, 1 mM ATP (approx. 5-7 x 10⁵ cpm ³²P-γ-ATP), 1 % (v/v) DMSO and variable amounts of substrate and recombinant protein kinase. Samples were incubated for 60 min at 30°C, and the reaction was stopped by addition of 50 μl 2% H₃P0₄. Plates were washed twice with 200 μl 0.9% NaCl, left to dry and finally measured using a Scintillation Counter.

The data were expressed as percentage of inhibition compared to DMSO control.

Examples

The following Examples illustrate the invention.

General experimental conditions

Certain exemplary compounds of the invention described herein were prepared, characterised and assayed for their PI3Koc, mTOR and Flt3 enzymatic activities.

Abbreviations. Herein after, the term "DCM" means dichloromethane, "CHCl₃" means chloroform, "MeOH" means methanol, "EtOH" means ethanol, "EtOAc" means ethyl acetate, "THF" means tetrahydrofuran, "ACN" means acetonitrile, "DMAP" means 4-dimethylaminopyridine, "DMF" means dimethylformamide, "DME" means dimethoxyethane, "DMSO" means dimethylsulfoxide, "Et₂O" means diethyl ether, "Hex" means hexane, "EtOAc" means ethyl acetate, "BA/BE" means boronic acid/ester, "Pd(PPh₃)₄" means tetrakis(triphenylphosphine)palladium, "Pd(Ph₃P)₂Cl₂" means dichlorobis(triphenylphosphine)palladium(II), "Pd(dpff)Cl₂·DCM" means 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, dichloromethane complex, "NIS" means N-iodosuccinimide, "Na₂S0₄" means disodium sulphate, "MgSO₄" means magnesium sulphate, "K₂C0₃" means dipotassium carbonate, "Na₂C0₃" means disodium carbonate, "NaHCO₃" means sodium bicarbonate, "TEA" means triethylamine, "TFA" means trifluoroacetic acid, "TsCl" means toluenesulfonyl chloride, "sat." means saturated, "aq." means aqueous, "HPLC" means high performance liquid chromatography, "tR" means retention time, "MS" means mass spectrometry, "TLC" means thin layer chromatography, "Rf" means retardation factor, "g" means gram(s), "mmol"
means millimole(s), "eq" means equivalent(s), "mL" means milliliter(s), "min"
means minute(s), "h" means hour(s), "RT" means room temperature.

Analytical analysis. NMR spectra were recorded on a Bruker Avance II 300
spectrometer and Bruker Avance II 700 spectrometer fitted with 5mm QXI 700 S4
inverse phase, Z-gradient unit and variable temperature controller.

The HPLC measurements were performed using a HP 1100 from Agilent
Technologies comprising a pump (binary) with degasser, an autosampler, a
column oven, a diode-array detector (DAD) and a column as specified in the
respective methods below. Flow from the column was split to a MS spectrometer.
The MS detector was configured with an electrospray ionization source or
API/APCI. Nitrogen was used as the nebulizer gas. Data acquisition was
performed with ChemStation LC/MSD quad, software.

HPLC-Method 1
Reversed phase HPLC was carried out on a Gemini-NX C18 (100 x 2.0 mm;
5um), Solvent A : water with 0.1% formic acid; Solvent B : acetonitrile with 0.1%
formic acid. Gradient: 5% of B to 100% of B within 8 min at 50 °C, DAD.

HPLC-Method 2
Reversed phase HPLC was carried out on a Gemini-NX C18 (100 x 2.0 mm;
5um), Solvent A : water with 0.1% formic acid; Solvent B : acetonitrile with 0.1%
formic acid. Gradient: 50% of B to 100% of B within 8 min at 50 °C, DAD.

HPLC-Method 3
Reversed phase HPLC was carried out on a Gemini-NX C18 (100 x 2.0 mm;
5um), Solvent A : water with 0.1% formic acid; Solvent B : acetonitrile with 0.1%
formic acid. Gradient: 5% of B to 40% of B within 8 min at 50 °C, DAD.

HPLC-Method 4
Reversed phase HPLC was carried out on a Gemini C18 column (50 x 2 mm, 3
urn); Solvent A : water with 0.1% formic acid; Solvent B : acetonitrile with 0.1%
formic acid. Gradient: 10-95 % of B within 4 min at a flow rate of 0.5 mL/min
followed by 2 min of 100 % of B at 0.8 mL/min, controlled temperature at 50 °C,
DAD.

HPLC-Method 5
Reversed phase HPLC was carried out on a Gemini C18 column (50 x 2 mm, 3
urn); Solvent A : water with 10mM ammonium bicarbonate; Solvent B : acetonitrile.
Gradient: 20-100 % of B within 3 min at a flow rate of 0.5 mL/min followed by 2 min of 100 % of B at 0.8 mL/min, controlled temperature at 40 °C, DAD.

**HPLC-Method 6**

Reversed phase HPLC was carried out on a Gemini-NX C18 (100 x 2.0 mm; 5μm), Solvent A: water with 0.1% formic acid; Solvent B: acetonitrile with 0.1% formic acid. Gradient: 0% of B to 30% of B within 8 min at 50 °C, DAD.

"Found mass" refers to the most abundant isotope detected in the HPLC-MS.

**Compound preparation**

The synthesis of the following intermediates had been described in WO2009/040552:

2-Bromo-imidazo[2,1-b][1,3,4]thiadiazole
2-Bromo-6-methyl-imidazo[2, 1-b][1,3,4]thiadiazole
2-Bromo-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde

The synthesis of 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-3-sulfonic acid (2,4-difluoro-phenyl)-amide and 2,4-difluoro-/V-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide had been described in WO2008/1 50827.

The compound names given herein were generated in accordance with IUPAC using the AutoNom naming program in MDL ISIS Draw.

**Intermediate A**

2-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-ylamine

A mixture of 3-amino-5-bromo-2-methoxypyridine (2.7 g, 13.3 mmol, 1 eq), bis(pinacolato)diboron (4 g, 16 mmol, 1.2 eq) and KOAc (3.9 g, 40 mmol, 3 eq) was taken up in 1,4-dioxane (11 mL) and DMF (1.4 mL). After addition of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (1.1 g, 1.33 mmol, 0.1 eq) the mixture was treated under mw irradiation for 10 min at 150°C. The mixture was filtered through a pad of silica gel with celite on its top and eluted with EtOAc. The residue obtained by evaporation was purified by column chromatography (DCM/MeOH 98:2 to 96:4) affording 3.59 g of the crude product.

HPLC-MS (Method 4): t_R = 4.01 min, [M+H]^+ m/z 251.1
Intermediate B
2,4-Difluoro-N-[2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide

2,4-difluorobenzenesulfonyl chloride (2.0 mL, 14.6 mmol) was added at RT (water bath) to a solution of 2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-ylamine (3.6 g of crude) in pyridine (30 mL), and the mixture was stirred under argon overnight. The solvent was evaporated, and the residue was taken up in DCM and water. 1N HCl was added until reaching pH 4, and the mixture was extracted with DCM, dried (MgSO₄) and concentrated. The crude material was purified by column chromatography (DCM/MeOH 1 to 3%) followed by precipitation from ether/cyclohexane. Total yield: 5.7 g (56 % over 2 steps).

1H NMR (300 MHz, DMSO) δ 10.19 (s, 1H), 8.20 (d, J = 1.6 Hz, 1H), 7.70 (m, 2H), 7.57 (t, 1H), 7.20 (t, 1H), 3.61 (s, 3H), 1.29 (s, 12H) ppm.

Intermediate C
2-Bromo-5-iodoimidazo[2,1-b][1,3,4]thiadiazole

NIS (3.83 g, 16.2 mmol, 1.1 eq) was added to a solution of 2-bromo-imidazo[2,1-b][1,3,4]thiadiazole (3.0 g, 14.7 mmol, 1 eq) in dry DMF (50 mL). The mixture was stirred at RT for 4h and then poured into aq. Na₂S₂O₅ (10%) and diluted with EtOAc. The organic phase was washed with water, dried and concentrated to give the desired product (pale brown solid; 4.34 g, yield 89%). 1H (300 MHz, CDCl₃): δ/ppm 7.29 (1H, s).

Example 1 (Method A)
2,4-Difluoro-N-[5-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-yl]-benzenesulfonamide

Dioxane (30 mL) and 2M aq Na₂CO₃ (10 mL) were added to 2-bromo-5-iodoimidazo[2,1-b][1,3,4]thiadiazole (1.6 g, 4.85 mmol, 1 eq) and 2,4-difluoro-N-[2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide (2.5 g, 5.8 mmol, 1.2 eq), and the suspension was degassed by applying vacuum and filling with argon gas (3x). Dichlorobis(triphenylphosphine)palladium(II) (0.680 g, 0.97 mmol, 0.2 eq) was
quickly added, and the reaction mixture was stirred at reflux temperature for 3 h. The solvent was evaporated, and the residue was taken up in water, neutralized with 1 M HCl and extracted with CHCl3/iPrOH. The organic phase was dried (MgSO4) and concentrated, and the crude solid was purified by column chromatography (DCM/MeOH, 100:0 to 95:5) affording 0.827 g (31%) of the title compound.

HPLC-MS (Method 1): \( t_{R} = 5.74 \) min, [M+H]+ m/z 550.0, \( ^1 \)H NMR (300 MHz, DMSO) \( \delta \) 10.63 (s, 1H), 8.53 (s, 1H), 8.07 (d, \( J = 1.3 \) Hz, 1H), 7.82 (d, \( J = 6.5 \) Hz, 1H), 7.59 (s, 1H), 7.41 (s, 1H), 7.26 (s, 1H), 3.75 (s, 3H) ppm.

In the following Suzuki reactions, the protocol of Method A (see Example 1 above) was employed by reacting at reflux temperature for 2-3 hours 1 equiv of 2,4-difluoro-N-[5-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2-methoxy-pyridin-3-yl]-benzenesulfonamide with 1.2 equiv of the corresponding boronic acid/ester (as stated) in dioxane and aqueous sodium carbonate using 0.2 equiv of dichlorobis(triphenylphosphine)palladium(II) as catalyst. The product was extracted from the neutralised aqueous solution using chloroform/isopropanol and purified by column chromatography.

Example 2

2,4-Difluoro-N-[2-methoxy-5-(5-phenyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyridin-3-yl]-benzenesulfonamide

Standard protocol using phenylboronic acid; purified by column chromatography and prep HPLC.

Yield: 0.007 g, 15%

HPLC-MS (Method 1): \( t_{R} = 6.24 \) min, [M+H]+ m/z 500.1, \( ^1 \)H NMR (300 MHz, DMSO) \( \delta \) 10.58 (s, 1H), 8.55 (s, 1H), 8.05 (m, 3H), 7.89 - 7.79 (m, 2H), 7.55 (dd, \( J = 14.7, 7.3 \) Hz, 3H), 7.38 (m, 1H), 7.22 (m, 1H), 3.73 (s, 3H) ppm.

Example 3

2,4-Difluoro-N-[2-methoxy-5-(5-quinolin-3-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyridin-3-yl]-benzenesulfonamide

Standard protocol using quinoline-3-boronic acid pinacolate; title product precipitated from aqueous phase.
Yield: 0.013 g, 26%

HPLC-MS (Method 1): t\textsubscript{R} = 5.92 min, [M+H]+ m/z 551.1, \textsuperscript{1}H NMR (300 MHz, DMSO) \(\delta\) 10.66 (s, 1H), 9.54 (d, J = 2.3 Hz, 1H), 9.04 (s, 1H), 8.74 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 8.09 (t, J = 9.3 Hz, 2H), 7.91 - 7.75 (m, 2H), 7.73 - 7.66 (m, 1H), 7.60 (s, 1H), 7.27 (s, 1H), 3.78 (s, 3H) ppm.

Example 4
N-[5-[5-(1-Ethyl-1H\textsuperscript{y}razol-4-yl)Hmidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2-methoxy-pyridin-3-yl]-2,4-difluoro-benzenesulfonamide

Standard protocol using 1-ethyl-1H-pyrazole-4-boronic acid pinacol ester; purified by column chromatography and prep HPLC.

Yield: 0.010 g, 21%

HPLC-MS (Method 1): t\textsubscript{R} = 5.37 min, [M+H]+ m/z 518.1, \textsuperscript{1}H NMR (300 MHz, DMSO) \(\delta\) 10.60 (s, 1H), 8.68 (d, J = 2.1 Hz, 1H), 8.34 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 7.99 (s, 1H), 7.82 (m, 1H), 7.66 - 7.54 (m, 1H), 7.51 (s, 1H), 7.25 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H) ppm.

Example 5
N-[5-[5-(3-Chloro-pyridin-4-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2-methoxy-pyridin-3-yl]-2,4-difluoro-benzenesulfonamide

Standard protocol using 3-chloro-4-pyridineboronic acid hydrate; purified by column chromatography and prep HPLC.

Yield: 0.011 g, 23%

HPLC-MS (Method 1): t\textsubscript{R} = 5.75 min, [M+H]+ m/z 535.0, \textsuperscript{1}H NMR (300 MHz, DMSO) \(\delta\) 10.62 (s, 1H), 8.81 (s, 1H), 8.69 (d, J = 5.2 Hz, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 5.2 Hz, 1H), 8.10 (d, J = 6.7 Hz, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.81 (m, 1H), 7.64 - 7.52 (m, 1H), 7.23 (m, 1H), 3.75 (s, 3H) ppm.

Example 6
2,4-Difluoro-N-[2-methoxy-5-[5-(2-trifluoromethyl-pyridin-4-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyridin-3-yl]-benzenesulfonamide

Standard protocol using 2-(trifluoromethyl)pyridine-4-boronic acid; purified by column chromatography and prep HPLC.

Yield: 0.012 g, 19%
HPLC-MS (Method 1): $t_R = 6.1 \text{ min}$, [M+H]+ m/z 569.1, $^1$H NMR (300 MHz, DMSO) δ 10.64 (s, 1H), 8.87 (d, J = 5.2 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.51 (s, 1H), 8.39 (s, 2H), 8.19 (d, J = 2.3 Hz, 1H), 7.82 (dd, J = 14.9, 8.6 Hz, 1H), 7.66 - 7.53 (m, 1H), 7.24 (t, J = 9.6 Hz, 1H), 3.77 (s, 3H) ppm.

Example 7

2,4-Difluoro-N-[2-methoxy-5-(5-pyridazin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Standard protocol using pyridazine-4-boronic acid pinacolate, Pd(PPh$_3$)$_2$Cl$_2$; purified by column chromatography and prep HPLC.

Yield: 0.005 g, 6%

HPLC-MS (Method 1): $t_R = 4.57 \text{ min}$, [M+H]+ m/z 502.1, $^1$H NMR (300 MHz, DMSO) δ 10.56 (s, 1H), 9.82 (s, 1H), 9.25 (d, J = 5.5 Hz, 1H), 8.57 (s, 1H), 8.35 - 8.16 (m, 2H), 8.06 (s, 1H), 7.79 (dd, J = 15.0, 8.6 Hz, 1H), 7.50 (s, 1H), 7.20 (t, J = 8.3 Hz, 1H), 3.70 (s, 3H) ppm.

Alternatively, the compound of Example 7 may be prepared using the following methods:

Intermediate

5-(5-iodoimidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxypyridin-3-amine

Dioxane (5 ml.) and 2 M aq Na$_2$CO$_3$ (1.5 ml) were added to 2-bromo-5-iodoimidazo[2,1-b][1,3,4]thiadiazole (200 mg) and (5-amino-6-methoxypyridin-3-yl)boronic acid pinacol ester (200 mg), and the suspension was degassed under vacuum and filled with argon (3x). PdCl$_2$(PPh$_3$)$_2$ (90 mg) was quickly added, and the reaction mixture was stirred at reflux for 2h. Water was added, and a precipitate formed that was filtered off and washed with water followed by ether and ether/MeOH 10:1 and dried to give the desired product (150 mg) that was used without further purification in the subsequent step. HPLC-MS (10-95% B in 4 min at 0.5 mL + 2 min 100% B, flow 0.8 mL/min, 50°C): $t_R = 4.12 \text{ min}$, [M+H]+ m/z 373.9.

Intermediate

2,4-Difluoro-N-[2-methoxy-5-(5-iodoimidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Sulfonyl chloride (0.06 mL) was added at RT to a solution of 5-(5-iodoimidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxypyridin-3-amine in pyridine (1
(10 mL). The mixture was stirred under Ar overnight and additional 5 h after addition of further 0.05 mL of sulfonyl chloride. Water (10 mL) was added, and the mixture was extracted with CHCl/PrOH 1:1. The organic phase was separated, dried (MgSO₄) and concentrated affording a crude product that was treated with DCM, MeOH and ether. The precipitate that formed was separated by filtration, and the filtrate was purified by silica gel chromatography to afford the desired product (102 mg). HPLC-MS (10-95% B in 4 min at 0.5 mL + 2 min 100% B, flow 0.8 mL/min, 50°C): t_R = 4.59 min, [M+H]+ m/z 550.0.

2.4-Difluoro-N-[2-methoxy-5-(5-pyridazin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Dioxane (2 mL) and 2M aq Na₂CO₃ (0.5 mL) were added to 2,4-difluoro-N-[2-methoxy-5-(5-iodimidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide (100 mg) and pyridazin-4-boronic acid pinacol ester (80 mg), and the suspension was degassed under vacuum and filled with argon (2x). The catalyst (30 mg) was quickly added, and the reaction mixture was stirred at reflux for 2 h. Further boronate (50 mg) was added, and the mixture was degassed again, then more catalyst was added (25 mg) and stirring was continued at reflux for 4 h. The solvents were evaporated, and the residue was stirred in water for 36 h. The precipitate that had formed was removed by filtration, and the filtrate was concentrated and taken up in aq. NH₄Cl. A precipitate formed overnight and was filtered off, washed with water followed by ether and dried. The solid was purified by flash chromatography (DCM/MeOH 98:2 to 9:1, affording 24 mg of crude product) and subsequently by preparative HPLC to give the desired product (5 mg). HPLC-MS (5-100% B in 8 min at 0.8 mL): t_R = 4.57 min, [M+H]+ m/z 502.1; ¹H NMR (300 MHz, DMSO) δ = 10.56 (s, 1H), 9.82 (s, 1H), 9.25 (d, J = 5.5 Hz, 1H), 8.57 (s, 1H), 8.35 - 8.16 (m, 2H), 8.06 (s, 1H), 7.79 (dd, J = 15.0, 8.6 Hz, 1H), 7.50 (s, 1H), 7.20 (t, J = 8.3 Hz, 1H), 3.70 (s, 3H) ppm.

Example 8

2,4-Difluoro-N-[2-methoxy-5-(5-pyridin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Standard protocol using pyridine-4-boronic acid; column chromatography; title product precipitated from CH₃CN/Et₂O.

Yield: 0.075 g, 27%
HPLC-MS (Method 1): \( t_R = 3.47 \) min, [M+H]+ m/z 501.2, \(^1\)H NMR (300 MHz, DMSO) \( \delta 10.64 \) (s, 1H), 8.69 (d, \( J = 2.6 \) Hz, 3H), 8.17 (s, 2H), 8.05 (d, \( J = 5.6 \) Hz, 2H), 7.83 (d, \( J = 6.5 \) Hz, 1H), 7.61 (s, 1H), 7.25 (s, 1H), 3.76 (s, 3H) ppm.

Example 9
2,4-Difluoro-N42-methoxy-5-(5-pyridin-3-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide
Standard protocol using pyridine-3-boronic acid; column chromatography; title product precipitated from CH\(_3\)CN/Et\(_2\)O.
Yield: 0.025 g, 34%

HPLC-MS (Method 1): \( t_R = 4.54 \) min, [M+H]+ m/z 501.1, \(^1\)H NMR (300 MHz, DMSO) \( \delta 10.63 \) (s, 1H), 9.27 (s, 1H), 8.64 (s, 2H), 8.43 (d, \( J = 8.2 \) Hz, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 7.58 (d, \( J = 3.0 \) Hz, 3H), 7.28 (s, 1H), 3.77 (s, 3H) ppm.

Example 10
2,4-Difluoro-N-{2-methoxy-5-[5-(3-methyl-pyridin-4-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyridin-3-yl}-benzenesulfonamide
Standard protocol using 2-picoline-4-boronic acid; purified by column chromatography.
Yield: 0.015 g, 27%

HPLC-MS (Method 1): \( t_R = 3.37 \) min, [M+H]+ m/z 515.2, \(^1\)H NMR (300 MHz, DMSO) \( \delta 10.66 \) (s, 1H), 8.67 (s, 1H), 8.56 (d, \( J = 5.3 \) Hz, 1H), 8.24 - 8.06 (m, 2H), 7.92 (s, 3H), 7.59 (s, 1H), 7.25 (s, 1H), 3.77 (s, 4H), 2.56 (s, 6H) ppm.

Example 11
2,4-Difluoro-N-{2-methoxy-5-[5-(2-morpholin-4-yl-pyridin-4-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyridin-3-yl}-benzenesulfonamide
Standard protocol using 2-morpholinopyridine-4-boronic acid pinacol ester; crude product triturated with CH\(_3\)CN/Et\(_2\)O/MeOH.
Yield: 0.012 g, 23%

HPLC-MS (Method 1): \( t_R = 3.97 \) min, [M+H]+ m/z 586.2, \(^1\)H NMR (300 MHz, DMSO with drops of TFA) \( \delta 10.63 \) (s, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 8.35 (s, 1H), 8.14 (d, \( J = 6.3 \) Hz, 1H), 8.01 (s, 1H), 7.78 (m, 1H), 7.65 (d, 1H), 7.52 (t, 1H), 7.20 (t, 1H), 3.94 (s, 3H), 3.89 - 3.66 (m, 8H) ppm.
Example 12
2,4-Difluoro-[(2-methoxy-5-[5-(3-methoxy-phenyl)-imidazo[2,1-b][1,3,4]thiazol-2-yl]-pyridin-3-yl)-benzenesulfonamide

Standard protocol using 3-methoxyphenylboronic acid; purified by column chromatography and precipitation from CH$_3$CN/Et$_2$O/MeOH/DCM.
Yield: 0.035 g, 35 %
HPLC-MS (Method 1): t$_{R}$= 6.16 min, [M+H]$^+$ m/z 530.2; $^1$H NMR (300 MHz, DMSO) $\delta$ 10.62 (s, 1H), 8.60 (d, $J = 2.1$ Hz, 1H), 8.16 (d, $J = 2.2$ Hz, 1H), 7.89 (s, 1H), 7.86 - 7.79 (m, 1H), 7.67 (s, 1H), 7.64 - 7.55 (m, 2H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.28 - 7.19 (m, 1H), 6.95 (dd, $J = 8.1$, 2.1 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H) ppm.

Example 13
2,4-Difluoro-[(5-[5-(3-hydroxy-phenyl)-imidazo[2,1-b][1,3,4]thiazol-2-yl]-2-methoxy-pyridin-3-yl)-benzenesulfonamide

Standard protocol using 3-hydroxyphenylboronic acid; purified by column chromatography and precipitation from CH$_3$CN/Et$_2$O/MeOH.
Yield: 0.023 g, 21 %
HPLC-MS (Method 1): t*$^*$= 5.46 min, [M+H]$^+$ m/z 516.1; $^1$H NMR (300 MHz, DMSO) $\delta$ 10.62 (s, 1H), 9.67 (s, 1H), 8.65 (s, 1H), 8.11 (d, $J = 1.9$ Hz, 1H), 7.85 (m, 1H), 7.78 (s, 1H), 7.65 - 7.50 (m, 2H), 7.44 (d, 1H), 7.35 - 7.20 (m, 2H), 6.78 (d, $J = 7.9$ Hz, 1H), 3.76 (s, 3H) ppm.

Example 14
4-[(2-[5-(2,4-Difluoro-benzenesulfonylamino)-6-methoxy-pyridin-3-yl]-imidazo[2,1-b][1,3,4]thiazol-5-yl]-3,6-dihydro-2H-pyrldine-1-carboxylic acid tert-butyl ester

Standard protocol using 1-A/-Boc-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)> 3,6-dihydro-2/-/-pyridine; purified by column chromatography.
Yield: 0.084 g, 48 %.
HPLC-MS (Method 1): t*$^*$= 6.45 min, [M+H]$^+$ m/z 605.3; $^1$H NMR (300 MHz, DMSO) $\delta$ 10.53 (s, 1H), 8.55 (d, $J = 2.2$ Hz, 1H), 8.01 (d, $J = 2.2$ Hz, 1H), 7.76 (m, 1H), 7.54 (m, 1H), 7.33 (s, 1H), 7.19 (m, 1H), 6.73 (s, 1H), 4.06 (s, 2H), 3.68 (s, 3H), 3.52 (m, 2H), 2.5 (2H, under DMSO signal, see COSY), 1.37 (s, 9H) ppm.
Example 15
/V-[5-(5-Cyclohex-1-enyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-yl]-2,4-difluoro-benzenesulfonamide

5 Standard protocol using 1-cyclohexen-1-yl-boronic acid (3 eq); purified by column chromatography followed by prep HPLC and trituration with CH3CN/Et20 . Yield: 0.005 g, 8%.

HPLC-MS (Method 1): tR= 6.51 min, [M+H]+ m/z 504.2, 1H NMR (300 MHz, DMSO) δ 10.61 (s, 1H), 8.56 (s, 1H), 8.04 (s, 1H), 7.82 (m, 1H), 7.59 (m, 1H), 7.31 (s, 1H), 7.25 (m, 1H), 6.84 (s, 1H), 3.75 (s, 3H), 2.40 (m, 2H), 2.28 (m, 2H), 1.74 (m, 2H), 1.67 (m, 2H) ppm.

Example 16
2,4-Difluoro-N-[2-methoxy-5-(5-methyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

2,4-Difluoro-N-[5-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-yl]-benzenesulfonamide (0.033 g, 1 eq) and methylboronic acid (0.020 g, 3 eq) were taken up in 1,2-DME (1 mL) and aq 2M Na2CO3 (0.3 mL), and Pd(dppf)Cl2 DCM complex (0.012 mg, 0.1 eq) was added. The mixture was heated at 130 °C for 30 min in a microwave apparatus, neutralized by adding 1M aq HCl and extracted with DCM and DCM/MeOH. The organic phase was dried (MgSO4) and concentrated, and the residue was purified by column chromatography (DCM/MeOH 100:0 to 95:5). The crude product (0.048 g) was repurified by prep HPLC affording the title compound.

Yield: 0.005 g
HPLC-MS (Method 1): tR= 4.96 min, [M+H]+ m/z 438.2, 1H NMR (300 MHz, DMSO with drops of TFA) δ 10.62 (s, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 2 Hz, 1H), 7.80 (m, 1H), 7.64 (s, 1H), 7.58-7.51 (m, 1H), 7.21 (m, 1H), 3.75 (s, 3H), 2.55 (s, 3H) ppm.

Example 17
2,4-Difluoro-N-(5-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-benzenesulfonamide

Method A using 2-bromo-imidazo[2,1-b][1,3,4]thiadiazole (0.100 g, 1 eq) and 2,4-difluoro-N-[2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide

Example 16...
yl]-benzenesulfonamide (0.250 g, 1.2 eq); purified by column chromatography followed by trituration from Et<sub>2</sub>O.

Yield: 0.016 g, 8%.

HPLC-MS (Method 1): \( t_f = 4.91 \text{ min}, [M+H]^+ \text{ m/z 424.1}, \) \(^1\)H NMR (300 MHz, DMSO) \( \delta 10.58 \) (s, 1H), 8.54 (d, \( J = 2.2 \text{ Hz}, 1\)H), 8.24 (d, \( J = 1.2 \text{ Hz}, 1\)H), 8.09 (d, \( J = 2.2 \text{ Hz}, 1\)H), 7.80 (m, 1H), 7.64 - 7.51 (m, 1H), 7.36 (s, 1H), 7.24 (m, 1H), 3.75 (s, 3H) ppm.

Example 18

2,4-Difluoro-N-[5-(5-formyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2-methoxy-pyridin-3-yl]-benzenesulfonamide

Method A using 2-bromo-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (0.064 g, 1 eq) and 2,4-difluoro-A/-[2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide (0.141 g, 1.2 eq); purified by column chromatography.

Yield: 0.065 g, 52%.

HPLC-MS (Method 1): \( t_f = 4.64 \text{ min}, [M+H]^+ \text{ m/z 452.1}, \) \(^1\)H NMR (300 MHz, DMSO) \( \delta 10.63 \) (s, 1H), 9.90 (s, 1H), 8.61 (d, \( J = 2.3 \text{ Hz}, 1\)H), 8.27 (s, 1H), 8.14 (d, \( J = 2.3 \text{ Hz}, 1\)H), 7.81 (m, 1H), 7.66-7.52 (m, 1H, overl. with \( \text{Pb}_3\)PO), 7.25 (m, 1H), 3.75 (s, 3H).

Example 19

2,4-Difluoro-A/-[2-methoxy-5-(5-morpholin-4-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyridin-3-yl]-benzenesulfonamide

A solution of 2,4-difluoro-/V-[5-(5-formyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxypyridin-3-yl]-benzenesulfonamide (0.062 g, 1 eq) and morpholine (0.012 g, 1 eq) in methanol (2 ml) was treated with sodium cyanoborohydride (0.014 g, 1.5 eq) and subsequently with acetic acid (0.025 g, 3 eq). The reaction mixture was stirred at room temperature overnight and then concentrated. The crude was treated with saturated aqueous NaHCO<sub>3</sub> solution and extracted with dichloromethane. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated, and the crude was purified by column chromatography (gradient of 0-5% MeOH in DCM, affording 0.05 g) and subsequently by prep. HPLC affording the title compound as a white solid (0.03 g, yield 42%).
HPLC-MS (Method 1): $t_R = 2.49$ min (broad) and 2.81 min (sharp), [M+H]+ m/z 523.1; $^1$H NMR (300 MHz, DMSO) δ 10.58 (s, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 15.0, 8.6 Hz, 1H), 7.57 (t, J = 9.9 Hz, 1H), 7.29 - 7.18 (m, 2H), 3.86 (s, 2H), 3.75 (s, 3H), 3.64 - 3.54 (m, 3H), 2.47 (s, 4H, overl. with DMSO signal)

Intermediate D

2-Bromo-5-iodo-6-methyl-imidazo[2,1-b][1,3,4]thiadiazole

2-Bromo-6-methyl-imidazo[2,1-b][1,3,4]thiadiazole (0.53 g, 1 eq) was dissolved in abs. DMF (8 mL), and NIS (0.60 g, 1.1 eq) was added in portions. The yellow suspension was stirred at RT overnight and then quenched with some Na$_2$S$_2$O$_3$ (10% aq. sol.) in an ice-bath. Water was added, and the mixture was extracted with EtOAc. The organic phase was separated and washed with brine, aq NH$_4$Cl and again brine, dried (Na$_2$SO$_4$), filtered and concentrated to afford the title compound as a yellowish solid. Yield: 0.75 g, 89%.

HPLC-MS (Method 4): $t_R$ = 4.21 min, [M+H]+ m/z 343.9; $^1$H NMR (300 MHz, DMSO) δ 2.24 ppm.

Intermediate E

2,4-Difluoro-A/-[5-(5-iodo-6-methyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-yl]-benzenesulfonamide

Method A using 2-bromo-5-iodo-6-methyl-imidazo[2,1-b][1,3,4]thiadiazole (0.12 g, 1 eq) and 2,4-difluoro-A/-[2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide (0.19 g, 1.3 eq); purified by column chromatography; a second batch precipitated from aqueous phase. Yield: 0.077 g, 39%.

HPLC-MS (Method 4): $t_R$ = 4.72 min, [M+H]+ m/z 564.1.

Example 20

2,4-Difluoro-N-[2-methoxy-5-(6-methyl-5-pyridin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Method A using 2,4-difluoro-/N-[5-(5-iodo-6-methyl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-yl]-benzenesulfonamide (0.040 g, 1 eq) and pyridine-4-boronic acid (0.017 g, 2 eq), after 3h more boronic acid (0.018 g) and catalyst
(some mg) were added and the reaction was continued for 3h; purified by column chromatography and prep HPLC.

Yield: 0.002 g, 6%.

HPLC-MS (Method 1): t_R = 3.51 min, [M+H]^+ m/z 515.2, \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.76 (d, \(J = 6.1\) Hz, 2H), 8.38 (d, \(J = 2.2\) Hz, 1H), 8.19 (d, \(J = 2.2\) Hz, 1H), 7.96 (m, 1H), 7.77 (m, 2H), 7.06-6.86 (m, 2H), 4.04 (s, 3H), 2.66 (s, 3H) ppm.

**Intermediate F**

2ADifluoro-/\%/\%-[5-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Method A using 2-bromo-5-iodo-imidazo[2,1-b][1,3,4]thiadiazole (0.150 g, 0.455 mmol, 1 eq) and 2,4-difluoro-/\%/\%-[5-(4,4,5 ,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide (WO2008/150827; 0.216 g, 0.546 mmol, 1.2 eq); purified by column chromatography.

Yield: 0.045 g (20%).

HPLC-MS (Method 4): t_R = 4.34 min, [M+H]^+ m/z 519.9.

**Example 21**

2,4-Difluoro-N-[5-(5-pyridin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide

Method A using 2,4-difluoro-/\%/\%-[5-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-yl]-benzenesulfonamide (0.045 g, 1 eq) and pyridine-4-boronic acid (0.016 g, 1.5 eq); purified by column chromatography and trituration with CH\(_3\)CN/Et\(_2\)O.

Yield: 0.008 g, 20%.

HPLC-MS (Method 1): t_R = 3.16 min, [M+H]^+ m/z 471.0.

\(^1\)H NMR (300 MHz, DMSO) \(\delta\) 11.44 (b.s, 1H), 8.94 (d, \(J = 2.4\) Hz, 1H), 8.70 (d, \(J = 6.3\) Hz, 2H), 8.56 (d, \(J = 2.4\) Hz, 1H), 8.20 (s, 1H), 8.10-8.03 (m, 4H), 7.64-7.56 (m, 1H), 7.36-7.29 (m, 1H) ppm.
Intermediate H
5-(5-ido-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-ylamine
Method A using 2-bromo-5-ido-imidazo[2,1-b][1,3,4]thiadiazole (1.1g, 3.33 mmol, 1 eq) and (5-amino-6-methoxypyridin-3-yl)boronic acid (0.672 g, 4.00 mmol, 1.2 eq); crude product precipitated from aqueous phase, triturated with Et₂O.
Yield: 1.0 g (crude product, brownish solid).
HPLC-MS (Method 4): tᵣ= 4.17 min, [M+H]+ m/z 374.0.

Intermediate J
2-Methoxy-5-(5-pyridin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyridin-3-ylamine
Method A using 5-(5-ido-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2-methoxy-pyridin-3-ylamine (1.0 g, 2.68 mmol, 1 eq) and pyridine-4-boronic acid (0.50 g, 4.0 mmol, 1.5 eq); purified by column chromatography.
Yield: 0.330 g (crude product, used as such).
HPLC-MS (Method 4): tᵣ= 2.3 min (broad peak), [M+H]+ m/z 325.1.

Intermediate K
2-Bromo-5-nitro-imidazo[2,1-b][1,3,4]thiadiazole
Fuming nitric acid (0.15 mL) was added at 0°C to a solution of 2-bromo-imidazo[2,1-b][1,3,4]thiadiazole (0.200 g, 1 mmol) in cone, sulfuric acid (0.24 mL), and the mixture was stirred for 5h. Ice was added, and stirring was continued for 30 min. The solid was filtered off, washed with cold water and dried to give the title compound (0.244 g; 83%)
¹H NMR (300 MHz, DMSO) δ 8.55 (s, 1H ppm).

Intermediate L
N-(2-Bromo-imidazo[2,1-b][1,3,4]thiadiazol-5-yl)-acetamide
Iron (0.100 g, 3.5 eq) was added to a solution of 2-bromo-5-nitro-imidazo[2,1-b][1,3,4]thiadiazole (0.130 g, 0.5 mmol) in AcOH (1.6 mL) and Ac₂O (0.2 mL, 4 eq), and the mixture was stirred at 75-80 °C for 2h. After cooling, ice was added, and the mixture was filtered through celite and eluted with EtOAc. The filtrate was washed with sat aq NaHCO₃ and brine, dried (MgSO₄) and concentrated to give the title compound (0.082 g). From the aqueous phase additional compound was
extracted using DCM/MeOH 95:5 to yield a total of 0.098 g (75%) of crude material which was used as such.

HPLC-MS (Method 4): t_R = 1.02 min, [M+H]^+ m/z 263.0/261.0. ^1H NMR (300 MHz, DMSO) δ 10.41 (s, 1H), 7.24 (s, 1H), 2.08 (s, 3H) ppm.

Example 22

N-[2-[5-(2,4-Difluoro-benzenesulfonylamino)-6-methoxy-pyridin-3-yl]-imidazo[2,1-b][1,3,4]thiadiazol-5-yl]-acetamide

Method A using 2-(bromo-imidazo[2,1-b][1,3,4]thiadiazol-5-yl)-acetamide (0.065 g, 0.25 mmol) and 2,4-difluoro-2-[5-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-3-yl]-benzenesulfonamide (0.160 g, 0.37 mmol, 1.5 eq); column chromatography. Yield: 0.031 g, 26%.

HPLC-MS (method 1): t_R = 4.26 min, [M+H]^+ m/z 481.2. ^1H NMR (300 MHz, DMSO) δ 10.59 (b.s, 1H), 10.40 (s, 1H), 8.52 (d, J = 2.1 Hz, 1H), 8.09 (d, J = 2.1 Hz, 1H), 7.84-7.75 (m, 1H), 7.61-7.54 (m, 1H), 7.25-7.20 (m, 2H), 3.72 (s, 3H), 2.13 (s, 3H) ppm.

Example 23

N-[3-[5-(6-Amino-5-trifluoromethyl-pyridin-3-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-phenyl]-methanesulfonamide

A mixture of 2-bromo-5-iodoimidazo[2,1-b][1,3,4]thiadazole (150 mg, 0.455 mmol, 1 eq), 3-(methylsulfonylamino)phenylboronic acid (127 mg, 0.591 mmol, 1.3 eq), PdCl_2(PPh_3)_2 (64 mg, 0.091 mmol, 0.2 eq) and 2M aq Na_2CO_3 (1 mL) in dioxane (3 mL) was refluxed for 2h. Dioxane was evaporated, water added and the mixture was extracted with DCM. The organic layers were dried, filtered and evaporated. The residue (130 mg) was used as such for the second coupling which was done under the same conditions (using 170 mg of 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trifluoromethyl-pyridin-2-ylamine and 70 mg of PdCl_2(PPh_3)_2). The solvents were removed under reduced pressure, water was added and the solid was filtered and washed with water. Upon standing, a solid appeared in the aqueous filtrate. It was filtered and washed with ether to give the desired product (43 mg, 21%). HPLC-MS (5-100% B in 8 min at 0.8 mL): t_R = 5.57 min, [M+H]^+ m/z 458.1; ^1H NMR (700 MHz, CDCl_3) δ 7.24 (s, 3H), 7.1 1 (s, 2H), 3.95 (s, 6H), 3.93 (s, 6H), 3.92 (s, 3H), 3.89 (s, 3H).
Example 24
Exemplary compounds of the invention described herein were assayed for their PI3K alpha and mTOR enzymatic activities using the methods described above. The activities are expressed in IC_{50} values ranging from <10 nM (XXX) to 10-500 nM (XX) and to 0.5-10 μM (X), see Table 1. For example, selected exemplary compounds have the following IC_{50} values (μM): Example 2 (PI3Ka 0.003; mTOR 0.050), Example 5 (PI3Kcc 0.001; mTOR 0.006), Example 15 (PI3Koc 0.001; mTOR 0.031).

Table 1: PI3K alpha and mTOR enzymatic activities expressed as IC_{50} ranges (** <0.010 uM; ** 0.010-0.500 uM, * 0.500-10 uM).
Example 25

A selection of exemplary compounds of the invention displaying Flt3 activity with IC$_{50}$ values ranging from $<100$ nM (XXX) to 100-500 nM (XX) and to 0.5-10 µM (X) is listed in Table 2. Examples 8 and 7 have IC$_{50}$ values of 0.079 and 3.15 µM, respectively.

Table 2: Flt3 enzymatic activities expressed as IC$_{50}$ ranges (** <0.100 µM; * 0.100-0.500 µM, * 0.500-10 µM).

<table>
<thead>
<tr>
<th>Example</th>
<th>Flt3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
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<tr>
<td>7</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>XXX</td>
</tr>
<tr>
<td>9</td>
<td>XX</td>
</tr>
<tr>
<td>10</td>
<td>XX</td>
</tr>
<tr>
<td>11</td>
<td>X</td>
</tr>
<tr>
<td>15</td>
<td>XXX</td>
</tr>
<tr>
<td>21</td>
<td>XXX</td>
</tr>
</tbody>
</table>

Example 26

Combination Therapy

Table A: Example 8 in combination with MEK inhibitor PD-0325901

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>A549</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Types</td>
<td>Lung</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>Ras G12S</td>
</tr>
<tr>
<td>Chemotherapeutic</td>
<td>PD-0325901</td>
</tr>
<tr>
<td>Chemot. EC50 (µM)</td>
<td>1</td>
</tr>
<tr>
<td>Example 8 EC50 (µM)</td>
<td>0.14</td>
</tr>
<tr>
<td>Combination Index (CI)</td>
<td>0.03</td>
</tr>
<tr>
<td>Synergy</td>
<td>++++</td>
</tr>
</tbody>
</table>
Table B: Example 7 in combination with MEK inhibitor PD-0325901, lapatinib and docetaxel

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>A549</th>
<th>A549</th>
<th>SKOV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Types</td>
<td>Lung</td>
<td>Lung</td>
<td>Ovarian</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>Ras G12S</td>
<td>Ras G12S</td>
<td></td>
</tr>
<tr>
<td>Chemotherapeutic</td>
<td>PD-0325901</td>
<td>lapatinib</td>
<td>docetaxel</td>
</tr>
<tr>
<td>Chemot. EC50 (µM)</td>
<td>2.5</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Example 7 EC50 (µM)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Combination Index (CI)</td>
<td>0.11</td>
<td>0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>Synergy</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
</tr>
</tbody>
</table>

5 Example 27
Kinase Selectivity Data
Inhibitory activity for the kinases BRAF-V600E, Kit, PDGFRα and VEGFR2 (measurements performed at ProQinase GmbH) has been detected in single point measurements at 1 µM compound concentration and is represented as percentage of inhibition data for Example 8: BRAF-V600E (79 %), Kit (84 %), PDGFRα (80 %) and VEGFR2 (75 %).

Example 28
The following table demonstrated PI3Kcc, mTOR, FLT3 and PI3K cellular activities as measured by the IC50 values (in µM) for certain examples, using the tests described hereinbefore:
<table>
<thead>
<tr>
<th>Example</th>
<th>PI3K</th>
<th>mTOR</th>
<th>FLT3</th>
<th>P-AKT ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>0.23</td>
<td>0.94</td>
<td>1.46</td>
</tr>
<tr>
<td>2</td>
<td>0.003</td>
<td>0.050</td>
<td>0.18</td>
<td>0.13</td>
</tr>
<tr>
<td>3</td>
<td>0.0008</td>
<td>0.004</td>
<td>100</td>
<td>0.0015</td>
</tr>
<tr>
<td>4</td>
<td>0.001</td>
<td>0.009</td>
<td>1.02</td>
<td>0.007</td>
</tr>
<tr>
<td>5</td>
<td>0.001</td>
<td>0.006</td>
<td>0.70</td>
<td>0.023</td>
</tr>
<tr>
<td>6</td>
<td>0.001</td>
<td>0.001</td>
<td>0.56</td>
<td>0.005</td>
</tr>
<tr>
<td>7</td>
<td>0.0002</td>
<td>0.001</td>
<td>3.15</td>
<td>0.002</td>
</tr>
<tr>
<td>8</td>
<td>0.001</td>
<td>0.0007</td>
<td>0.079</td>
<td>0.003</td>
</tr>
<tr>
<td>9</td>
<td>0.001</td>
<td>0.003</td>
<td>0.37</td>
<td>0.032</td>
</tr>
<tr>
<td>10</td>
<td>0.003</td>
<td>0.001</td>
<td>0.22</td>
<td>0.003</td>
</tr>
<tr>
<td>11</td>
<td>0.001</td>
<td>0.007</td>
<td>0.89</td>
<td>0.005</td>
</tr>
<tr>
<td>14</td>
<td>0.0001</td>
<td>0.001</td>
<td>2</td>
<td>0.031</td>
</tr>
<tr>
<td>15</td>
<td>0.001</td>
<td>0.031</td>
<td>0.074</td>
<td>0.22</td>
</tr>
<tr>
<td>16</td>
<td>0.051</td>
<td>0.65</td>
<td>18.2</td>
<td>1.53</td>
</tr>
<tr>
<td>17</td>
<td>0.078</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0.058</td>
<td>0.038</td>
<td>30.8</td>
<td>1.07</td>
</tr>
<tr>
<td>19</td>
<td>0.13</td>
<td>0.13</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.008</td>
<td>0.026</td>
<td>6.54</td>
<td>0.53</td>
</tr>
<tr>
<td>21</td>
<td>0.002</td>
<td>0.043</td>
<td>0.055</td>
<td>0.091</td>
</tr>
<tr>
<td>22</td>
<td>0.22</td>
<td>2.05</td>
<td>&gt;100</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Claims

1. A compound of formula I,

\[ \text{I} \]

wherein:

\( R_1 \) represents:

\[
\begin{array}{c}
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\text{X}^1 \text{X}^2 \\
\end{array}
\]

in which the squiggly line represents the point of attachment to the requisite imidazothiadiazole core of formula I;

each \( X^1 \) independently represents \(-N=, -C(H)= \) or \(-C(A^1)=\);

each \( X^2 \) independently represents \(-C(H)= \) or \(-C(A^2)=;\)

\( R^2 \) represents hydrogen, halo, \(-CN\) or \(C_{1-3}\) alkyl optionally substituted by one or more fluoro atoms;

\( R^3 \) represents hydrogen, \( Q^1 \text{a}, -CN, C_{1-6} \) alkyl (optionally substituted by one or more substituents selected from \(=0 \) and \(A^5 \)), heterocycloalkyl (optionally substituted by one or more substituents selected from \(=0 \) and \(A^6 \)), aryl (optionally substituted by one or more substituents selected from \(A^3 \)) or heteroaryl (optionally substituted by one or more substituents selected from \(A^4 \));

each \( A^1, A^2, A^3, A^4, A^5 \) and \( A^6 \) independently represents, on each occasion when used herein:

(i) \( Q^1 \);

(ii) \( C_{1-12} \) alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from \(=0, =S, =N(R^{10a}) \) and \(Q^2 \);
(iii) aryl or heteroaryl, both of which are optionally substituted by one or more substituents selected from \( Q^3 \); each \( Q^1 \), \( Q^1 \), \( Q^2 \) and \( Q^3 \) independently represents, on each occasion when used herein:

- \(-\text{CN}, -\text{NO}_2, -\text{N}(\text{R}^{10a})\text{R}^{11a}, -\text{OR}^{10a}, -\text{C}(=\text{Y})-\text{R}^{10a}, -\text{C}(=\text{Y})-\text{OR}^{10a}, -\text{C}(=\text{Y})\text{N}(\text{R}^{10a})\text{R}^{11a}, -\text{OC}(=\text{Y})-\text{R}^{10a}, -\text{OC}(=\text{Y})-\text{OR}^{10a}, -\text{OC}(=\text{Y})\text{N}(\text{R}^{10a})\text{R}^{11a}, -\text{OS}(\text{O})_2\text{OR}^{10a}, -\text{OP}(=\text{Y})(\text{OR}^{10a})(\text{OR}^{11a}), -\text{OP}(\text{OR}^{10a})(\text{OR}^{11a}), -\text{N}(\text{R}^{12a})\text{C}(=\text{Y})\text{R}^{11a}, -\text{N}(\text{R}^{12a})\text{C}(=\text{Y})\text{OR}^{11a}, -\text{N}(\text{R}^{12a})\text{N}(\text{R}^{10a})\text{R}^{11a}, -\text{NR}^{12a}\text{S}(\text{O})_2\text{R}^{10a}, -\text{NR}^{12a}\text{S}(\text{O})_2\text{N}(\text{R}^{10a})\text{R}^{11a}, -\text{SC}(=\text{Y})\text{R}^{10a}, -\text{SC}(=\text{Y})\text{OR}^{10a}, -\text{SC}(=\text{Y})\text{N}(\text{R}^{10a})\text{R}^{11a}, -\text{S}(\text{O})_2\text{R}^{10a}, -\text{SR}^{10a}, -\text{S}(\text{O})\text{R}^{10a}, -\text{S}(\text{O})_2\text{OR}^{10a}, \text{C}_{1-12} \text{ alkyl, heterocycloalkyl} (\text{which latter two groups are optionally substituted by one or more substituents selected from } =\text{O}, =\text{S}, =\text{N}(\text{R}^{20})) \text{ and } \text{E}^3, \text{aryl or heteroaryl} (\text{which latter two groups are optionally substituted by one or more substituents selected from } \text{E}^4); \)

each \( \text{R}^{10a} \) independently represents, on each occasion when used herein, hydrogen, \(-\text{N}(\text{R}^{21})(\text{R}^{22}), \text{Cl}_{1-2} \text{ alkyl, heterocycloalkyl} (\text{which latter two groups are optionally substituted by one or more substituents selected from } =\text{O}, =\text{S}, =\text{N}(\text{R}^{20}) \text{ and } \text{E}^3, \text{aryl or heteroaryl} (\text{which latter two groups are optionally substituted by one or more substituents selected from } \text{E}^4); \)
each \( \text{R}^1, \text{R}^2, \text{R}^{10a}, \text{R}^{11a} \text{ and } \text{R}^{12a} \) independently represents, on each occasion when used herein, hydrogen, \( \text{C}_{1-12} \text{ alkyl, heterocycloalkyl} (\text{which latter two groups are optionally substituted by one or more substituents selected from } =\text{O}, =\text{S}, =\text{N}(\text{R}^{20}) \text{ and } \text{E}^3, \text{aryl or heteroaryl} (\text{which latter two groups are optionally substituted by one or more substituents selected from } \text{E}^4); \) or

any relevant pair of \( \text{R}^1, \text{R}^2, \text{R}^{10a}, \text{R}^{11a} \text{ and } \text{R}^{12a} \) may (for example, when attached to the same atom, adjacent atom (i.e. 1,2-relationship) or to atoms that are two atom atoms apart, i.e. in a 1,3-relationship) be linked together to form (e.g. along with the requisite nitrogen atom to which they may be attached) a 4- to 20- (e.g. 4- to 12-) membered ring, optionally containing one or more heteroatoms (for example, in addition to those that may already be present, e.g. (a) heteroatom(s) selected from oxygen, nitrogen and sulfur), optionally containing one or more
unsaturations (e.g. triple or, preferably, double bonds), and which ring is optionally substituted by one or more substituents selected from \(=0, =S, =N(R^{20})\) and \(E^5\);

each \(E^1, E^2, E^3, E^4\) and \(E^5\) independently represents, on each occasion when used herein:

(i) \(Q^4\);

(ii) \(C_{1,12}\) alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from \(=0\) and \(Q^5\);

(iii) aryl or heteroaryl, both of which are optionally substituted by one or more substituents selected from \(Q^6\);

each \(Q^4\), \(Q^5\) and \(Q^6\) independently represents, on each occasion when used herein:

halo, -CN, -N\(^2\)O, -N(R\(^{20}\))R\(^{21}\), -OR\(^{20}\), -C(\(=\)Y)-R\(^{20}\), -C(\(=\)Y)-OR\(^{20}\), -C(\(=\)Y)N(R\(^{20}\))R\(^{21}\), -OC(\(=\)Y)-R\(^{20}\), -OC(\(=\)Y)-OR\(^{20}\), -OC(\(=\)Y)N(R\(^{20}\))R\(^{21}\), -OS(0)\(^2\)OR\(^{20}\), -OP(\(=\)Y)OR\(^{20}\), -OP(\(=\)Y)(OR\(^{20}\))\(^2\), -OP(OR\(^{20}\))(OR\(^{21}\)), -N(R\(^{22}\))C(\(=\)Y)R\(^{21}\), -N(R\(^{22}\))C(\(=\)Y)OR\(^{21}\), -N(R\(^{22}\))C(\(=\)Y)N(R\(^{20}\))R\(^{21}\), -NR\(^{22}\)S(O)\(^2\)R\(^{20}\), -NR\(^{22}\)S(O)\(^2\)N(R\(^{20}\))R\(^{21}\), -S(O)\(^2\)N(R\(^{20}\))R\(^{21}\), -SC(\(=\)Y)R\(^{20}\), -SC(\(=\)Y)OR\(^{20}\), -SC(\(=\)Y)N(R\(^{20}\))R\(^{21}\), -S(O)\(^2\)R\(^{20}\), -SR\(^{20}\), -S(O)R\(^{20}\), -S(0)\(^2\)OR\(^{20}\), C\(_{1,2}\) alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from \(=0\) and \(J^1\)), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from \(J^3\));

each \(Y\) independently represents, on each occasion when used herein, \(=0, =S\) or \(=NR^{23}\);

each \(R^{20}, R^{21}, R^{22}\) and \(R^{23}\) independently represents, on each occasion when used herein, hydrogen, \(C_{1,6}\) alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from \(J^3\) and \(=0\)), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from \(J^4\)); or

any relevant pair of \(R^{20}, R^{21}\) and \(R^{22}\), may (for example, when attached to the same atom, adjacent atom (i.e. 1,2-relationship) or to atoms that are two atom
atoms apart, i.e. in a 1,3-relationship) be linked together to form (e.g. along with
the requisite nitrogen atom to which they may be attached) a 4- to 20- (e.g. 4- to
12-) membered ring, optionally containing one or more heteroatoms (for example, in
addition to those that may already be present, e.g. (a) heteroatom(s) selected
from oxygen, nitrogen and sulfur), optionally containing one or more
unsaturations (e.g. triple or, preferably, double bonds), and which ring is
optionally substituted by one or more substituents selected from \( J^5 \) and \( =0 \);

each \( J^1, J^2, J^3, J^4 \) and \( J^5 \) independently represents, on each occasion when used
herein:

(0) \( Q^7 \);

(ii) \( C-8 \) alkyl or heterocycloalkyl, both of which are optionally substituted by one or
more substituents selected from \( =0 \) and \( Q^8 \);

(iii) aryl or heteroaryl, both of which are optionally substituted by one or more
substituents selected from \( Q^9 \);

each \( Q^7, Q^8 \) and \( Q^9 \) independently represents, on each occasion when used
herein:

- \( \text{CN} \) or, more preferably, halo, -\( N(R^{50})R^{61} \), -\( OR^{50} \), -\( C(=Y^a)-R^{50} \), -\( C(=Y^a)-OR^{50} \),
-\( C(=Y^a)N(R^{50})R^{61} \), -\( N(R^{52})C(=Y^a)R^{61} \), -\( NR^{52}S(O)2R^{60} \), -\( S(S(0)_2)R^{50} \), -\( SR^{50} \), -\( S(0)R^{50} \) or
\( C_{1-6} \) alkyl optionally substituted by one or more fluoro atoms;

each \( Y^3 \) independently represents, on each occasion when used herein, \( =0, =S \)
or \( =NR^{53} \);

each \( R^{50}, R^{51}, R^{52} \) and \( R^{53} \) independently represents, on each occasion when
used herein, hydrogen or \( C_{1-6} \) alkyl optionally substituted by one or more
substituents selected from fluoro, -\( OR^{50} \) and -\( N(R^{61})R^{62} \); or
any relevant pair of \( R^{50}, R^{51} \) and \( R^{52} \) may (for example when attached to the same
or adjacent atoms) be linked together to form, a 3- to 8-membered ring, optionally
containing one or more heteroatoms (for example, in addition to those that may
already be present, heteroatoms selected from oxygen, nitrogen and sulfur),
optionally containing one or more unsaturations (e.g. triple or, preferably, double
bonds), and which ring is optionally substituted by one or more substituents
selected from \( =0 \) and \( C_{1-3} \) alkyl;
R⁶⁰, R⁵¹ and R⁵² independently represent hydrogen or C₁₋₆ alkyl optionally substituted by one or more fluoro atoms;

or a pharmaceutically acceptable ester, amide, solvate or salt thereof.

2. A compound as claimed in Claim 1, wherein, R¹ represents:

\[
\begin{array}{c}
\text{A}^2 \\
\text{R}^{12a} \\
\text{N} \\
\text{SO}_2 \\
\text{R}^{10a}
\end{array}
\]

in which the squiggly line represents the point of attachment to the requisite imidazothiadiazole core of formula I (and the other substituents, i.e. A², R¹₀ and R¹²a are as defined in Claim 1).

3. A compound as claimed in Claim 1 or Claim 2, wherein R² represents hydrogen or C₁₋₂ alkyl (e.g. methyl) (most preferably R² represents hydrogen); R³ represents hydrogen, Q¹¹, C₁₋₆ alkyl (optionally substituted as defined herein; which group is preferably cyclic or bears a cyclic group), heterocycloalkyl (optionally substituted as defined herein) or, preferably, aryl or heteroaryl (both of which latter two substituents are optionally substituted by one or more substituents selected from A³ and A⁴, respectively); R³ preferably represents a cyclic aromatic or non-aromatic group; Q¹¹ preferably represents -C(=Y)-R¹₀ or -N(R¹₂a)C(=Y)R¹₁₈; when R³ represents C₁₋₆ alkyl, it is preferably acyclic C₁₋₃ alkyl (e.g. methyl; optionally substituted by A⁵) or C₃₋₆ cycloalkyl (optionally containing two or preferably one double bond, e.g. cyclohexenyl); and/or when R³ represents heterocycloalkyl, it is preferably a 5- or 6-membered heterocycloalkyl group (containing one or two heteroatoms, preferably selected from oxygen and, especially, nitrogen, and optionally containing two or preferably one double bond; e.g. a piperidinyl group optionally containing one double bond).

4. A compound as claimed in any one of the preceding claims, wherein A⁵ and A⁶ independently represent Q¹; when A⁶ represents Q¹, then Q¹ preferably

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represents \(-\text{C}(=\text{Y})\text{-OR}^{10a}\); when \(\text{A}^5\) represents \(\text{Q}^4\), then \(\text{Q}^4\) preferably represents \(-\text{C}(=\text{Y})\text{-OR}^{10a}\) or, preferably, \(-\text{N}\text{(R}^{10a}\text{)}\text{R}^{11a}\); \(\text{A}^3\) and \(\text{A}^4\) independently represent optionally substituted heterocycloalkyl or, preferably, \(\text{Q}^1\), \(\text{C}_{1-4}\) alkyl (e.g. methyl or ethyl); which alkyl group is optionally substituted by one or more substituents selected from \(\text{Q}^2\), in which \(\text{Q}^2\) is preferably fluoro, so forming e.g. a \(-\text{CF}_3\) group); when \(\text{A}^3\) and \(\text{A}^4\) represent heterocycloalkyl, then it is preferably a 5- or 6-membered group containing one or two heteroatoms preferably selected from nitrogen and oxygen; when \(\text{A}^3\) and \(\text{A}^4\) represent \(\text{Q}^1\), then \(\text{Q}^1\) represents halo (e.g. chloro), \(-\text{OR}^{10a}\), or \(-\text{N}\text{(R}^{10a}\text{)}\text{R}^{11a}\) (e.g. in which \(\text{R}^{10a}\) and \(\text{R}^{11a}\) are linked together to form a 5- or 6-membered heterocycloalkyl group optionally containing a further heteroatom (e.g. nitrogen or oxygen)); \(\text{Q}^2\) represents halo (e.g. fluoro); \(\text{A}^1\) and \(\text{A}^2\) independently represent \(\text{Q}^1\); when \(\text{A}^2\) (or \(\text{A}^1\)) represents \(\text{Q}^1\), it is preferably \(-\text{OR}^{10a}\) (in which \(\text{R}^{10a}\) is preferably \(\text{C}_{1-2}\) alkyl, such as methyl); \(\text{R}^{10a}\) preferably represents optionally substituted heteroaryl or, preferably, aryl optionally substituted by one or more (e.g. one to three) substituents selected from \(\text{E}^4\); \(\text{E}^3\) and \(\text{E}^4\) independently represent \(\text{Q}^4\); when \(\text{E}^3\) or \(\text{E}^4\) represent \(\text{Q}^4\), then \(\text{Q}^4\) preferably represents halo (e.g. fluoro); \(\text{R}^{10a}\) represents hydrogen or \(\text{C}_{1-4}\) (e.g. \(\text{C}_{1-2}\)) alkyl (e.g. tert-butyl or methyl); \(\text{R}^{12a}\) represents hydrogen; \(\text{R}^{11a}\) represents \(\text{C}_{1-3}\) (e.g. \(\text{C}_{1-2}\)) alkyl (e.g. methyl); or \(\text{R}^{10a}\) and \(\text{R}^{11a}\) may be linked together to form a 5- or 6-membered heterocycloalkyl group optionally containing a further heteroatom (e.g. nitrogen or oxygen); and/or \(\text{Y}\) represents =0.

5. A compound of formula I as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use as a pharmaceutical.

6. A pharmaceutical formulation including a compound of formula I, as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

7. A compound, as defined in any one of Claims 1 to 4 but without the provisos, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use in the treatment of a disease in which inhibition of a PI3-K, mTOR and/or Flt3 is desired and/or required.
8. Use of a compound of formula I, as defined in any one of Claims 1 to 4 but without the provisos, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for the manufacture of a medicament for the treatment of a disease in which inhibition of a PI3-K, mTOR and/or Flt3 is desired and/or required.

9. A compound as claimed in Claim 7 or a use as claimed in Claim 8, wherein the disease is cancer, an immune disorder, a cardiovascular disease, a viral infection, inflammation, a metabolism/endocrine function disorder, a neurological disorder, an obstructive airways disease, an allergic disease, an inflammatory disease, immunosuppression, a disorder commonly connected with organ transplantation, an AIDS-related disease, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, a bone disorder, atherosclerosis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis, restenosis, stroke, diabetes, hepatomegaly, Alzheimer’s disease, cystic fibrosis, a hormone-related disease, an immunodeficiency disorder, a destructive bone disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukaemia, liver disease, a pathologic immune condition involving T cell activation, CNS disorders, and other associated diseases.

10. A method of treatment of a disease in which inhibition of a PI3-K is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 4 but without the provisos, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof, to a patient suffering from, or susceptible to, such a condition.

11. A combination product comprising:
(A) a compound of formula I as defined in any one of Claims 1 to 4 but without the provisos, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof; and
(B) another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease,
wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

12. A combination comprising:

   a compound of formula I as defined in any one of Claims 1 to 4 but without the provisos, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof; and

   one or more treatments independently selected from surgery, one or more anti-cancer/anti-neoplastic/anti-tumoral agent, one or more hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation (e.g. an agent that modulates the Ras/Raf/Mek pathway (e.g. an inhibitor of MEK), the Jak/Stat pathway (e.g. an inhibitor of Jak), the PI3K/Akt pathway (e.g. an inhibitor of Akt), the DNA damage response mechanism (e.g. an inhibitor of ATM or ATR) or the stress signaling pathway (an inhibitor of p38 or NF-KB)).

13. A combination as claimed in Claim 12, wherein the compound of formula I is the compound of Example 7 or 8 as defined herein, and the other treatment is a therapeutic agent preferably selected from PD-0325901, lapatinib and docetaxel.

14. A process for the preparation of a compound of formula I as defined in Claim 1, which process comprises:

   (i) for compounds of formula I in which $R^3$ is other than hydrogen or halo, reaction of a corresponding compound of formula II,

   \[
   \text{II}
   \]

   wherein $L^1$ represents a suitable leaving group, and $R^1$ and $R^2$ are as defined in Claim 1, with a compound of formula III,

   \[
   \text{III}
   \]

   wherein $L^2$ represents a suitable group, and $R^{3a}$ represents $R^3$ as defined in Claim 1, provided that it does not represent hydrogen or halo;

   (ii) reaction of a compound of formula IV,
wherein $L^3$ represents a suitable leaving group, and $R^2$ and $R^3$ are as defined in Claim 1, with a compound of formula V,

$$R^1\cdot L^4$$

wherein $L^4$ represents a suitable leaving group;

(iii) for compounds of formula I in which there is a $Q^1$ to $Q^9$ substituent present, in which such groups represent $-OR^{10a}$, $-OR^{20}$ or $-OR^{50}$, as appropriate, in which $R^{10a}$, $R^{20}$ and $R^{50}$ do not represent hydrogen, reaction of a corresponding compound of formula I in which there is a $Q^1$ to $Q^9$ present, which represents $-OR^{10a}$, $-OR^{20}$ and $-OR^{50}$ (as appropriate), in which $R^{10a}$, $R^{20}$ and $R^{50}$ do represent hydrogen, with a compound of formula VI,

$$R^x\cdot L^5$$

wherein $L^5$ represents a suitable leaving group and $R^x$ represents $R^{10a}$, $R^{20}$ or $R^{50}$ (as appropriate), provided that it does not represent hydrogen;

(iv) reaction of a compound corresponding to a compound of formula I but in which $R^1$ represents the relevant aryl or heteroaryl group (defined in Claim 1) substituted by $-NH_2$, with a compound of formula VIA,

$$L^6\cdot S(O)_2\cdot R^{10x}$$

wherein $L^6$ represents a suitable leaving group, and $R^{10x}$ is as defined in Claim 1.

15. A process for the preparation of:

(I) a pharmaceutical formulation as defined in Claim 6, which process comprises bringing into association a compound of formula I, as defined in any one of one of Claims 1 to 4, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier; and/or

(II) a combination product as defined in Claim 11, 12 or 13, which process comprises bringing into association a compound of formula I, as defined in any one of Claims 1 to 4 but without the provisos, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with the other therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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**ADD.**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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

**Electronic data base consulted during the international search (name of data base and, where practical, search terms used)**

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2009/055418 AI (SMITHKLINE BEECHAM CORP [US]; ADAMS NICHOLAS D [US]; DARCY MICHAEL G, (GER) 30 April 2009 (2009-04-30) cited in the application on page 8, line 24 - page 9, line 27 page 26, line 4 - line 9</td>
<td>1-15</td>
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<td>WO 2009/040552 A (CT NAC DE INVESTIGACIONES ONC0 [ES]; PEVARELLO PAOLO IT; GARCIA COLL) 2 April 2009 (2009-04-02) cited in the application on page 41, line 12 - line 18; claim 1; examples 1-5</td>
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**Further documents are listed in the continuation of Box C.**

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

25 July 2011

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

01/08/2011

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

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- "Z" document member of the same patent family
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<td>WO 2009040552 A</td>
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<tr>
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