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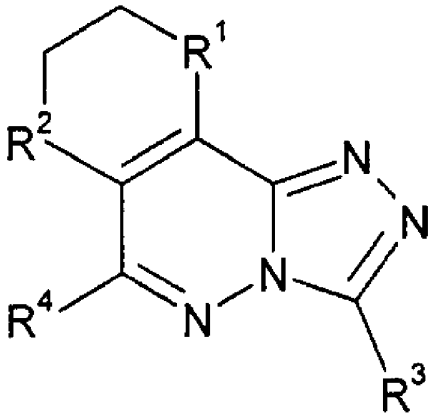
(54) Title: 6, 7-RING-FUSED TRIAZOLO [4, 3 - B] PYRIDAZINE DERIVATIVES AS PIM INHIBITORS



(I)

(57) Abstract: There is provided compounds of formula I, wherein R^1, R^2, R^3 and R^4 (and the $-CH_2-CH_2$ moiety) 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. a PIM family kinase, such as PIM-1, PIM-2 and/or PIM-3) is desired and/or required, and particularly in the treatment of cancer or a proliferative disease.

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6, 7-RING-FUSED TRIAZOLO [4 , 3 - B] PYRIDAZINE DERIVATIVES AS PIM INHIBITORS

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 a member of the PIM family kinases, e.g. PIM-1, PIM-2 or PIM-3). 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.

PIM-1 is the protooncogene activated by murine leucemia virus (Provirus Integration site for Moloney murine leucemia virus – MoMuLV) that induces T-cell lymphoma [Cuypers, H.T., et. al. *Cell*, **1984**, 37, 141-150].

The expression of the protooncogene produces a non-transmembrane serine/threonine kinase of 313 residues, including a kinase domain consisting of

253 amino acid residues. Two isoforms are known through alternative initiation (p44 and p33) [Saris, C.J.M. et al. *EMBO J.* **1991**, 10, 655-664].

PIM-1, PIM-2 and PIM-3 phosphorylate protein substrates that are important in cancer neogenesis and progression. For example, PIM-1 phosphorylates *inter alia* p21, Bad, c-myb, Cdc 25A and eIF4B (see e.g. Quian, K. C. *et al*, *J. Biol. Chem.* 2005, 280(7), 6130-6137, and references cited therein).

Two PIM-1 homologs have been described [Baytel, D. *Biochem. Biophys. Acta* **1998**, 1442, 274-285; Feldman, J. et al. *J. Biol. Chem.* **1998**, 273, 16535.16543]. PIM-2 and PIM-3 are respectively 58% and 69% identical to PIM-1 at the amino acid level. PIM-1 is mainly expressed in thymus, testis, and cells of the hematopoietic system [Mikkers, H.; Nawijn, M.; Allen, J.; Brouwers, C.; Verhoeven, E.; Jonkers, J.; Berns, *Mol. Cell. Biol.* **2004**, *24*, 6104; Bachmann, M.; Moroy, T. *Int. J. Biochem. Cell Biol.* **2005**, *37*, 726-730. 6115]. PIM-1 expression is directly induced by STAT (Signal Transducers and Activators of Transcription) transcription factors, and PIM-1 expression is induced by many cytokine signalling pathways such as interleukins (IL), granulocyte-macrophage colony stimulating factor (GM-CSF), α- and γ-interferon, erythropoietin, and prolactin [Wang, Z et al. *J. Vet. Sci.* **2001**, *2*, 167-179].

PIM-1 has been implicated in lymphoma development. Induced expression of PIM-1 and the protooncogene c-myc synergise to increase the incidence of lymphomagenesis [Breuer, M. et al. Nature 1989, 340, 61-63; van Lohuizen M. et al. Cell, 1991, 65, 737-752]. PIM-1 functions in cytokine signalling pathways and has been shown to play a role in T cell development [Schmidt, T. et al. EMBO J. 1998, 17, 5349-5359; Jacobs, H. et al. JEM 1999, 190, 1059-1068]. Signalling through gp130, a subunit common to receptors of the IL-6 cytokine family, activates the transcription factor STAT3 and can lead to the proliferation of hematopioetic cells [Hirano, T. et al. Oncogene 2000, 19, 2548-2556]. A kinase-active PIM-1 appears to be essential for the gp130-mediated STAT3 proliferation signal. In cooperation with the c-myc PIM-1 can promote STAT3-mediated cell cycle progression and antiapoptosis [Shirogane, T. et al., immunity, 1999, 11, 709-719]. PIM-1 also appears to be necessary for IL-3-stimulated growth in bone marrow-derived mast cells [Domen, J. et al., Blood, 1993, 82, 1445-1452] and

survival of FDCP1 cells after IL-3 withdrawal [Lilly, M. et al., Oncogene, 1999, 18, 4022-4031].

Additionally, control of cell proliferation and survival by PIM-1 may be effected by means of its phosphorylation of the well-established cell cycle regulators cdc25 [Mochizuki, T. et al., J. Biol. Chem. 1999, 274, 18659-18666] and/or p21(Cip1/WAF1) [Wang Z. et al. Biochim. Biophys. Acta 2002, 1593, 45-55] or phosphorylation of heterochromatin protein 1, a molecule involved in chromatin structure and transcriptional regulation [Koike, N. et al, FEBS Lett. 2000, 467, 17-21].

Mice deficient for all three PIM genes showed an impaired response to hematopoietic growth factors and demonstrated that PIM proteins are required for efficient proliferation of peripheral T lymphocyes. In particular, it was shown that PIM function is required for efficient cell cycle induction of T cells in response to synergistic T-cell receptor and IL-2 signalling. A large number of interaction partners and substrates of PIM-1 have been identified, suggesting a pivotal role for PIM-1 in cell cycle control, proliferation, as well as in cell survival.

The oncogenic potential of this kinase has been first demonstrated in E μ PIM-1 transgenic mice in which PIM-1 over-expression is targeted to the B-cell lineage which leads to formation of B-cell tumors [van Lohuizen, M. et al.; *Cell* **1989**, *56*, 673-682. Subsequently PIM-1 has been reported to be over-expressed in a number of prostate cancers, erythroleukemias, and several other types of human leukemias [Roh, M. et al.; *Cancer Res.* **2003**, *63*, 8079-8084; Valdman, A. et al; *Prostate* **2004**, *60*, 367-371;

For example, chromosomal translocation of PIM-1 leads to overexpression of PIM-1 in diffuse large cell lymphoma. [Akasaka, H. et al.; *Cancer Res.* **2000**, *60*, 2335-2341]. Furthermore, a number of missense mutations in PIM-1 have been reported in lymphomas of the nervous system and AIDS-induced non-Hodgkins' lymphomas that probably affect PIM-1 kinase activity or stability [Pasqualucci, L. et al, *Nature* **2001**, *412*, 341-346; Montesinos-Rongen, M. et al., *Blood* **2004**, *103*, 1869-1875; Gaidano, G. et al., *Blood* **2003**, *102*, 1833-184]. Thus, the strong

linkage between reported overexpression data and the occurrence of PIM-1 mutations in cancer suggests a dominant role of PIM-1 in tumorigenesis.

Several other protein kinases have been described in the literature, in which the activity and/or elevated activity of such protein kinases have been implicated in diseases such as cancer, in a similar manner to PIM-1, PIM-2 and PIM-3.

There is a constant need to provide alternative and/or more efficacious inhibitors of protein kinases, and particularly inhibitors of PIM-1, PIM-2 and/or PIM-3. Such modulators are expected to offer alternative and/or improved approaches for the management of medical conditions associated with activity and/or elevated activity of PIM-1, PIM-2 and/or PIM-3 protein kinases.

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.

Journal articles *J. Med. Chem.* **2005**, 48, 1367-1383 by Russell *et al* and *J. Med. Chem.* **2005**, Vol 48, No. 23, 7089 by Carling *et al* both disclose *inter alia* triazolophthalazine compounds of potential use as $GABA_A$ receptor agonists, which may be useful therefore as *inter alia* hypnotics (and therefore for treating sleep disorders) and muscle relaxants. However, these documents only relate to fused tricyclic compounds in which one of the cyclic moieties is bridged. Further, there is no mention that the compounds disclosed therein may be useful as kinase inhibitors.

International patent application WO 2005/041971 discloses *inter alia* fused tricyclic compounds that may bind to $\alpha_2\delta$-1 sub-units of Ca channels, and may therefore be useful in the treatment of *inter alia* psychiatric and mood disorders. International patent applications WO 99/025353 and WO 98/04559 disclose various compounds that may act as ligands for $GABA_A$ receptors, WO 98/04560 discloses those that may act as inverse agonists of $GABA_A$ receptors, UK patent GB 2345443 discloses *inter alia* tricyclic compounds, which may be of use in treating premenstrual syndrome, and international patent application WO 2005/041971 discloses various tricyclic compounds for use in the treatment of

bipolar diseases and the like. All of these documents only disclose fused tricyclic compounds that necessarily have oxy substituents, and do not disclose the use of those compounds as kinase inhibitors.

US patent application US 5,011,835 discloses *inter alia* fused tricyclic compounds that may be useful as bronchodilators and antiallergic agents, but does not disclose tricyclic compounds that are substituted with an aromatic substituent, nor does it mention that the compounds may be useful as kinase inhibitors.

European patents EP 0 104 506 and EP 0 029 130 both disclose *inter alia* tricyclic compounds that may be useful as bronchodilators, but does not disclose any that bear an aromatic substituent, nor does it disclose the potential use of those compounds as kinase inhibitors.

Journal article *J. Het. Chem.* **1988**, 25(2), 393-8 by Branko *et al* discloses various tricyclic compounds, including those that contain an aromatic triazolopyridazine bicycle as an integral part of the tricycle. However, this journal article does not disclose that those compounds have a medical use, and further only discloses tricycles in which the 'third' ring fused to the triazolopyridazine bicycle contains an unsaturation (double bond).

European patent applications EP 0 548 923 and EP 0 562 439 disclose *inter alia* tricyclic compounds containing an aromatic imidazopyridazine bicyclic core or a [1,2,4]triazolo[1,5-b]pyridazine core. However, it does not disclose any tricyclic compounds containing a [1,2,4]triazolo[4,3-b]pyridazine core, nor does it mention that any of the compounds disclosed therein may be useful as kinase inhibitors.

European patent application EP 0 620 224 discloses *inter alia* [1,2,4]triazolo[4,3-b]pyridazines, but none in which such a bicycle is a sub-component of a fused tricyclic compound. Nor does this document disclose that the compounds therein may be useful as kinase inhibitors.

US patent application US 2003/0078277 discloses tricyclic compounds that may be useful as a corticotrophin, and therefore of use in the treatment of e.g.

depression. However, this document does not primiarly relate to [1,2,4]triazolo[4,3-b]pyridazines, nor does it disclose that the compounds therein may be useful as kinase inhibitors.

US patent application US 2007/0167453 discloses *inter alia* tricyclic compounds that may be useful as histamine-H3 receptor antagonists. However, this document does not specifically relate to [1,2,4]triazolo[4,3-b]pyridazines substituted with an amino moiety and an aromatic group. Further, this document does not mention that the compounds disclosed therein may be useful as kinase inhibitors.

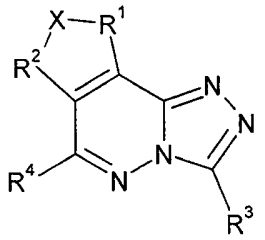
International patent application WO 99/06404 discloses various fused tricyclic compounds containing a triazolopyridazine core, for use as phosphodiesterase 4 inhibitors. However, this document only relates to fused tricyclic compounds in which each of the three rings is aromatic.

International patent application WO 2008/109104 discloses various triazolopyridazines for use as Akt kinase inhibitors, but this document does not disclose any fused tricyclic compounds.

International patent applications WO 2009/060197 and WO 2009/040552 disclose various imidazopyridazine-based and imidazolothiadiazolo-based compounds, for use as certain protein kinase inhibitors. However, these documents do not mention fused tricyclic compounds containing an aromatic triazolopyridazine core. Unpublished European patent application EP 09380202.3 discloses various triazolopyridazines, but none that bear a heteroaryl group directly attached to the bicyclic core.

Disclosure of the Invention

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



I

wherein:

the ring containing R^1, X and R^2 is non-aromatic, in which:

R^1 and R^2 are independently selected from -O-, -S-, -S(O)-, $-S(O)_2-$, $-C(R^6)(R^{6a})-$ and $-N(R^6)-$; and

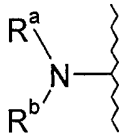
X represents $-CH_2-CH_2-$ optionally substituted by one or more substituents selected from E^2;

each R^6 and R^{6a} independently represents, on each occasion when used herein, H, $-C(O)NHR^{d1}$, $-C(O)R^{d2}$ or R^{d3};

R^{d1}, R^{d2} and R^{d3} independently represent C_{1-12} (e.g. C_{1-6}) alkyl optionally substituted by one or more substituents selected from E^1;

R^3 represents heteroaryl optionally substituted by one or more substituents selected from E^3;

R^4 represents a fragment of formula IA,



IA

R^a and R^b independently represent H, C_{1-12} (e.g. C_{1-8}) alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from Q^1), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from Q^2); or

R^a and R^b are linked together, along with the requisite nitrogen atom to which they are necessarily attached, to form a (first) 3- to 7-membered cyclic group, optionally containing one further heteroatom selected from nitrogen, sulfur and oxygen, and which ring optionally:

(a) is fused to a second ring that is either a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen, sulfur and nitrogen (preferably oxygen and nitrogen), a 3- to 12-membered saturated carbocyclic ring, or an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring (in which the heteroatoms are preferably selected from sulfur and, especially, nitrogen and oxygen);

(b) comprises a linker group $-(C(R^x)_2)_p-$ and/or $-(C(R^x)_2)_r-O-(C(R^x)_2)_s-$ (wherein p is 1 or 2; r is 0 or 1; s is 0 or 1; and each R^x independently represents hydrogen or C_{1-6} alkyl), linking together any two non-adjacent atoms of the first 3- to 7-membered ring (i.e. forming a bridged structure); or

(c) comprises a second ring that is either a 3- to 12-membered saturated carbocyclic ring or a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen and nitrogen, and which second ring is linked together with the first ring *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle),

all of which cyclic groups, defined by the linkage of R^a and R^b, are optionally substituted by one or more substituents selected from =O, $=NOR^{7b}$ and E^4;

each Q^1 and Q^2 independently represents, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-C(=Y)N(R^{10a})-OR^{11c}$, $-OC(=Y)-R^{10a}$, $-OC(=Y)-OR^{10a}$, $-OC(=Y)N(R^{10a})R^{11a}$, $-OS(O)_2OR^{10a}$, $-OP(=Y)(OR^{10a})(OR^{11a})$, $-OP(OR^{10a})(OR^{11a})$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, =S,

=N(R^{10a}) and E^5), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^6);

R^{7b} represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

each R^{11c} independently represents, on each occasion when used herein, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, =S, =N(R^{20}) and E^7), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^8);

each R^{10a}, R^{11a} and R^{12a} independently represent, 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 =O, =S, =N(R^{20}) and E^7), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^8); or

any relevant pair of R^{10a}, R^{11a} and R^{12a} (for example, when attached to the same atom, adjacent atom (i.e. 1,2-relationship) or to atoms that are two atoms apart, i.e. in a 1,3-relationship) may 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. double bonds), and which ring is optionally substituted by one or more substituents selected from =O, =S, =N(R^{20}) and E^9;

each E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 and E^9 independently represents, on each occasion when used herein:

(i) Q^4;

(ii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^5; or

any two E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 or E^9 groups, for example on C_{1-12} alkyl groups or on aryl groups, e.g. when they are attached to the same or adjacent carbon atoms (e.g. two E^3 groups may be attached to adjacent carbon atoms of an aryl group, so forming a fused bicycle), may be linked together to form a 3- to 12-membered ring (in which each of the atoms of the ring may be a carbon atom or a heteroatom), optionally containing one or more (e.g. one to three) unsaturations (e.g. double bonds), and which ring is optionally substituted by one or more substituents selected from =O and J^1;

each Q^4 and Q^5 independently represent, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y)-R^{20}$, $-C(=Y)-OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-C(=Y)N(R^{20})-O-R^{21a}$, $-OC(=Y)-R^{20}$, $-OC(=Y)-OR^{20}$, $-OC(=Y)N(R^{20})R^{21}$, $-OS(O)_2OR^{20}$, $-OP(=Y)(OR^{20})(OR^{21})$, $-OP(OR^{20})(OR^{21})$, $-N(R^{22})C(=Y)R^{21}$, $-N(R^{22})C(=Y)OR^{21}$, $-N(R^{22})C(=Y)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{20})R^{21}$, $-SC(=Y)R^{20}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and J^2), 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, =O, =S, $=NR^{23}$ or =N-CN;

each R^{21a} independently represents, on each occasion when used herein, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from J^4 and =O), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from J^5);

each R^{20}, R^{21}, R^{22} and R^{23} independently represent, 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^4 and =O), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from J^5); 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 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. double bonds), and which ring is optionally substituted by one or more substituents selected from J^6 and =O;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represents, on each occasion when used herein:
(i) Q^7;
(ii) C_{1-6} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^8;

each Q^7 and Q^8 independently represents, on each occasion when used herein: halo, $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2R^{50}$, $-SR^{50}$, $-S(O)R^{50}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

each Y^a independently represents, on each occasion when used herein, =O, =S, $=NR^{53}$ or =N-CN;

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, $-OR^{60}$ 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. double bonds), and which ring is optionally substituted by one or more substituents selected from =O and C_{1-3} alkyl;

R^{60}, R^{61} and R^{62} 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. Specific salts that may be mentioned include carboxylic acid salts, such as formic acid salts.

By "pharmaceutically acceptable ester, amide, solvate or salt thereof", we include salts of pharmaceutically acceptable esters or amides, and solvates of pharmaceutically acceptable esters, amides or salts. 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 the invention may be formed from corresponding compounds that have an appropriate group, for example an acid group, converted to the appropriate ester or amide. For example, pharmaceutically acceptable esters (of carboxylic acids of compounds of the invention) 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 of compounds of the invention) that may be mentioned include those of the formula $-C(O)N(R^{z1})R^{z2}$, in which R^{z1} and R^{z2} independently

represent optionally substituted C_{1-6} alkyl, C_{5-10} aryl, or C_{5-10} aryl-C_{1-6} alkylene-. 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.

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, sulfhydryl, 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, sulfhydryl, 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. I-92, Elesevier, New York-Oxford (1985).

As stated above, 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.

Prodrugs of compounds of the invention that may be mentioned also include salts of compounds of the invention. For instance when R^3 represents a pyridine ring, this also includes quaternary salts for instance those containing the following sub-group $-N^+-R^{xx}$ (wherein the nitrogen atom is the atom that is an integral part of the pyridine ring) associated with an anion (e.g. halide, such as Cl^-) and in which R^{xx} may represent optionally substituted alkyl (e.g. C_{1-6} alkyl, such as methyl, optionally substituted by one or more (e.g. one) substituent(s) selected from $-O-(O)-R^{yy}$, in which R^{yy} represents aryl/heteroaryl (optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy) or C_{1-6} alkyl (optionally substituted by one or more substituents selected from halo and C_{1-6} alkoxy)). Such quaternary salts include those that may be disclosed in e.g. *J. Med. Chem.,* 1994, 37 (26), 4423-4429 and *Bioorg. Med. Chem. Lett.* 15 (2005) 2491-2494.

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".

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 "tautomeric 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 , ^{13}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}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-l4 (^{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, ^{11}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 specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-

chain, and/or cyclic (so forming a C_{3-q}-cycloalkyl group). Such cycloalkyl groups may be monocyclic or bicyclic and may further be bridged. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group).

Unless otherwise stated, the term C_{1-q} alkylene (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 saturated or unsaturated (so forming, for example, an alkenylene or alkynylene linker group). Such C_{1-q} alkylene groups may be branched (if sufficient number of atoms), but are preferably straight-chained.

C_{3-q} cycloalkyl groups (where q is the upper limit of the range) that may be specifically 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 bonds (forming for example a cycloalkenyl 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.

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

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl 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 from 3 to 20 (i.e. between 3 and 20 (e.g. between three and ten, e.g between 3 and 8, such as 5- to 8-)). Such heterocycloalkyl groups may also be bridged. Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{3-q} heterocycloalkenyl (where q is the upper limit of the range) group. C_{3-q} heterocycloalkyl groups that may be mentioned include 7-aza-spiro[3.5]non-2-ylamine, 2,9-diaza-spiro[5.5]undecane, 1-oxa-4,9-

diaza-spiro[5.5]undecane, 8-diaza-spiro[4.5]decan-1-one, 2,8-diaza-spiro[4.5]decan-3-one and, particularly, 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, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), 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, non-aromatic pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heterocycloalkyl 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. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form. Heterocycloalkyl mentioned herein may be stated to be specifically monocyclic or bicyclic.

For the avoidance of doubt, the term "bicyclic" (e.g. when employed in the context of heterocycloalkyl 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 heterocycloalkyl 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 C_{6-20}, such as C_{6-12} (e.g. C_{6-10}) aryl groups. Such groups may be monocyclic, bicyclic or tricyclic and have from 6 to 12 (such as between 6 and 12 (e.g. 6 and 10)) ring carbon atoms, in which at least one ring is aromatic. C_{6-10} aryl groups include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydronaphthyl. The point of attachment of aryl groups is *via* any atom of an aromatic ring.

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 from 5 to 20 (such as between 5 and 20) members (e.g. from 5 to 10 (such as between 5 and 10)) 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). The point of attachment of such heteroaryl groups (e.g. monocyclic and polycyclic heteroaryl groups) is *via* any atom of an aromatic ring of that heteroaryl group. Heteroaryl groups that may be mentioned include azaindolyl or, particularly, 3,4-dihydro-1*H*-isoquinolinyl, 1,3-dihydroisoindolyl, 1,3-dihydroisoindolyl (e.g. 3,4-dihydro-1*H*-isoquinolin-2-yl, 1,3-dihydroisoindol-2-yl, 1,3-dihydroisoindol-2-yl; i.e. heteroaryl groups that are linked *via* a non-aromatic ring), or, preferably, acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), benzothiazolyl, benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiaziolyl, 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, thiophenetyl, 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. 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. Heteroaryl groups mentioned herein may be stated to be specifically monocyclic or bicyclic. When heteroaryl groups are polycyclic in which there is a non-aromatic ring present, then that non-aromatic ring may be substituted by one or more =O group.

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 sulfur.

For the avoidance of doubt, where it is stated herein that a group (e.g. a C_{1-12} alkyl group) may be substituted by one or more substituents (e.g. selected from E^5), then those substituents (e.g. defined by E^5) are independent of one another. That is, such groups may be substituted with the same substituent (e.g. defined by E^5) or different substituents (defined by E^5).

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 e.g. Q^1 or Q^2, or, E^1 to E^9 (such as E^6) substituent present, then those Q^1 or Q^2, or, E^1 to E^9 (e.g. E^6) substituents may be the same or different. Further, in the case where there are e.g. Q^1 or Q^2, or, E^1 to E^9 (such as E^6) substituents present, in which one represents $-OR^{10a}$ (or e.g. $-OR^{20}$, as appropriate) and the other represents $-C(O)_2R^{10a}$ (or e.g. $-C(O)_2R^{20}$, as appropriate), then those R^{10a} or R^{20} groups are not to be regarded as being interdependent. Also, when e.g. there are two $-OR^{10a}$ substituents present, then those $-OR^{10a}$ groups may be the same or different (i.e. each R^{10a} group may be the same or different).

For the avoidance of doubt, when a term such as "*E^1 to E^9*" is employed herein, this will be understood by the skilled person to mean E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 and E^9, inclusively.

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.

Preferred compounds of the invention include those in which:
R^1 does not represent -N(R^6)- (e.g. R^1 is selected from -O-, -S-, -S(O)-, -S(O)$_2$- and -C(R^6)(R^{6a})-), especially when R^2 represents -C(R^6)(R^{6a})-;
when R^3 represents a substituted heteroaryl group (i.e. substituted by one or more E^3 substituents), then that/those E^3 substituent(s) are preferably not located at the position *ortho* to the point of attachment of the R^3 group (to the requisite triazolopyridazine bicycle of formula I).

Further preferred compounds of the invention include those in which R^1 and R^2 each independently represents -O- or -N(R^6)-.

Preferred heteroaryl groups include monocyclic heteroaryl groups and bicyclic heteroaryl groups (but in this case, bicyclic heteroaryl groups must be attached to the requisite triazolopyridazine of formula I *via* a heteroaryl ring i.e. it is essential that the first ring attached to the requisite tricyclic core is a heteroaryl ring, but the second ring fused to the first may be either a monocyclic aryl or heteroaryl group) and hence preferred groups that R^3 may represent include the following groups (which may be unsubstituted or substituted): azaindolyl or, particularly, pyrrole, pyrazole, triazole, tetrazole, thiazole, isothiazole, oxazole, isoxazole, isoindole, 1,3-dihydro-indol-2-one, pyridine-2-one, pyridine, pyridine-3-ol, imidazole,1H-indazole, 1H-indole, indolin-2-one, 1-(indolin-1-yl)ethanone, pyrimidine,

pyridazine, pyrazine and isatin groups, 1H-benzo[d][1,2,3]triazole, 1H-pyrazolo [3,4-b]pyridine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-benzo[d]imidazole, 1H-benzo[d]imidazol-2(3H)-one, 1H-pyrazolo[3,4-c]pyridine, 1H-pyrazolo[4,3-d]pyrimidine, 5H-pyrrolo[3,2-d]pyrimidine, 2-amino-1H-purin-6(9H)-one, quinoline, quinazoline, quinoxaline, isoquinoline, isoquinolin-1(2H)-one, 3,4-dihydroisoquinolin-1(2H)-one, 3,4-dihydroquinolin-2(1H)-one, quinazolin-2(1H)-one, quinoxalin-2(1H)-one, 1,8-napthyridine, pyrido[3,4-d]pyrimidine, and pyrido[3,2-b]pyrazine, 1,3-dihydro benzimidazolone, benzimidazole, benzothiazole and benzothiadiazole (provided that when R^3 is a bicyclic heteroaryl group, it is always linked to the requisite triazolopyridazine core with a first heteroaryl ring).

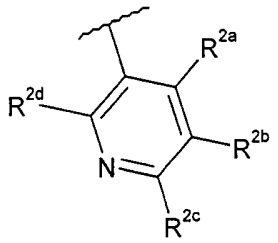
Preferred R^3 groups include those in which:
when R^3 represents monocyclic heteroaryl (e.g. a 5- or 6-membered heteroaryl group), then that group preferably contains 1 oxygen or sulfur atom or, particularly, 1, 2, 3 or 4 nitrogen atoms, and optionally 1 or 2 additional heteroatoms selected from oxygen and sulfur, and which heteroaryl group is optionally substituted by one or more substituents selected from E^3;
when R^3 represents bicyclic heteroaryl (e.g. a 8-, 9- or 10-membered heteroaryl group), then that group preferably consists of a 5- or 6-membered ring fused to another 5- or 6-membered ring (in which the first ring, attached to the requisite tricycle of formula I, contains one to four heteroatoms and the second ring, fused to the first, may contain one to four (e.g. one to three) heteroatoms), in which the total number of heteroatoms is preferably one to four, and which ring (i.e. bicyclic heteroaryl group) is optionally substituted by one or more (e.g. one or two) substituent(s) selected from E^3 (and, if there is a non-aromatic ring present in the bicyclic heteroaryl group, then such a group may also be substituted by one or more (e.g. one) =O groups).

Further preferred R^3 groups include those in which R^3 represents azaindolyl, benzofuranyl, benzothienyl, furanyl, isoquinolinyl, pyrazinyl, pyridyl, quinolinyl, thiazolyl or thienyl.

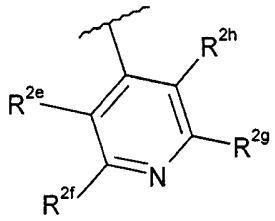
Still further preferred R^3 groups include those in which:

R^3 represents heteroaryl (e.g. a monocyclic 5- or, preferably 6-membered group, preferably containing one or two (e.g. one) nitrogen heteroatom(s), so forming e.g. pyridyl such as 3-pyridyl) substituted by one or two E^3 substituents;

R^3 is represented by a moiety of formula IB or IC:



IB



IC

in which R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f}, R^{2g} and R^{2h} independently represent hydrogen or a substituent selected from E^3;

one or two of R^{2a} to R^{2d} (e.g. R^{2b} and/or R^{2c}) represent a substituent selected from E^3 (and the other two or three represent hydrogen);

one or two (e.g. one) of R^{2e} to R^{2h} (e.g. R^{2g} and/or R^{2h}, preferably only R^{2g}) represent a substituent selected from E^3 (and the other two or three represent hydrogen);

E^3 represents C_{1-3} alkyl (optionally substituted by Q^5; so forming e.g. a $-CF_3$ group), or, E^3 represents Q^4;

Q^4 represents halo (e.g. fluoro), $-N(R^{20})R^{21}$ or $-OR^{20}$;

Q^5 represents halo (e.g. fluoro);

R^{20} and R^{21} independently represent hydrogen or C_{1-2} alkyl (e.g. methyl), or, may be linked together to form a morpholinyl group.

Preferred monocyclic heteroaryl groups that R^a or R^b or Q^1, Q^2, Q^4 or Q^5 (if applicable) may independently represent include 5- or 6-membered rings, containing one to three (e.g. one or two) heteroatoms selected from sulfur, oxygen and nitrogen. Preferred bicyclic heteroaryl groups that R^3 (provided that it is attached to be requisite bicycle of formula I *via* a heteroaryl ring of the bicycle), R^a or R^b, or Q^1, Q^2, Q^4 or Q^5 may represent include 8- to 12- (e.g. 9- or 10-) membered rings containing one to four (e.g. one to three, or, preferably, one or two) heteroatoms selected from sulfur, oxygen and nitrogen (e.g. an indolyl group). Further, bicyclic rings may consist of benzene rings fused with a monocyclic heteroaryl group (as hereinbefore defined), e.g. a 6- or, preferably 5-

membered monocyclic heteroaryl group optionally containing two, or, preferably, one heteroatom selected from sulfur, oxygen and nitrogen.

Preferred heterocycloalkyl groups that R^a or R^b or Q^1, Q^2, Q^4 or Q^5 may independently represent include 4- to 8-membered (e.g. 5- or 6-membered) heterocycloalkyl groups, which groups preferably contain one or two heteroatoms (e.g. sulfur or, preferably, nitrogen and/or oxygen heteroatoms), so forming for example, an optionally substituted 7-aza-spiro[3.5]non-2-ylamine, 2,9-diaza-spiro[5.5]undecane, 1-oxa-4,9-diaza-spiro[5.5]undecane, 8-diaza-spiro[4.5]decan-1-one, 2,8-diaza-spiro[4.5]decan-3-one group or, particularly, a pyrrolidinyl, piperidinyl, morpholinyl or tetrahydropyranyl group.

Preferred C_{3-6} cycloalkyl groups that R^a or R^b or Q^1, Q^2, Q^4 or Q^5 may independently represent include optionally substituted C_{3-8} (e.g. C_{3-6}) cycloalkyl groups, such as cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl.

Further preferred compounds of the invention include those in which:
each R^{10a}, R^{11a} and R^{12a} independently represent, on each occasion when used herein, hydrogen or C_{1-12} (e.g. C_{1-6}) alkyl (which latter group is optionally substituted by one or more substituents selected from =O and E^7); or
any relevant pair of R^{10a}, R^{11a} and R^{12a} may be linked together as defined herein (although they are preferably not linked);
R^{11c} represents C_{1-12} (e.g. C_{1-6}) alkyl (which latter group is optionally substituted by one or more substituents selected from =O and E^7);
each of E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 and E^9 independently represent, on each occasion when used herein, Q^4 or C_{1-6} (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from =O and Q^5;
each Q^4 and Q^5 independently represents phenyl (optionally substituted by one or more fluoro atoms) or, particularly, halo, -CN, $-NO_2$, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y)-R^{20}$, $-C(=Y)-OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-N(R^{22})C(=Y)R^{21}$, $-N(R^{22})C(=Y)OR^{21}$, $-N(R^{22})C(=Y)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{20})R^{21}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms (and each Q^5 more preferably represents halo, such as fluoro);
any two E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 and/or E^9 groups may be linked together (e.g. any two E^3 substituents may also be linked togethe

example when attached to the same or, preferably, adjacent carbon atoms), but (e.g. any two E^1, E^2, E^4, E^5, E^6, E^7, E^8 and/or E^9) are preferably not linked together;

each R^{20}, R^{21}, R^{22} and R^{23} independently represent, on each occasion when used herein, aryl (e.g. phenyl; preferably unsubstituted, but which may be substituted by one to three J^5 groups) or, more preferably, hydrogen or C_{1-6} (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from =O and J^4; or

any pair of R^{20} and R^{21}, may, when attached to the same nitrogen atom, be linked together to form a 4- to 8-membered (e.g. 5- or 6-membered) ring, optionally containing one further heteroatom selected from nitrogen and oxygen, optionally containing one double bond, and which ring is optionally substituted by one or more substituents selected from J^6 and =O;

R^{21a} represents C_{1-6} (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from =O and J^4;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represents C_{1-6} alkyl (e.g. acyclic C_{1-4} alkyl or C_{3-6} cycloalkyl) optionally substituted by one or more substituents selected from =O and Q^8, or, such groups independently represent a substituent selected from Q^7;

each Q^7 and Q^8 independently represents a substituent selected from halo (e.g. fluoro), $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2R^{50}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

each R^{50}, R^{51}, R^{52} and R^{53} 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;

when any relevant pair of R^{50}, R^{51} and R^{52} are linked together, then those pairs that are attached to the same nitrogen atom may be linked together (i.e. any pair of R^{50} and R^{51}), and the ring so formed is preferably a 5- or 6-membered ring, optionally containing one further nitrogen or oxygen heteroatom, and which ring is optionally substituted by one or more substituents selected from =O and C_{1-3} alkyl (e.g. methyl);

R^{60}, R^{61} and R^{62} independently represent hydrogen or C_{1-3} (e.g. C_{1-2}) alkyl optionally substituted by one or more fluoro atoms.

Preferred optional substituents on R^3, R^4 and the R^1, R^2 and X-containing ring (if applicable) include:

=O (unless the group is aromatic);

-CN;

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

C_{1-6} (e.g. 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, *t*-butyl or, preferably, *n*-butyl or methyl), all of which are optionally substituted with one or more =O, $-N(R^{20})R^{21}$ or, particularly, halo (e.g. fluoro) groups (so forming, for example, fluoromethyl, difluoromethyl or, preferably, trifluoromethyl) or substituted with an aryl, heteroaryl or heterocycloalkyl group (which themselves may be substituted with one or more $-OR^{z1}$, $-C(O)R^{z2}$, $-C(O)OR^{z3}$, $-N(R^{z4})R^{z5}$, $-S(O)_2R^{z6}$, $-S(O)_2N(R^{z7})R^{z8}$; $-N(R^{z9})-C(O)-R^{z10}$, $-C(O)-N(R^{z11})R^{z12}$, $-N(R^{z9})-C(O)-N(R^{z10})$, $-N(R^{z9})-S(O)_2-R^{z10}$ and/or $-N(R^{z9})-S(O)_2-N(R^{z10})R^{z11}$ substituents);

aryl (e.g. phenyl) (e.g. which substitutent may also be present on an alkyl group, thereby forming e.g. a benzyl group) optionally substituted by one or more J^3 substituents;

$-OR^{z1}$;

$-C(O)R^{z2}$;

$-C(O)OR^{z3}$;

$-N(R^{z4})R^{z5}$;

$-S(O)_2R^{z6}$;

$-S(O)_2N(R^{z7})R^{z8}$;

$-N(R^{z9})-C(O)-R^{z10}$;

$-C(O)-N(R^{z11})R^{z12}$;

$-N(R^{z9})-C(O)-N(R^{z10})R^{z11}$;

$-N(R^{z9})-S(O)_2-R^{z10}$;

$-N(R^{z9})-S(O)_2-N(R^{z10})R^{z11}$;

wherein each R^{z1} to R^{z12} independently represents, on each occasion when used herein, H or C_{1-4} alkyl (e.g. ethyl, *n*-propyl, *t*-butyl or, preferably, *n*-butyl, methyl, isopropyl or cyclopropylmethyl (i.e. a part cyclic alkyl group)) optionally substituted by one or more halo (e.g. fluoro) groups (so forming e.g. a trifluoromethyl group). Further, any two R^z groups (e.g. R^{z4} and R^{z5}), when attached to the same nitrogen heteroatom may also be linked together to form a

ring such as one hereinbefore defined in respect of corresponding linkage of R^{10a} and R^{11a} groups.

Preferred compounds of the invention include those in which:

each R^{10a}, R^{11a} and R^{12a} independently represent phenyl (optionally substituted by one or more E^8 substituents), preferably, heterocycloalkyl (optionally substituted by one or more =O and/or E^7 substituents) and, more preferably, hydrogen or C_{1-12} (e.g. C_{1-6}) alkyl (optionally substituted by one or more =O and/or E^7 substituents), or any pair of R^{10a}, R^{11a} and R^{12a} (e.g. any pair of R^{10a} and R^{11a} when attached to the same nitrogen atom) may be linked together to form a 4- to 10-membered (e.g. a 4- to 6-membered monocyclic) ring, optionally substituted by one or more substituents selected from =O and E^9;

each E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 and E^9 independently represents C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^5, or, each E^1 to E^9 independently represents Q^4; or, any two E^1 to E^9 substituents (e.g. when attached to the same or adjacent atoms) may be linked together to form a 3- to 8-membered ring, optionally containing one to three double bonds, one to three heteroatoms, and which ring may be substituted by one or more substituents selected from =O and J^1 (but preferably any two E^1 to E^9 substituents are not linked together);

each R^{20}, R^{21}, R^{22} and R^{23} (e.g. each R^{20} and R^{21}) independently represents heteroaryl, preferably, aryl (e.g. phenyl) (which latter two groups are optionally substituted by one or more substituents selected from J^5), or, more preferably, hydrogen or C_{1-6} (e.g. C_{1-4}) alkyl optionally substituted by one or more substituents selected from =O and J^4; or

any relevant pair of R^{20}, R^{21} and R^{22} (e.g. R^{20} and R^{21}) may (e.g. when both are attached to the same nitrogen atom) may be linked together to form a 3- to 8- (e.g. 4- to 8-) membered ring, optionally containing a further heteroatom, and optionally substituted by one or more substituents selected from =O and J^6;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represents C_{1-6} alkyl (e.g. C_{1-4} acyclic alkyl or C_{3-5} cycloalkyl) optionally substituted by one or more substituents selected from Q^8, or, J^1 to J^6 more preferably represent a substituent selected from Q^7;

each R^{50}, R^{51}, R^{52} and R^{53} independently represents hydrogen or C_{1-6} (e.g. C_{1-4}) alkyl optionally substituted by one or more fluoro atoms;

each R^{60}, R^{61} and R^{62} independently represents hydrogen or C_{1-2} alkyl (e.g. methyl).

More preferred compounds of the invention include those in which:

R^{d1}, R^{d2} and R^{d3} independently represent C_{1-6} (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from E^1, but which is preferably unsubstituted;

X represents unsubstituted $-CH_2-CH_2-$;

when R^a and R^b are linked together, they may represent a 3- to 6-membered ring (e.g. a 5- or, preferably, 6-membered ring), optionally containing one further heteroatom selected from nitrogen and oxygen, which ring may be: (a) fused to another saturated 5- or 6-membered carbocyclic or heterocyclic ring, in which the latter contains one to four heteroatoms preferably selected from nitrogen and oxygen; (b) comprises a $-(CH_2)_{n1}-$, -O- or $-CH_2-O-CH_2-$ linker group linking any two non-adjacent atoms (n1 represents 1 or 2); or (c) comprises a further 4- to 6-membered saturated carbocyclic or heterocyclic ring, in which the latter contains one or two heteroatoms preferably selected from nitrogen and oxygen, which second ring is linked to the first *via* a single atom;

Q^4 and Q^5 independently represent $-S(O)_2R^{20}$ or , particularly, halo (e.g. chloro or, particularly, fluoro), $-OR^{20}$, $-N(R^{20})R^{21}$, $-C(=Y)R^{20}$, $-C(=Y)OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-N(R^{22})C(=Y)R^{21}$, $-NR^{22}S(O)_2R^{20}$, heterocycloalkyl, aryl, heteroaryl (which latter three groups are optionally substituted with one or more substitutents selected from J^2 or J^3, as appropriate) and/or C_{1-6} alkyl (e.g. C_{1-3} alkyl) optionally substituted by one or more fluoro atoms;

each Y represents, on each occasion when used herein, =S, or preferably =O;

each R^{20}, R^{21}, R^{22} and R^{23} (e.g. each R^{20} and R^{21}) independently represents hydrogen or C_{1-4} (e.g. C_{1-3}) alkyl (e.g. a C_{1-4} acyclic alkyl group or a part cyclic C_4 group) optionally substituted (but preferably unsubstituted) by one or more (e.g. one) J^4 substituent(s); or

any relevant pair of R^{20}, R^{21} and R^{22} (e.g. R^{20} and R^{21}) may (e.g. when both are attached to the same nitrogen atom) be linked together to form a 5- or, preferably, a 6-membered ring, optionally containing a further heteroatom (preferably selected from nitrogen and oxygen), which ring is preferably saturated, and optionally substituted by one or more substituents selected from =O and J^6;

R^{22} represents C_{1-3} alkyl or hydrogen;

R^{11c} and R^{21a} independently represent C_{1-3} alkyl;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represent a substituent selected from Q^7, or J^1 to J^6 independently represent C_{1-6} alkyl (e.g. C_{1-4} alkyl);

each Q^7 and Q^8 independently represent halo (e.g. fluoro), $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms (and, more preferably, Q^7 and Q^8 independently represent halo (e.g. fluoro), $-N(R^{50})R^{51}$, $-OR^{50}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms);

each Y^a independently represents =S or, preferably, =O;

each R^{50}, R^{51}, R^{52} and R^{53} independently represents H or C_{1-4} alkyl (e.g. *t*Bu, Me).

Preferred compounds of the invention include those in which:

R^1 and R^2 independently represent $-C(R^6)(R^{6a})-$, preferably, $-S(O)-$, $-S(O)_2-$, and, more preferably, -O-, -S- or $-N(R^6)-$;

each R^6 and R^{6a} independently represents, on each occasion when used herein, H or R^{d3};

R^{d3} represents C_{1-6} (e.g. C_{1-4}) alkyl;

X represents optionally substituted (i.e. by E^2) $-CH_2-CH_2-$;

R^3 represents a 5- or 6-membered monocyclic heteroaryl group (e.g. pyridyl) or a 9- or 10-membered heteroaryl group, which heteroaryl groups are optionally substituted by one or more (e.g. one to three) substituent(s) selected from E^3;

R^a and R^b independently represents H, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more (one to three) substituent(s) selected from Q^1); or R^a and R^b may be linked together to form a 3- to 6-membered ring (e.g. a 5- or, preferably, 6-membered ring), preferably containing no further heteroatoms, which ring may be linked to a further 4- to 6-membered ring (e.g. 4-membered ring) *via* a single atom (i.e. forming a spiro cycle), all of which cyclic groups are optionally substituted by one or more substituents selected from E^4;

Q^1 and Q^2 independently represent halo, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents

selected from =O, =S, =N(R^{10a}) and E^5), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^6);

R^{10a}, R^{11a} and R^{12a} independently represent H or C_{1-6} (e.g. C_{1-4}) alkyl optionally substituted by one or more groups selected from =O and E^7;

R^{11c} represents C_{1-6} (e.g. C_{1-4}) alkyl optionally substituted by one or more groups selected from =O and E^7;

E^1 to E^9 independently represent Q^4 or C_{1-6} (e.g. C_{1-3}, such as methyl) alkyl optionally substituted by one or more Q^5 substituents; or

any two E^1 to E^9 substituents (e.g. two E^3 substituents) when attached to adjacent carbon atoms may be linked together to form a 3- to 8-membered (e.g. 5- or 6-membered) ring (preferably containing one to three double bonds, e.g. forming an aromatic ring), preferably containing one to three (e.g. one) heteroatom(s), and which ring is optionally substituted by one or more substituents selected from =O and, preferably, J^1 (when the ring is aromatic, then it may only be substituted by one or more J^1 substituents);

Q^4 and Q^5 independently represent $-S(O)_2R^{20}$, phenyl (optionally substituted by one or more J^3 substituents) or, particularly, C_{1-6} alkyl (optionally substituted by one or more =O and/or J^2 substituents, but preferably, unsubstituted) or, preferably, halo, -CN, $-OR^{20}$, $-N(R^{20})R^{21}$, $-C(=Y)R^{20}$, $-C(=Y)OR^{20}$ or $-N(R^{22})C(=Y)R^{21}$;

Y represents =S or, preferably, =O;

R^{20} and R^{21} independently represent hydrogen, C_{1-4} alkyl, which latter group is optionally substituted by one or more (e.g. one) substituent(s) selected from J^4;

when there is a $-N(R^{20})R^{21}$ moiety present, then one of R^{20} and R^{21} represents hydrogen, and the other represents hydrogen or C_{1-4} alkyl (e.g. methyl, ethyl or isopropyl), which latter group is optionally substituted by one or more (e.g. one) substituent(s) selected from J^4;

R^{22} and R^{23} independently represent hydrogen or C_{1-3} alkyl (e.g. methyl);

R^{21a} represents C_{1-3} alkyl (e.g. methyl);

J^3 represents Q^7;

J^4 represents Q^7 or C_{1-6} (e.g. C_{1-3}) alkyl, which is preferably unsubstituted;

Q^7 represents halo (e.g. fluoro).

Other preferred compounds of the invention include those in which:

Q^1 and Q^2 independently represent aryl (such as phenyl) (optionally substituted by one or more E^6 substituents) or, particularly, halo, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2R^{10a}$, C_{1-6} alkyl or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and E^5);

Q^4 and Q^5 independently represent phenyl (optionally substituted by one or more J^3 substituents) or, particularly, halo (e.g. fluoro or chloro), -CN, $-OR^{20}$, $-N(R^{20})R^{21}$, $-C(=Y)R^{20}$, $-C(=Y)OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-N(R^{22})C(=Y)R^{21}$, $-N(R^{22})C(=Y)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2R^{20}$ or C_{1-6} alkyl optionally substituted by one or more substituents selected from =O and J^2 (but preferably unsubstituted);

Q^7 and Q^8 independently represent halo, $-N(R^{50})R^{51}$, $-OR^{50}$ or C_{1-3} alkyl optionally substituted by one or more fluoro atoms.

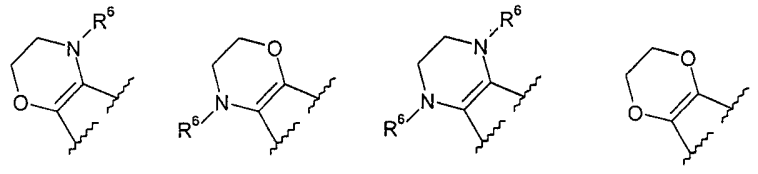
Further preferred compounds of the invention include those in which:

Q^1 and Q^2 independently represent aryl (such as phenyl) (optionally substituted by one or more E^6 substituents) or, particularly, halo, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-S(O)_2-R^{10a}$, C_{1-6} alkyl or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and E^5);

Q^4 and Q^5 independently represent phenyl (optionally substituted by one or more J^3 substituents) or, particularly, halo (e.g. fluoro or chloro), -CN, $-OR^{20}$, $-N(R^{20})R^{21}$, $-C(=Y)R^{20}$, $-C(=Y)OR^{20}$, $-N(R^{22})C(=Y)R^{21}$, $-S(O)_2R^{20}$ or C_{1-6} alkyl optionally substituted by one or more substituents selected from =O and J^2 (e.g. by one or more fluoro atoms, but preferably unsubstituted);

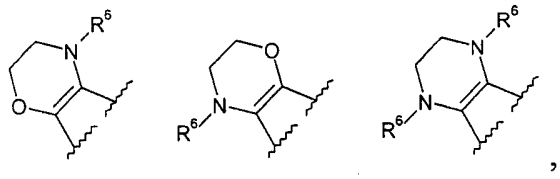
Q^7 and Q^8 independently represent halo or C_{1-3} alkyl optionally substituted by one or more fluoro atoms.

Preferred R^1, R^2 and X-containing rings of the compounds of the invention include:



wherein the squiggly lines represent the point of attachment to the requisite triazolopyridazine of the compound of formula I, and R^6 is as defined herein (the rings containing at least one oxygen atom are particularly preferred).

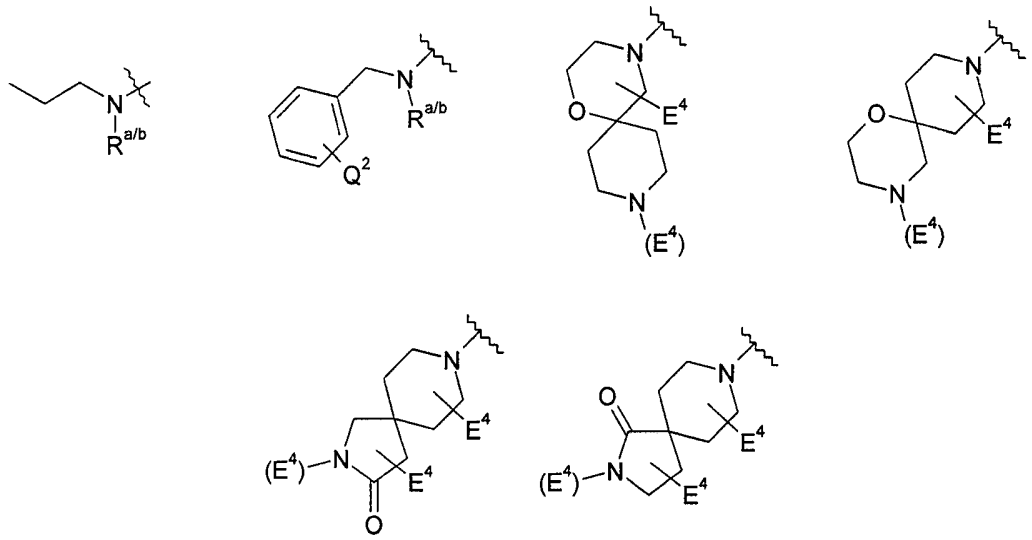
Preferred R^1, R^2 and X-containing rings of the compounds of the invention include:



wherein the squiggly lines represent the point of attachment to the requisite triazolopyridazine of the compound of formula I, and R^6 is as defined herein (the morpholinyl rings are particularly preferred).

Preferred R^3 groups of the compounds of the invention include optionally substituted benzofuranyl (such as benzofuran-2-yl), optionally substituted benzothienyl (such as benzothien-2-yl, 4-CF_3-benzothien-2-yl and 6-CF_3-benzothien-2-yl), optionally substituted furanyl (such as furan-3-yl), optionally substituted pyrazinyl (such as 2-NH_2-5-(4-fluorophenyl)-pyrazin-3-yl), optionally substituted thiazolyl (such as 4-CF_3-thiazol-2-yl), optionally substituted thienyl (such as 2-(C(O)CH_3)-thien-4-yl and 2-CH_3-thienyl-3-yl), or, particularly, optionally substituted pyridyl (such as 4-pyridyl and 3-pyridyl; e.g. 2-NH_2-4-pyridyl, 2-(4-fluorophenyl)-6-pyridyl or, particularly, 2-CF_3-4-pyridyl, 2-OCH_3-4-pyridyl, 2-OH-5-pyridyl, 2-OCH_3-5-pyridyl, 3-CF_3-5-pyridyl, 2-methyl-4-pyridyl, 3-pyridyl, 3-CF_3-5-pyridyl, 3-fluoro-5-pyridyl, 2-morpholin-4-yl-4-pyridyl, 2-chloro-4-pyridyl, 4-pyridyl, 4-CH_3-5-pyridyl, 2-CF_3-5-pyridyl, 2-NH_2-5-pyridyl and 2-fluoro-4-pyridyl), optionally substituted isoquinolinyl (e.g. 3-isoquinolinyl) and optionally substituted azaindolyl (e.g. 7-azaindol-4-yl), or the various tautomers thereof (e.g. 2-OH-pyridyl may exist as 5-pyridin-2-one). Particularly preferred R^3 groups include optionally substituted pyridyl.

Preferred R^4 groups of compounds of the invention include:



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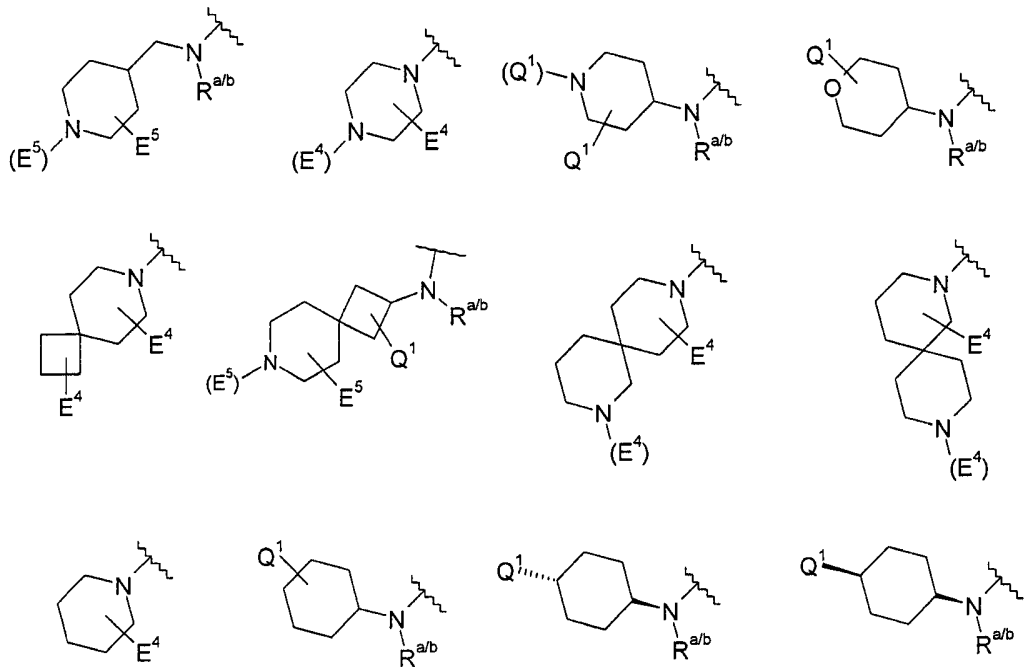
or, particularly,



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wherein the squiggly line represents the point of attachment to the requisite triazolopyridazine of the compound of formula I, $R^{a/b}$ represents R^a or R^b, and the other integers (e.g. E^4, E^5 and Q^1; which are optional substituents that may be attached to specific atoms, or, may be depicted as 'floating', in which case the

relevant group is optionally substituted by one or more of those $E^5/Q^1/E^4$ substituents) are as defined herein. The depiction of a substituent in brackets signifies that that substituent is optionally present, and may therefore be absent (i.e. N-(E^5) may signify N-E^5 or N-H).

More preferred compounds of the invention include those in which:

each of R^1 and R^2 independently represents -O- or, particularly, one of R^1 and R^2 represents -N(R^6)- and the other represents -O- or -N(R^6)-;

R^6 represents H or R^{d3};

R^{d3} represents C_{1-3} alkyl (e.g. methyl or ethyl);

X represents unsubstituted -CH_2-CH_2-;

one of R^a and R^b represents H or C_{1-3} alkyl (e.g. methyl) and the other represents a substituent other than hydrogen (or the foregoing groups);

when either of R^a and R^b represents a substituent (other than hydrogen; see above), then it may be:

(i) C_{1-6} alkyl (e.g. C_{1-3} acyclic alkyl or C_{3-6} cycloalkyl) (e.g. methyl, ethyl, *n*-propyl, cyclobutyl or cyclohexyl) optionally substituted by one or more substituents (and preferably substituted by at least one (e.g. one) substituent) selected from Q^1;

(ii) heterocycloalkyl (e.g. a 5- to 11-membered heterocycloalkyl group containing one or two (e.g. one) heteroatom(s) in which one is preferably nitrogen or oxygen, which 5- to 11-membered heterocycloalkyl group may be formed of two rings linked together *via* a single atom (i.e. forming a spiro cycle, which is preferably a [3.5], [5.3] or [5.5] spiro-cycle) or, particularly, a 5- or, preferably 6-membered heterocycloalkyl group containing one or two (e.g. one) heteroatom(s) in which one is preferably nitrogen or oxygen, so forming e.g. piperidinyl or tetrahydropyranyl, such as 4-piperidinyl or 4-tetrahydropyranyl) and which heterocycloalkyl group is optionally substituted by one or more substituents (e.g. one; which substituent(s) may be attached to a nitrogen heteroatom) selected from Q^1; or

R^a and R^b may be linked together to form a 3- to 6-membered ring (e.g. a 5- or, preferably, a 4- or 6-membered ring), preferably containing one or no further heteroatoms, which ring may be linked to a further 4- to 6-membered ring (e.g. a 4- or 6-membered ring) *via* a single atom (i.e. forming a spiro cycle, which is preferably a [4.5], [5.4], [5.5] or, particularly, a [3.5] or [5.3] spiro-cycle), all of

which cyclic groups are optionally substituted by one or more substituents selected from =O and, particularly, E^4;

Q^1 may represent (for instance, when it is attached to a heterocycloalkyl group) C_{1-6} (e.g. C_{1-3}) alkyl (e.g. methyl) (which alkyl group is optionally substituted by one or more substituents selected from E^5), $-N(R^{10a})R^{11a}$ (e.g. $-N(CH_3)_2$), $-OR^{10a}$ (e.g. -OH) or $-S(O)_2R^{10a}$;

Q^1 may represent (for instance, when it is a substituent on an alkyl group): $-N(R^{10a})R^{11a}$; C_{1-6} alkyl (e.g. C_{3-6} cycloalkyl, such as cyclopropyl or cyclohexyl) optionally substituted by one or more (e.g. two or, preferably, one) substituents selected from =O and, preferably E^5; heterocycloalkyl (e.g. a 5- or, preferably 6-membered heterocycloalkyl group containing one or more (e.g. one or two) heteroatom(s) in which one is preferably nitrogen, so forming e.g. a piperidinyl, morpholinyl or piperazinyl group, such as a 4-piperidinyl, 4-morpholinyl or 1-piperazinyl, which heterocycloalkyl groups may be attached to a single cabon atom of a C_{3-6} cycloalkyl group, thereby forming a spiro-cycle) (which heterocycloalkyl group is optionally substituted by one or more (e.g. one) substituent (which may be on a nitrogen heteroatom) selected from =O and, preferably, E^5, and which heterocyclalkyl group may further be bridged, i.e. two non-adjacent atoms (which may be in a 1,4-relationship) of the first ring may be linked together with $-(CH_2)_{n1}-$ (where n1 is 2 or, preferably, 1), so forming for example a 1-aza-bicyclo[2.2.1]hept-4-yl group); aryl (e.g. phenyl) (which is optionally substituted by one or more substituents selected from E^6); or heteroaryl (e.g. a 5- or, preferably, a 6-membered heteroaryl group preferably containing one nitrogen heteroatom, so forming e.g. pyridyl, such as 3-pyridyl), which group is preferably unsubstituted;

E^3 represents Q^4 or C_{1-3} alkyl (e.g. methyl) optionally substituted by one or more substituents selected from =O or, particularly, Q^5 (so forming e.g. a trifluoromethyl group); or

two E^3 groups (e.g. when attached to adjacent carbon atoms of an aryl (e.g. phenyl) group) may be linked together to form an aromatic (e.g. 5-membered) ring, preferably containing one or two (e.g. one) heteroatom(s) (selected from sulfur, oxygen and, preferably nitrogen), but two E^3 groups are preferably not linked together;

E^4 represents Q^4, or, C_{1-3} alkyl (e.g. methyl) optionally substituted by one or more (e.g. one) Q^5 substituent;

E^5 represents Q^4 or C_{1-6} (e.g. C_{1-4}) alkyl (acyclic or part-cyclic; so forming e.g. methyl or cyclopropylmethyl, i.e. C_{1-2} alkyl (e.g. methyl) substituted by C_{3-6} cycloalkyl (e.g. cyclopropyl)), which is preferably unsubstituted;

E^6 represents Q^4;

Q^4 represents aryl (optionally substituted by a substitutent selected from J^3 (e.g. Q^4 represents fluorophenyl)), halo (e.g. fluoro or chloro), -CN, $-OR^{20}$, $-N(R^{20})R^{21}$, $-C(=Y)R^{20}$, $-C(=Y)OR^{20}$ or $-S(O)_2R^{20}$;

Q^5 represents C_{1-6} alkyl (preferably unsubstituted) or, preferably, halo (e.g. fluoro), $-N(R^{20})R^{21}$ or $-N(R^{22})C(=Y)R^{21}$;

R^{10a} and R^{11a} independently represent H or C_{1-3} alkyl (e.g. methyl);

R^{20} represents H or C_{1-4} alkyl (e.g. ethyl or, preferably, methyl, isopropyl or *tert*-butyl) optionally substituted by one or more J^4 substituents (in particular J^4 may represent halo, such as fluoro, and hence R^{20} may represent a trifluoromethyl group);

R^{21} represents hydrogen or C_{1-4} (e.g. C_{1-3}) alkyl (e.g. isopropyl or, preferably, methyl);

R^{22} represents hydrogen;

Y represents =O;

J^4 represents Q^7;

Q^7 represents halo (e.g. fluoro).

Particularly preferred compounds of the invention include those in which:

one of R^1 and R^2 represents $-N(R^6)-$ and the other represents -O- or $-N(R^6)-$;

R^6 represents H or, more preferably, R^{d3};

R^{d3} represents C_{1-3} alkyl (e.g. methyl or ethyl, preferably methyl);

X represents unsubstituted $-CH_2-CH_2-$;

R^3 represents a monocyclic 5- or 6-membered heteroaryl group (e.g. pyridyl) or a 9- or 10-membered bicyclic heteroaryl group (e.g. isoquinolinyl or azaindolyl, such as 3-isoquinolinyl and 7-azaindol-4-yl), which heteroaryl groups are optionally substituted by one or more (e.g. one or two) substituents selected from E^3;

one of R^a and R^b represents hydrogen or C_{1-3} alkyl (e.g. methyl) and the other represents a substituent other than hydrogen, or, R^a and R^b are linked together as defined herein;

when R^a or R^b represents a substituent other then hydrogen, then it is preferably: C_{1-6} alkyl (e.g. acyclic C_{1-3} alkyl or C_{3-6} cycloalkyl) optionally (and preferably) substituted by one or more (e.g. one) substituent(s) selected from Q^1; or a 5- or preferably 6-membered heterocycloalkyl group (e.g. containing one heteroatom, so forming e.g. piperidinyl or tetrahydropyranyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^1;

when R^a and R^b are linked together, they form a 5- or, preferably, a 6-membered ring optionally containing one further heteroatom (e.g. nitrogen; so forming e.g. a piperazinyl group), which ring may further comprise a 3- to 6- membered cycloalkyl group (e.g. cyclobutyl) or heterocycloalkyl group (e.g. a 5- or, preferably, 6-membered group containing one heteroatom, so forming e.g. piperazinyl) linked *via* a single atom (so forming a spiro-cycle), all of which rings are optionally substituted by one or more substituents selected from E^4;

Q^1 (e.g. when present on an alkyl/cycloalkyl group) represents $-N(R^{10a})R^{11a}$ or a 5- or 6-membered heterocycloalkyl group (e.g. containing two or preferably one nitrogen atom; so forming e.g. a piperidinyl group, which may be attached to a cycloalkyl group *via* a single carbon atom so forming a spiro-cycle), which is optionally substituted by one or more (e.g. one) substituent(s) selected from E^5;

Q^1 (e.g. when present on a heterocycloalkyl group) represents $-S(O)_2R^{10a}$ (which is preferably attached to a nitrogen heteroatom);

E^3 represents Q^4 or C_{1-3} alkyl (e.g. methyl) optionally substituted by one or more substituents selected from Q^5 (e.g. fluoro; so forming a $-CF_3$ group);

E^4 represents Q^4 or C_{1-3} alkyl (e.g. methyl or ethyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^5;

E^5 represents C_{1-3} alkyl (e.g. methyl);

when E^3 represents Q^4, then Q^4 represents halo (e.g. fluoro or chloro), $-OR^{20}$ or $-N(R^{20})R^{21}$;

when E^4 represents Q^4, then Q^4 represents $-N(R^{20})R^{21}$ or $-S(O)_2R^{20}$;

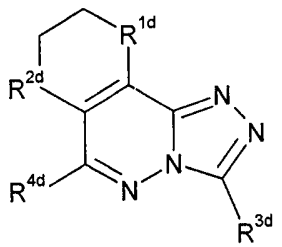
Q^5 represents halo (e.g. fluoro) or $-N(R^{20})R^{21}$;

R^{10a} and R^{11a} independently represent hydrogen or preferably C_{1-3} alkyl (e.g. methyl or ethyl);

R^{20} and R^{21} independently represent hydrogen or C_{1-6} (e.g. C_{1-3}) alkyl (e.g. methyl or ethyl); or

R^{20} and R^{21} are linked together to form a 5- or preferably 6-membered ring optionally containing one further heteroatom (e.g. nitrogen or oxygen; so forming e.g. a morpholinyl group).

In certain embodiments of the invention, the compound of formula I may be represented as a compound of formula ID,



ID

wherein the $-CH_2-CH_2-$ linker between R^{1d} and R^{2d} is unsubstituted;

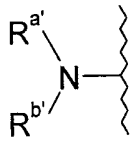
R^{1d} and R^{2d} are independently selected from -O-, -S-, and $-N(R^{6d})-$;

R^{6d} represents, on each occasion when used herein, H, or R^{d3d};

R^{d3d} represents linear or branched C_{1-4} alkyl optionally substituted by one or more substituents selected from E^{1d};

R^{3d} represents a mono- or bicyclic aromatic group containing from 5 to 10 skeleton atoms, in which from 1 to 3 of the skeleton atoms are heteroatoms selected from N, O and S, which aromatic group is optionally substituted by one or more substituents selected from E^{3d};

R^{4d} represents a fragment of formula IA',



IA'

;

$R^{a'}$ and $R^{b'}$ independently represent H, linear or branched C_{1-6} alkyl, heterocycloalkyl (particularly a 4- to 6-membered saturated heterocycloalkyl ring

containing at least one heteroatom selected from O, S and N, or two 4- to 6-membered rings linked together *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle) wherein at least one of said two rings contains from 1 to 3 heteroatoms selected from O, S and N) (which C_{1-6} alkyl and heterocycloalkyl groups are optionally substituted by one or more substituents selected from Q^{1d}), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from Q^{2d}); or

$R^{a'}$ and $R^{b'}$ are linked together, along with the requisite nitrogen atom to which they are necessarily attached, to form a (first) 3- to 7-membered cyclic group, optionally containing one further heteroatom selected from nitrogen, sulfur and oxygen, and which ring optionally:

(a) is fused to a second ring that is either a 4- to 6-membered saturated heterocycloalkyl group containing one to three heteroatoms selected from oxygen, sulfur and nitrogen (preferably oxygen and nitrogen), a 4- to 10-membered saturated carbocyclic ring, or an unsaturated 4- to 10-membered carbocyclic or heterocyclic ring (in which the heteroatoms are preferably selected from sulfur and, especially, nitrogen and oxygen);

(b) comprises a linker group $-C(R^{xd})_2-$ (wherein each R^{xd} independently represents hydrogen or linear or branched C_{1-4} alkyl), linking together any two non-adjacent atoms of the first 3- to 7-membered ring (i.e. forming a bridged structure); or

(c) comprises a second ring that is either a 4- to 10-membered saturated carbocyclic ring or a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen and nitrogen, and which second ring is linked together with the first ring *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle),

all of which cyclic groups, defined by the linkage of $R^{a'}$ and $R^{b'}$, are optionally substituted by one or more substituents selected from =O, and E^{4d};

each Q^{1d} and Q^{2d} independently represents, on each occasion when used herein:

halo, -CN, $-NO_2$, $-N(R^{d1})R^{d2}$, $-OR^{d1}$, $-C(O)-R^{d1}$, $-C(O)-OR^{d1}$, $-C(O)N(R^{d1})R^{d2}$, $-OC(O)-R^{d1}$, $-OS(O)_2OR^{d1}$, $-N(R^{d3})C(O)R^{d2}$, $-NR^{d3}S(O)_2R^{d1}$, $-S(O)_2N(R^{d1})R^{d2}$, $-S(O)_2R^{d1}$, $-SR^{d1}$, $-S(O)R^{d1}$, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, and E^{5d}), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^{6d});

each R^{d1}, R^{d2} and R^{d3} independently represents, on each occasion when used herein, hydrogen, linear or branched C_{1-6} alkyl, (which latter group is optionally substituted by one or more substituents selected from =O and E^{7d});

each E^{1d}, E^{3d}, E^{4d}, E^{5d}, E^{6d} and E^{7d} independently represents, on each occasion when used herein:
(i) Q^{4d};
(ii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^{5d};

each Q^{4d} and Q^{5d} independently represent, on each occasion when used herein:
halo, -CN, $-NO_2$, $-N(R^{d4})R^{d5}$, $-OR^{d4}$, $-C(=O)-R^{d4}$, $-C(=O)-OR^{d4}$, $-C(=O)N(R^{d4})R^{d5}$, $-OC(=O)-R^{d4}$, $-OS(O)_2OR^{d4}$, $-N(R^{d6})C(=O)R^{d5}$, $-NR^{d6}S(O)_2R^{d4}$, $-S(O)_2N(R^{d4})R^{d5}$, $-S(O)_2R^{d4}$, $-SR^{d4}$, $-S(O)R^{d4}$, linear or branched C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and Q^{7d}), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from Q^{7d});

each R^{d4}, R^{d5}, R^{d6} independently represents, on each occasion when used herein, hydrogen, linear or branched C_{1-4} alkyl, or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from Q^{7d} and =O);

Q^{7d} represents, on each occasion when used herein:
halo, $-N(R^{d7})R^{d8}$, $-OR^{d7}$, $-C(=O)-R^{d7}$, $-S(O)_2R^{d7}$, or linear or branched C_{1-6} alkyl optionally substituted by one or more fluoro atoms; and

each R^{d7} and R^{d8}, independently represents, on each occasion when used herein, hydrogen or linear or branched C_{1-6} alkyl;

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

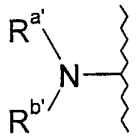
Preferred compounds of formula ID include those in which:

R^{1d} and R^{2d} are independently selected from -O-, and -N(R^{6d})-;

R^{6d} represents, on each occasion when used herein, H, or methyl;

R^{3d} represents a mono- or bicyclic aromatic group containing from 5 to 10 skeleton atoms, in which from 1 to 3 of the skeleton atoms are heteroatoms selected from N, O and S, which aromatic group is optionally substituted by one or more substituents selected from E^{3d};

R^{4d} represents a fragment of formula IA',



IA'

;

$R^{a'}$ and $R^{b'}$ independently represent H, linear or branched C_{1-6} alkyl, heterocycloalkyl (particularly a 4- to 6-membered saturated heterocycloalkyl ring containing at least one heteroatom selected from O, S and N, or two 4- to 6-membered rings linked together *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle) wherein at least one of said two rings contains from 1 to 3 heteroatoms selected from O, S and N), which C_{1-6} alkyl and heterocycloalkyl groups are optionally substituted by one or more substituents selected from Q^{1d}); or

$R^{a'}$ and $R^{b'}$ are linked together, along with the requisite nitrogen atom to which they are necessarily attached, to form a (first) 3- to 7-membered cyclic group, optionally containing one further heteroatom selected from nitrogen, sulfur and oxygen, and which ring optionally comprises a second ring that is either a 4- to 8-

membered saturated carbocyclic ring or a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen and nitrogen, and which second ring is linked together with the first ring *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle),

which cyclic group, defined by the linkage of $R^{a'}$ and $R^{b'}$, is optionally substituted by one or more substituents selected from E^{4d};

Q^{1d} represent, on each occasion when used herein:
halo, $-NO_2$, $-N(R^{d1})R^{d2}$, $-OR^{d1}$, $-C(O)-R^{d1}$, $-OS(O)_2OR^{d1}$, $-S(O)_2R^{d1}$, $-SR^{d1}$, $-S(O)R^{d1}$, linear or branched C_{1-4} alkyl, a 5- to 7-membered heterocycloalkyl group (which latter two groups are optionally substituted by one or more substituents selected from E^{5d}), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^{6d});

each R^{d1} and R^{d2} independently represents, on each occasion when used herein, hydrogen, linear or branched C_{1-4} alkyl;

each E^{3d}, E^{4d}, E^{5d} and E^{6d} independently represents, on each occasion when used herein:
(i) Q^{4d};
(ii) linear or branched C_{1-4} alkyl optionally substituted by one or more substituents selected from Q^{5d};

each Q^{4d} and Q^{5d} independently represents, on each occasion when used herein:
halo, -CN, $-NO_2$, $-N(R^{d4})R^{d5}$, $-OR^{d4}$, $-C(=O)-R^{d4}$, $-OS(O)_2OR^{d4}$, $-NR^{d6}S(O)_2R^{d4}$, $-S(O)_2N(R^{d4})R^{d5}$, $-S(O)_2R^{d4}$, $-SR^{d4}$, $-S(O)R^{d4}$, linear or branched C_{1-6} alkyl, heterocycloalkyl, aryl or heteroaryl (which latter four groups are optionally substituted by one or more substituents selected from Q^{7d});

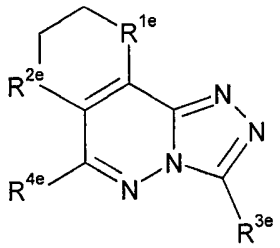
each R^{d4}, R^{d5}, R^{d6} independently represents, on each occasion when used herein, hydrogen, linear or branched C_{1-4} alkyl, or he terocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from Q^{7d} and =O);

Q^{7d} represents, on each occasion when used herein:
halo, $-N(R^{d7})R^{d8}$, $-OR^{d7}$, or linear or branched C_{1-4} alkyl optionally substituted by one or more fluoro atoms; and/or

each R^{d7} and R^{d8}, independently represents, on each occasion when used herein, hydrogen or C_{1-2} alkyl;

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

In certain embodiments of the invention, the compound of formula I may be represented as a compound of formula IE,



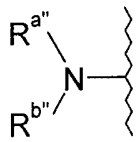
IE

wherein the $-CH_2-CH_2-$ linker between R^{1e} and R^{2e} is unsubstituted;

One of R^{1e} and R^{2e} is -O- and the other is selected from -O-, and $-N(CH_3)-$;

R^{3e} represents a mono- or bicyclic aromatic group containing from 5 to 10 skeleton atoms, in which from 1 to 3 of the skeleton atoms are heteroatoms selected from N, O and S, which aromatic group is optionally substituted by one or more substituents selected from E^{3e};

R^{4e} represents a fragment of formula IA",



IA"

$R^{a''}$ and $R^{b''}$ independently represent H, linear or branched C_{1-6} alkyl or heterocycloalkyl (particularly a 4- to 6-membered saturated heterocycloalkyl ring

containing at least one heteroatom selected from O, S and N, or two 4- to 6-membered rings linked together *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle) wherein at least one of said two rings contains from 1 to 3 heteroatoms selected from O, S and N), which C_{1-6} alkyl and heterocycloalkyl groups are optionally substituted by one or more substituents selected from Q^{1e}; or

$R^{a''}$ and $R^{b''}$ are linked together, along with the requisite nitrogen atom to which they are necessarily attached, to form a (first) 3- to 7-membered cyclic group, optionally containing one further heteroatom selected from nitrogen, sulfur and oxygen, and which ring optionally comprises a second ring that is either a 4- to 6-membered (particularly 4-membered) saturated carbocyclic ring or a 4- to 6-membered (particularly 5- or 6-membered) saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen and nitrogen, and which second ring is linked together with the first ring *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle),

all of which cyclic groups, defined by the linkage of $R^{a''}$ and $R^{b''}$, are optionally substituted by one or more substituents selected from E^{4e};

each Q^{1e} independently represents, on each occasion when used herein:
halo, $-N(R^{d1})R^{d2}$, $-OR^{d1}$, $-S(O)_2R^{d1}$, linear or branched C_{1-4} alkyl, 6-membered heterocycloalkyl group or phenyl (which latter three groups are optionally substituted by one or more substituents selected from E^{5e});

each R^{d1} and R^{d2} independently represents, on each occasion when used herein, hydrogen or C_{1-2} alkyl, (which latter group is optionally substituted by one or more fluoro atoms);

each E^{3e}, E^{4e} and E^{5e} independently represents, on each occasion when used herein:
(i) Q^{4e};
(ii) a linear or branched C_{1-4} alkyl optionally substituted by one or more substituents selected from =O and Q^{5e};

each Q^{4e} and Q^{5e} independently represents, on each occasion when used herein: halo, $-NO_2$, $-N(R^{e4})R^{e5}$, $-OR^{e4}$, $-SR^{e4}$, aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from halo atoms); and

each R^{e4} and R^{e5} independently represents, on each occasion when used herein, hydrogen, or C_{1-2} alkyl, (which latter group is optionally substituted by one or more halo atoms);

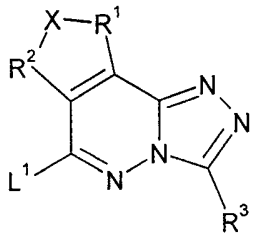
or a pharmaceutically acceptable ester, amide, solvate or salt thereof.

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) reaction of a compound of formula II,



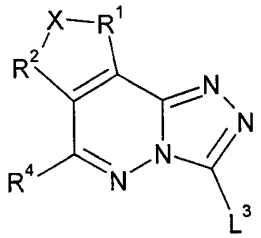
II

wherein L^1 represents a suitable leaving group, such as iodo, bromo, chloro or a sulfonate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$ or $-OS(O)_2PhMe$), and R^1, R^2, R^3 and X are as hereinbefore defined, with a compound of formula III,

R^4-H III

wherein R^4 is as hereinbefore defined, under standard conditions, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as Cu, $Cu(OAc)_2$, CuI (or CuI/diamine complex), copper tris(triphenyl-phosphine)bromide, $Pd(OAc)_2$, tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) or $NiCl_2$ and an optional additive such as Ph_3P, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, xantphos, NaI or an appropriate crown ether such as 18-crown-6-benzene, in the presence of an appropriate base such as NaH, Et_3N, pyridine, *N,N'*-dimethylethylenediamine, Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, *t*-BuONa or *t*-BuOK (or a mixture thereof, optionally in the presence of 4Å molecular sieves), in a suitable solvent (e.g. dichloromethane, dioxane, toluene, butanol, ethanol, isopropanol, dimethylformamide, ethylene glycol, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or a mixture thereof; which solvent may be degassed). This reaction may be carried out under microwave irradiation reaction conditions and/or the reaction may be performed in the absence of other reagents such as catalyst, base and even solvent (e.g. the reaction may be performed under microwave irradiation conditions, in the presence of an alcohol, such as *n*-butanol, for instance at elevated temperature such as at above 100°C, e.g. at about 150-200°C). Such a reaction may be accompanied by a rearrangement reaction, for instance if the compound of formula III is 2,7-diaza-spiro[3.5]nonane (or the 7-protected derivative thereof, e.g. the corresponding 7-carboxylic acid *tert*-butyl ester thereof), then such a spiro-cyclic amine may undergo ring-opening to form a 1-aza-bicyclo[2.2.1]hept-4-ylmethyl-amino moiety (i.e. a bridged amine) so forming a corresponding compound of formula I in which R^4 represents 1-aza-bicyclo[2.2.1]hept-4-ylmethyl-amino. When the amine of formula III is employed as a salt (e.g. a HCl salt), the skilled person will appreciate that additional base may need to be employed (e.g. DIPEA, sodium *tert*-butoxide or the like);

(ii) reaction of a compound of formula IV,



IV

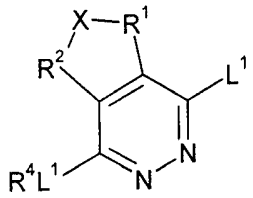
wherein L^3 represents a suitable leaving group such as one hereinbefore defined in respect of L^1 (e.g. halo, such as chloro or, preferably, bromo), and R^1, R^2, X and R^4 are as hereinbefore defined, with a compound of formula V,

$$R^3\text{-}L^4 \qquad \text{V}$$

wherein L^4 represents a suitable group, such as H, $-B(OH)_2$, $-B(OR^{wx})_2$ or $-Sn(R^{wx})_3$, in which each R^{wx} independently represents a C_{1-6} alkyl group, or, in the case of $-B(OR^{wx})_2$, the respective R^{wx} 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), thereby forming e.g. a pinacolato boronate ester group, (or L^4 may represent iodo, bromo or chloro, provided that L^3 and L^4 are mutually compatible) and R^3 is as hereinbefore defined. The reaction may be performed under Heck reaction conditions (e.g. with a compound of formula V in which L^4 represents H). The reaction may also be performed, for example in the presence of a suitable catalyst system, e.g. a metal (or a salt or complex thereof) such as Pd, CuI, Pd/C, $PdCl_2$, $Pd(OAc)_2$, $Pd(Ph_3P)_2Cl_2$, $Pd(Ph_3P)_4$ (i.e. palladium tetrakistriphenylphosphine), $Pd_2(dba)_3$ and/or $NiCl_2$ (preferred catalysts include palladium) and a ligand such as $PdCl_2$(dppf).DCM, *t*-Bu_3P, $(C_6H_{11})_3P$, Ph_3P, $AsPh_3$, P(*o*-Tol)$_3$, 1,2-bis(diphenylphosphino)ethane, 2,2'-bis(di-*tert*-butyl-phosphino)-1,1'-biphenyl, 2,2'-bis(diphenylphosphino)-1,1'-bi-naphthyl, 1,1'-bis(diphenyl-phosphino-ferrocene), 1,3-bis(diphenylphosphino)propane, xantphos, or a mixture thereof (preferred ligands include $PdCl_2$(dppf).DCM), together with a suitable base such as, Na_2CO_3, K_3PO_4, Cs_2CO_3, NaOH, KOH, K_2CO_3, CsF, Et_3N, (*i*-Pr)$_2$NEt, *t*-BuONa or *t*-BuOK (or mixtures thereof; preferred bases include Na_2CO_3 and K_2CO_3) in a suitable solvent such as dioxane, toluene, ethanol, dimethylformamide, dimethoxyethane, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or mixtures thereof (preferred solvents include

dimethylformamide and dimethoxyethane). The reaction may be carried out for example at room temperature or above (e.g. at a high temperature such as at about the reflux temperature of the solvent system). Alternative reaction conditions include microwave irradiation conditions, for example at elevated temperature of, e.g. above 70°C, e.g. between about 100 and 120°C or at about 130°C;

(iii) reaction of a compound of formula VI,



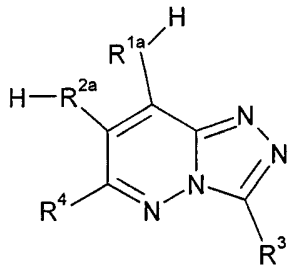
VI

wherein R^4L^1 represents either L^1 or R^4, and R^1, R^2, R^4, X and each L^1 (which are independent of each other) are as hereinbefore defined, with a compound of formula VII,

$$R^3\text{-C(O)-N(H)NH}_2 \qquad \text{VII}$$

wherein R^3 is as hereinbefore defined, under standard reaction conditions to promote the formation of the requisite triazolopyridazine bicyclic core, for example, in the presence of base, such as an organic base (e.g. triethylamine or the like), and/or an acid, such as an organic acid (e.g. *para*-toluenesulfonic acid or the like), and the base and acid are preferably in a ratio of about 1:1. The reaction may also take place in the presence of a suitable solvent, such as a polar solvent (e.g. 1,4-dioxane and the like), which may be heated at room termperature, or, preferably, above room temperature, e.g. above 50°C, such as at about 100°C. In the case where reaction takes place with a compound of formula VI in which R^4L^1 represents either L^1, then the reaction may be proceeded by reaction with a compound of formula III, for example as defined in respect of process step (i) above;

(iv) for compounds of formula I in which R^1 and R^2 are independently selected from -O-, -S- and -NR^6-, reaction of a compound of formula VIII,



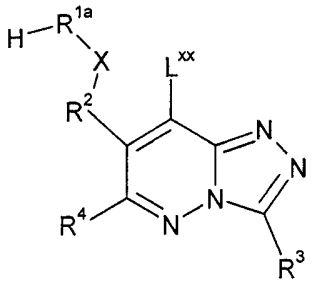
VIII

wherein R^{1a} and R^{2a} independently represent -O-, -S- and -NR^6-, and R^3 and R^4 are as hereinbefore defined, with a compound of formula IX,

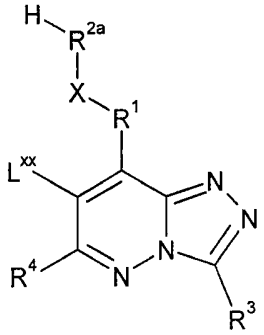
L^5-X-L^6 IX

wherein L^5 and L^6 independently represent a suitable leaving group, such as one hereinbefore defined in respect of L^1 (e.g. halo, such as chloro), and X is as hereinbefore defined, under standard reaction conditions (to promote the nucleophilic substitution reactions), for example in the presence of a suitable base, such as Na_2CO_3, K_3PO_4, Cs_2CO_3, NaOH, KOH, K_2CO_3, CsF, Et_3N, $(i\text{-Pr})_2NEt$, *t*-BuONa or *t*-BuOK (or mixtures thereof) in a suitable solvent such as dioxane, toluene, ethanol, *tert*-butanol, dimethylformamide, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or mixtures thereof. Preferred bases include *t*-BuOK;

(v) for compounds of formula I in which one of R^1 and R^2 represents -O-, -S- or -NR^6-, reaction of a compound of formula IXA or IXB,



IXA



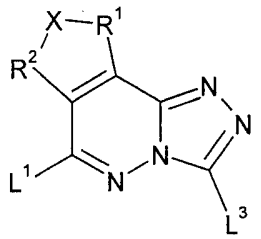
IXB

wherein L^{xx} represents a suitable leaving group (e.g. chloro) and R^{1a}, R^{2a}, X, R^1, R^2, R^3 and R^4 are as hereinbefore defined, for example in the presence of a

suitable base, e.g. an inorganic metal alkoxide, such as an alkali metal alkoxide (in which the alkali metal may be sodium or potassium and the alkoxide may be a C_{1-6} alkyl oxide, such as *tert*-butyl; hence the base is preferably potassium *tert*-butoxide).

Compounds of formula II may be prepared by reaction of a compound of formula VI as hereinbefore defined but in which R^4L^1 represents L^1 and a compound of formula VII as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of preparation of compounds of formula I (process step (iii)).

Compounds of formula II may alternatively be prepared by reaction of a compound of formula X,

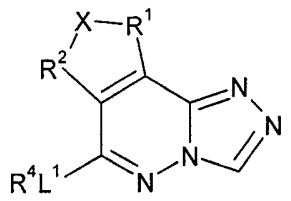


X

wherein L^1, L^3, R^1, R^2 and X are as hereinbefore defined, with a compound of formula V as hereinbefore defined, under reaction conditions such as those described in respect of preparation of compounds of formula I (process step (ii) above).

Compounds of formula IV may be prepared by reaction of a compound of formula X as hereinbefore defined with a compound of formula III as hereinbefore defined, for example under reaction conditions such as those described in respect of preparation of compounds of formula I (process step (i) above).

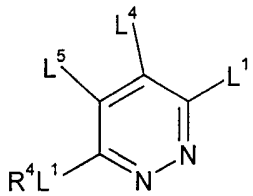
Compounds of formula IV and compounds of formula X (in which L^3 represents halo, e.g. bromo) may be prepared by reaction of a compound of formula XI,



XI

wherein R^4L^1, R^1, R^2 and X are as hereinbefore defined, for example by reaction in the presence of a source of halide (e.g. bromide) 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 *N*-bromosuccinimide and bromine, and a source of chloride ions includes *N*-chlorosuccinimide, chlorine and iodine monochloride, for instance in the presence of a suitable solvent, such as an alcohol (e.g. methanol), a halogenated solvent (e.g. chloroform) or e.g. acetonitrile, and which reaction may take place under microwave irradiation conditions (e.g. at above 100°C, such as at about 120°C) or may alternatively take place in the presence of a suitable base, such as a weak inorganic base, e.g. sodium bicarbonate.

Compounds of formula VI may be prepared by reaction of a compound of formula XII,



XII

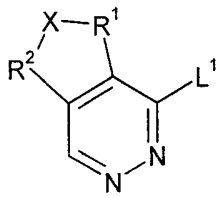
wherein L^4 and L^5 independently represent a suitable leaving group (e.g. chloro), and R^4L^1, L^1 are as hereinbefore defined, with a compound of formula XIII,

$$H\text{-}R^{1a}\text{-}X\text{-}R^{2a}\text{-}H \qquad \text{XIII}$$

wherein R^{1a}, R^{2a} and X are as hereinbefore defined, under standard aromatic nucleophilic reaction conditions, for example in the presence of a base and solvent (such as one hereinbefore described in respect of process step (iv)

above, e.g. NaO*t*-Bu in the presence of a solvent such as acetonitrile) or under reaction conditions such as those described in respect of process step (ii) above.

Compounds of formula VI in which R^4L^1 represents L^1 (in which L^1 is halo, such as chloro) may be prepared by reaction of a compound of formula XIIIA,



XIIIA

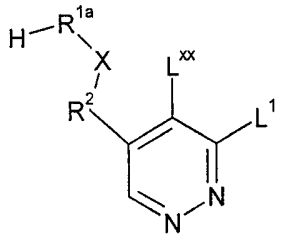
wherein L^1, R^1, R^2 and X are as hereinbefore defined, with a compound that is a source of halide ions, such as one mentioned hereinbefore (e.g. in respect of preparation of compounds of formula IV and X), for instance with *N*-chlorosuccinimide (in order to form a corresponding compound in which R^4L^1 represents chloro.

Compounds of formula XI may be prepared by reaction of a compound of formula VI as hereinbefore defined, with a compound of formula XIV,

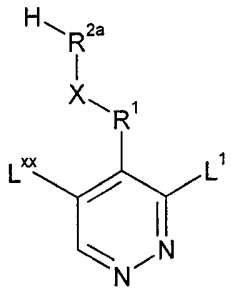
H-C(O)-N(H)-NH_2 XIV

for example under reaction conditions described herein (e.g. process step (iii) above).

Compounds of formula XIIIA may be prepared by reaction of a compound of formula XV or XVA,



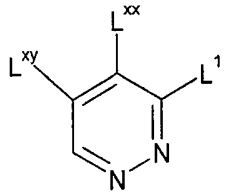
XV



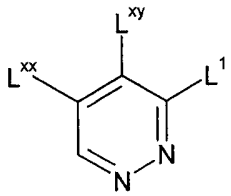
XVA

wherein L^1, R^{1a}, R^{2a}, X, R^1, R^2 and L^{xx} are as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of preparation of compounds of formula I (process step (v) above), e.g. an intramolecular reaction in the presence of base (e.g. sodium or potassium *tert*-butoxide).

Compounds of formula XV and XVA may be prepared by reaction of a corresponding compound of formula XVI or XVIA, as appropriate,



XIV



XIVA

wherein L^{xy} represents a suitable leaving group, such as one defined in respect of L^{xx} (e.g. chloro), with a compound of formula XVII,

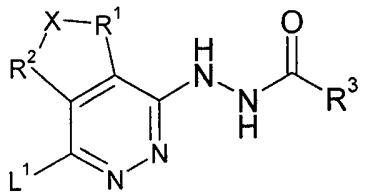
$$H(R^{1a})\text{-}X\text{-}R^2\text{-}H \qquad \text{XVII}$$

or a compound of formula XVIIA,

$$H(R^{2a})\text{-}X\text{-}R^1\text{-}H \qquad \text{XVIIA}$$

as appropriate, wherein R^{1a}, X, R^2, R^{2a} and R^1 are as hereinbefore defined, for instance under reaction conditions such as those hereinbefore described, e.g. in respect of preparation of compounds of formula I (process step (i) above), or e.g. the reaction may take place simply in the presence of an appropriate solvent (e.g. an alcohol, e.g. methanol).

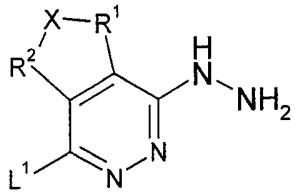
Compounds of formula II may alternatively be prepared by reaction of a compound of formula XVIII,



XVIII

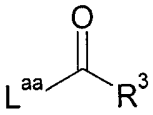
wherein L^1, R^3, R^1, R^2 and X are as hereinbefore defined, in the presence of an appropriate base such as NaH, Et_3N, pyridine, *N,N'*-dimethylethylenediamine, Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, *t*-BuONa or *t*-BuOK (or a mixture thereof, optionally in the presence of 4Å molecular sieves), in a suitable solvent (e.g. acetonitrile, dichloromethane, dioxane, toluene, dimethylformamide, ethylene glycol dimethyl ether, dimethylsulfoxide, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or a mixture thereof; which solvent may be degassed), op tionally in the presence of a halogenating agent (e.g. a triarylphenylphosphine dihalide such as triphenylphosphine dibromide).

Compounds of formula XVIII may alternatively be prepared by reaction of a compound of formula XIX,



XIX

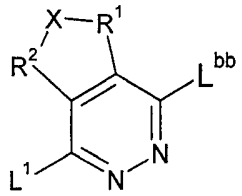
wherein L^1, R^1, R^2 and X are as hereinbefore defined, with a compound of formula XX,



XX

wherein R^3 is as hereinbefore defined and L^{aa} is a leaving group such as one hereinbefore defined in respect of L^3, in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide, O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or the like), 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).

Compounds of formula XIX may alternatively be prepared by reaction of a compound of formula XXI,



XXI

wherein R^1, R^2, X and L^1 are as hereinbefore defined, L^{bb} is a leaving group such as one hereinbefore defined in respect of L^1, with hydrazine, or a salt, solvate or derivative thereof, under standard conditions known to those skilled in the art (e.g. optionally in the presence of a suitable solvent and/or in an inert atmosphere).

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(O)OH (or an ester thereof), may be converted to a -C(O)H or $-CH_2$-OH group, using DIBAL and $LiAlH_4$, respectively (or similar chemoselective reducing agents));

(ii) reductions of an aldehyde (-C(O)H) group to an alcohol group ($-CH_2OH$), 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. $-CH_2OH$) to an aldehyde (e.g. -C(O)H), for example in the presence of a suitable oxidising agent, e.g. MnO_2 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 triacetoxyborohydride, 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 $MgSO_4$ 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 $NaBH_4$, AlH_4, or the like), for instance the conversion of $-NH_2$ to -N(H)-isopropyl by condensation in the presence of acetone

(H_3C-C(O)-CH_3) followed by reduction in the presence of a reducing agent such as sodium cyanaoborohydride (i.e. overall a reductive amination);

(v) amide coupling reactions, i.e. the formation of an amide from a carboxylic acid (or ester thereof), for example when Q^1 or Q^2 represents -C(O)OH (or an ester thereof), it may be converted to a -C(O)N(R^{10a})R^{11a} group (in which R^{10a} and R^{11a} are as hereinbefore defined, and may be linked together, e.g. as defined above), and which reaction may (e.g. when $Q^{1/2}$ represents -C(O)OH) be performed in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide, or the like) or, in the case when R^2 represents an ester (e.g. -C(O)OCH_3 or -C(O)OCH_2CH_3), in the presence of e.g. trimethylaluminium, or, alternatively the -C(O)OH group may first be activated to the corresponding acyl halide (e.g -C(O)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(R^{10a})R^{11a} (in which R^{10a} and R^{11a} 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 $POCl_3$, or the like;

(vii) nucleophilic substitution reactions, where any nucleophile replaces a leaving group, e.g. methylsulfonylpiperazine may replace a chloro 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 in respect of preparation of compounds of formula I, process step (iv) above, for instance, a -N(H)- or -OH or -NH_2 (or a protected version of the latter) moiety may be alkylated, acylated or sulfonylated by employing a reactant that is an alkyl, acyl or sulfonyl moiety attached to a leaving group (e.g. C_{1-6} alkyl-halide (e.g. ethylbromide), C_{1-6} alkyl-C(O)-halide (e.g. H_3C-C(O)Cl), an anhydride (e.g. H_3C-C(O)-O-C(O)-CH_3, i.e. "-O-C(O)-CH_3" is the leaving group), dimethylformamide (i.e. -N(CH_3)$_2$ is the leaving group) or a sulfonyl halide (e.g. H_3C-S(O)$_2$Cl) and the like);

(x) specific deprotection steps, such as deprotection of an *N*-Boc protecting group by reaction in the presence of an acid, or, a hydroxy group protected as a silyl ether (e.g. a *tert*-butyl-dimethylsilyl protecting group) may be deprotected by reaction with a source of fluoride ions, e.g. by employing the reagent tetrabutylammonium fluoride (TBAF).

Intermediate compounds described herein 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, 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;

Andanappa K. Gadad et al. *Bioorg. Med. Chem.* **2004**, *12,* 5651-5659;

Paul Heinz et al. *Monatshefte für Chemie*, **1977**, 108, 665-680;

M.A. El-Sherbeny et al. *Boll. Chim. Farm.* **1997**, *136*, 253-256;

Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 2-49;

Bretonnet et al. *J. Med. Chem.* **2007**, *50*, 1872 ;

Asunción Marín et al. *Farmaco* **1992**, *47 (1),* 63-75;

Severinsen, R. et al. *Tetrahedron* **2005**, *61,* 5565-5575;

Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 2-49;

M. Kuwahara et al., *Chem. Pharm Bull.*, **1996**, *44*, 122;

Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65(20),* 6319-6337;

Shintani, R.; Okamoto, K. *Org. Lett.* **2005**, *7 (21)*, 4757-4759;

Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 2-49;

J. Kobe *et al.*, *Tetrahedron*, **1968**, *24*, 239 ;

P.F. Fabio, A.F. Lanzilotti and S.A. Lang, *Journal of Labelled Compounds and Pharmaceuticals*, **1978**, *15*, 407;

F.D. Bellamy and K. Ou, *Tetrahedron Lett.*, **1985**, *25*, 839;

M. Kuwahara et al., *Chem. Pharm Bull.*, **1996**, *44*, 122;

A.F. Abdel-Magid and C.A Maryanoff. *Synthesis*, **1990**, 537;

M. Schlosser *et al. Organometallics in Synthesis. A Manual*, (M. Schlosser, Ed.), Wiley &Sons Ltd: Chichester, UK, **2002**, and references cited therein;

L. Wengwei *et al.*, *Tetrahedron Lett.*, **2006**, *47*, 1941;

M. Plotkin *et al. Tetrahedron Lett.*, **2000**, *41*, 2269;

Seyden-Penne, J. *Reductions by the Alumino and Borohydrides*, VCH, NY, **1991**;
O. C. Dermer, *Chem. Rev.*, **1934**, *14*, 385;
N. Defacqz, *et al.*, *Tetrahedron Lett.*, **2003**, *44*, 9111;
S.J. Gregson *et al., J. Med. Chem.*, **2004**, *47*, 1161;
A. M. Abdel Magib, *et al.*, *J. Org. Chem.*, **1996**, *61*, 3849;
A.F. Abdel-Magid and C.A Maryanoff. *Synthesis*, **1990**, 537;
T. Ikemoto and M. Wakimasu, *Heterocycles*, **2001**, *55*, 99;
E. Abignente *et al.*, *Il Farmaco*, **1990**, *45*, 1075;
T. Ikemoto *et al.*, *Tetrahedron*, **2000**, *56*, 7915;
T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis,* Wiley, NY, **1999**;
S. Y. Han and Y.-A. Kim. *Tetrahedron*, **2004**, *60*, 2447;
J. A. H. Lainton *et al.*, *J. Comb. Chem.*, **2003**, *5*, 400; or
Wiggins, J. M. *Synth. Commun.*, **1988**, *18*, 741.

The substituents R^1, R^2, R^3, R^4 and X 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, alkylations, acylations, hydrolyses, esterifications, etherifications, halogenations or nitrations. 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, when substituents in the compounds of the invention such as CO_2Et, CHO, CN and/or CH_2Cl, are present, these groups can be further derivatized to other fragments described (e.g. by those integers mentioned above) in compounds of the invention, following synthetic protocols very well know to the person skilled in the art and/or according to the experimental part described in the patent. Other specific transformation steps that may be mentioned include: the reduction of a nitro or azido group to an amino group; the hydrolysis of a nitrile group to a carboxylic acid group; and standard nucleophilic aromatic substitution reactions, for example in which an iodo-, preferably, fluoro- or bromo-phenyl group is converted into a cyanophenyl group by employing a

source of cyanide ions (e.g. by reaction with a compound which is a source of cyano anions, e.g. sodium, copper (I), zinc or potassium cyanide, optionally in the presence of a palladium catalyst) as a reagent (alternatively, in this case, palladium catalysed cyanation reaction conditions may also be employed).

Other transformations that may be mentioned include: the conversion of a halo group (preferably iodo or bromo) to a 1-alkynyl group (e.g. by reaction with a 1-alkyne), which latter reaction may be performed in the presence of a suitable coupling catalyst (e.g. a palladium and/or a copper based catalyst) and a suitable base (e.g. a tri-(C_{1-6} alkyl)amine such as triethylamine, tributylamine or ethyldiisopropylamine); the introduction of amino groups and hydroxy groups in accordance with standard conditions using reagents known to those skilled in the art; the conversion of an amino group to a halo, azido or a cyano group, for example *via* diazotisation (e.g. generated *in situ* by reaction with $NaNO_2$ and a strong acid, such as HCl or H_2SO_4, at low temperature such as at 0°C or below, e.g. at about -5°C) followed by reaction with the appropriate nucleophile e.g. a source of the relevant anions, for example by reaction in the presence of a halogen gas (e.g. bromine, iodine or chlorine), or a reagent that is a source of azido or cyanide anions, such as NaN_3 or NaCN; the conversion of -C(O)OH to a $-NH_2$ group, under Schmidt reaction conditions, or variants thereof, for example in the presence of HN_3 (which may be formed in by contacting NaN_3 with a strong acid such as H_2SO_4), or, for variants, by reaction with diphenyl phosphoryl azide ($(PhO)_2P(O)N_3$) in the presence of an alcohol, such as *tert*-butanol, which may result in the formation of a carbamate intermediate; the conversion of $-C(O)NH_2$ to $-NH_2$, for example under Hofmann rearrangement reaction conditions, for example in the presence of NaOBr (which may be formed by contacting NaOH and Br_2) which may result in the formation of a carbamate intermediate; the conversion of $-C(O)N_3$ (which compound itself may be prepared from the corresponding acyl hydrazide under standard diazotisation reaction conditions, e.g. in the presence of $NaNO_2$ and a strong acid such as H_2SO_4 or HCl) to $-NH_2$, for example under Curtius rearrangement reaction conditions, which may result in the formation of an intermediate isocyanate (or a carbamate if treated with an alcohol); the conversion of an alkyl carbamate to $-NH_2$, by hydrolysis, for example in the presence of water and base or under acidic conditions, or, when a benzyl carbamate intermediate is formed, under

hydrogenation reaction conditions (e.g. catalytic hydrogenation reaction conditions in the presence of a precious metal catalyst such as Pd); halogenation of an aromatic ring, for example by an electrophilic aromatic substitution reaction in the presence of halogen atoms (e.g. chlorine, bromine, etc, or an equivalent source thereof) and, if necessary an appropriate catalyst/Lewis acid (e.g. $AlCl_3$ or $FeCl_3$).

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 need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods (and the need can be readily determined by one skilled in the art). Suitable amino-protecting groups

include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz), 9-fluorenylmethyleneoxycarbonyl (Fmoc) and 2,4,4-trimethylpentan-2-yl (which may be deprotected by reaction in the presence of an acid, e.g. HCl in water/alcohol (e.g. MeOH)) or the like. The need for such protection is readily determined by one skilled in the art.

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.

The use of protecting groups is fully described in "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

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, as hereinbefore defined, for use as a pharmaceutical.

Compounds of the invention may inhibit protein or lipid kinases, such as a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3, for example as may be shown in the tests described below and/or in tests known to the skilled person. 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) is desired and/or required.

The term "inhibit" may refer to any measurable reduction and/or prevention of catalytic kinase (e.g. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3)

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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) is known to play a role and which are characterised by or associated with an overall elevated activity of that protein kinase (due to, for example, increased amount of the kinase or increased catalytic activity of the kinase). 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).

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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3). Such conditions/disorders include cancer, immune

disorders, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders.

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, papilliary carcinoma, seminona, 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 lymphocitic 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 promyelocytic 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3), 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. a PIM family kinase, such as PIM-1, PIM-2 and/or PIM-3, preferably PI3K, such as class I PI3K, Flt3, EGFR, mTOR 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 (e.g. sequentially, concomitantly or simultaneously administered) with one or more treatments independently selected from surgery, one or more anti-cancer/anti-neoplastic/anti-tumoral agents, 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 (e.g. sequentially, concomitantly or simultaneously administered) 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 (e.g. 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) an Akt or PI3-K inhibitor, such as GDC-0941;

(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;

(viii) a B-Raf inhibitor, such as GDC-0879 or PLX-4720;

(ix) an anthracyclin, such as doxorubicin;

(x) a taxane, such as paclitaxel or, particularly, docetaxel (Taxotere);

(xi) a platin, such as carboplatin or, particularly, cisplatin;

(xii) a nucleotide analog, such as 5-fluorouracil (5-FU) or gemcitabine;

(xiii) an alkylating agent, such as temozolomide;

(xiv) a hormone therapeutic agent, such as an estrogen receptor antagonist e.g. tamoxifen;

(xv) an anti-tumour compound that has potential radiosensitising and/or chemosensitising effects, such as chloroquine;

(xvi) an mTOR inhibitor, such as rapamycin;

(xvii) a JAK inhibitor;

(xviii) a cyclin dependent kinase inhibitor (e.g. a CDK6 or CDK4 inhibitor, such as PD-0332991); and/or

(xix) 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-KB.

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 (e.g. sequentially, concomitantly or simultaneously administered) with other therapeutic agents (e.g. chemotherapeutic agents), and such combinations may be useful as medicaments.

Compounds of the invention may be combined (e.g. sequentially, concomitantly or simultaneously administered) with other therapeutic agents for use in the

treatment of a disease or condition as mentioned herein, such as a disease or condition in which the inhibition of growth of cancer cells are required and/or desired. Such disease or conditions include hyperproliferative disorders, particularly, cancer (e.g. cancer in mammals, particularly, humans). Specific cancers that may be mentioned include those mentioned above. Such active ingredients in combinations may act in synergy.

In particular, compounds of the invention may be combined (e.g. sequentially, concomitantly or simultaneously administered) 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 *in vitro*), for instance:

(i) a PI3K inhibitor, such as GDC-0941;

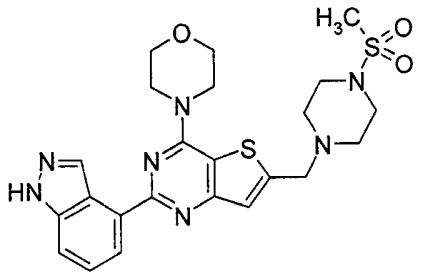
(ii) an EGFR inhibitor, such as Lapatinib;

(iii) a B-Raf inhibitor such as GDC-0879;

(iv) a MEK inhibitor, such as PD-0325901; and/or

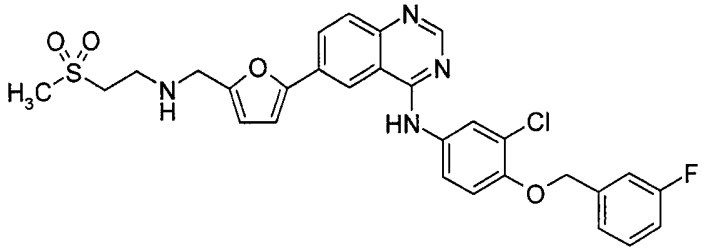
(v) a CDK4/6 inhibitor, such as PD-0332991.

GDC-0941 is a lead phosphatidylinositol-3 kinase (PI3K) inhibitor from a series of oral, small-molecule PI3K and/or mTOR inhibitors, for the potential oral treatment of cancer (see, for example, WO 2006/046031, US 7872003, WO 2007/129161, WO 2009/036082, WO 2009/055730, WO 2009/117277, WO 2010/105008, WO 2010/110782, WO 2011/054620 and WO 2011/130654). GDC-0941 is named as 2-(1H-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine and has the structure:

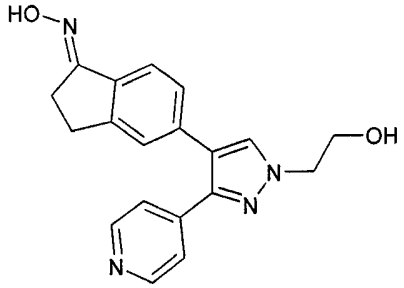


Lapatinib (TYKERB®, GW572016, Glaxo SmithKline) has been approved for use in combination with capecitabine (XELODA®, Roche) for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2

(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 (see, for example, 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 EGFRIHER2 protein kinase domain. Lapatinib is named as [3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-(6-{5-[(2-methanesulfonyl-ethylamino)-methyl]-furan-2-yl}-quinazolin-4-yl)-amine-quinazolin-4-yl amine), and has the structure:

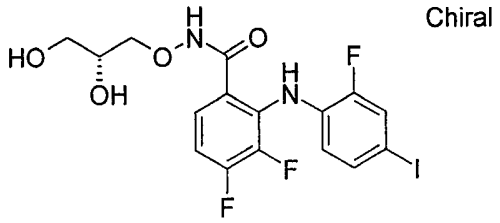


GDC-0879 is a B-Raf kinase inhibitor that is being investigated by Array BioPharma and Genentech for the potential treatment of cancer (see, for example, WO 2006/084015, WO 2011/028540). GDC-0879 stabilizes B-Raf/C-Raf heterodimers and is believed to effectively block the MAPK signaling pathway and decrease tumor growth. GDC-0879 is named as 5-[1-(2-hydroxy-ethyl)-3-pyridin-4-yl-1H-pyrazol-4-yl]-indan-1-one oxime and has the structure:

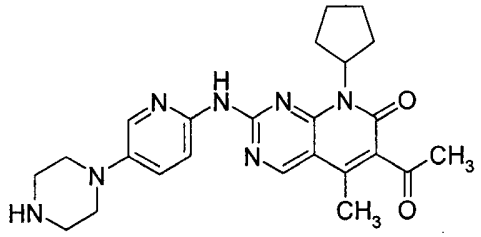


The MEK inhibitor PD-0325901 (CAS RN 391210-10-9, Pfizer) is a second-generation, non-ATP competitive, allosteric MEK inhibitor for the potential oral tablet treatment of cancer (see, for example: US 6960614; US 6972298; US

2004/1147478; and US 2005/085550). PD-0325901 is named N-((R)-2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide, and has the structure:



PD-332991 is a lead from a series of cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) inhibitors that is being developed for the potential oral treatment of cancer including diffuse large B-cell lymphoma (see, for example, WO 03/062236, WO 2005/005426, WO 2005/094830 and WO 2008/032157). PD-332991 is named as 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one and has the structure:



In certain embodiments of the invention that may be mentioned, 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3) 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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3), 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, wherein said patient is also administered one or more therapies, agents or therapeutic agents described above in relation to combination treatments.

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.

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. a PIM family kinase such as PIM-1, PIM-2 and/or PIM-3).

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.

Examples/Biological Tests

PIM-1 biochemical assay

The biochemical assay to measure PIM-1 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.

The enzyme has been expressed and purified in-house as a recombinant human protein with a C-terminal histidine tag. The protein is active and stable.

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 $MgCl_2$ and 0.1 mg/ml bovine γ-globulins/75 μl assay volume)
- Incubation time and temperature: 60 min at 30°C
- PIM-1 concentration: 50 pg/μl
- ATP concentration: 100 μM
- PIM-1 substrate peptide: PIMtide (ARKRRRHPSGPPTA)
- Peptide concentration: 60 μM
- Positive control for kinase activity inhibition: 1-10 μM Staurosporine
- DMSO concentration have to stay below 2% during the kinase reaction

Assays were performed in either 96 or 384-well plates. 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 (PerkinElmer) using an excitation filter at 544 nm and an emission filter at 580 nm.

PIM-2 biochemical assay

The biochemical assay to measure PIM-2 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.

The enzyme has been expressed and purified in-house as a recombinant human protein with a N-terminal histidine tag. The protein is active and stable.

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 $MgCl_2$ and 0.1 mg/ml bovine γ-globulins/20 μl assay volume)

- Incubation time and temperature: 30 min at 30°C
- PIM-2 concentration: 350 pg/μl
- ATP concentration: 100 μM
- PIM-1 substrate peptide: PIMtide (ARKRRRHPSGPPTA)
- Peptide concentration: 100 μM
- Positive control for kinase activity inhibition: 1-10 μM Staurosporine
- DMSO concentration have to stay below 2% during the kinase reaction

Assays were performed in either 96 or 384-well plates. 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 (PerkinElmer) using an excitation filter at 544 nm and an emission filter at 580 nm.

PIM-3 biochemical assay

The biochemical assay to measure PIM-3 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.

The enzyme has been bought from Millipore (# 14-738). The protein is active and stable.

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 $MgCl_2$ and 0.1 mg/ml bovine γ-globulins/20 μl assay volume)
- Incubation time and temperature: 30 min at 30°C
- PIM-3 concentration: 250 pg/μl
- ATP concentration: 100 μM
- PIM-1 substrate peptide: PIMtide (ARKRRRHPSGPPTA)
- Peptide concentration: 60 μM

- Positive control for kinase activity inhibition: 1-10 μM Staurosporine
- DMSO concentration have to stay below 2% during the kinase reaction

Assays were performed in either 96 or 384-well plates. 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 (PerkinElmer) using an excitation filter at 544 nm and an emission filter at 580 nm.

BAD S112 Phosphorylation inhibition assay

The efficacy of compounds of the invention in inhibiting BAD phosphorylation was measured by an In Cell ELISA. EC50 values were established for the tested compounds.

Assay conditions:
Cells: H1299 cells overexpressing PIM1 (H1299Pim1)
DMSO Plates: 96-well- Polystyrene, Untreated, Round-Bottom plates from Costar (Cat #3797)
Cell Plates: 96-Flat bottom biocoated with Poly-D-Lysin plates with lid from Becton Dickinson (Cat#354651)
Cell Culture Medium: DMEM high glucose, 10% Fetal Bovine Serum, 2mM L-Glutamine, P/S
Antibodies: phosphor Bad S112 antibody from Cell Signaling (cat. #9291S), anti rabbit conjugated with peroxidise from Amersham (cat.#3619)
Reagent: SuperSignal ELISA femto from Pierce (cat.#1001110)

Procedure:
Cells were seeded in 15000 cells per 200 µl per well into 96-well plates and incubated for 16 h at 37°C, 5% CO_2. On day two, nine serial 1:2 compound dilutions were made in DMSO in a 96-well plate. The compounds were added to duplicate wells in 96-well cell plates using a FX BECKMAN robot (Beckman Coulter) and incubated at 37°C with CO_2 atmosphere. After 4 hours, relative levels of Bad S112 phosphorylation were measured in Cell ELISA using

SuperSignal ELISA Femto substrate (Pierce) and read on VICTOR (Perkin Elmer). EC50 values were calculated using ActivityBase from IDBS.

MTT in vitro cell proliferarion assay

Proliferation assays (MTT) were performed as described in:
"Chemical interrogation of FOXO3a nuclear translocation identifies potent and selective inhibitors of phosphoinositide 3-kinases", W. Link, J. Oyarzabal, B.G. Serelde, M.I. Albarran, O. Rabal, A. Cebria,P. Alfonso, J. Fominaya, O. Renner, S. Peregrina, D. Soilan, P.A. Ceballos, A.I. Hernandez, M. Lorenzo, P. Pevarello, T.G. Granda, G. Kurz, A. Carnero, J.R. Bischoff, *J. Biol. Chem.* 284 (**2009**) 28392–28400.

Combination assay

Table 5 shows the combination index (CI) of combinations of certain example compounds and various chemotherapeutic agents in the MTT *in vitro* cell proliferarion assays. A combination index score is calculated by the Chou and Talalay method (CalcuSyn software, Biosoft). The strength of synergy is scored using the ranking system Chou and Talalay: CI less than 0.8 indicates synergy, CI between 0.8 and 1.2 indicates additivity and CI greater than 1.2 indicates antagonism.
The EC50 values of representative combinations were also calculated. The individually measured EC50 values of the chemotherapeutic agent and the example compounds are compared to the EC50 value of the combination. The cell lines are characterized by tumor type.

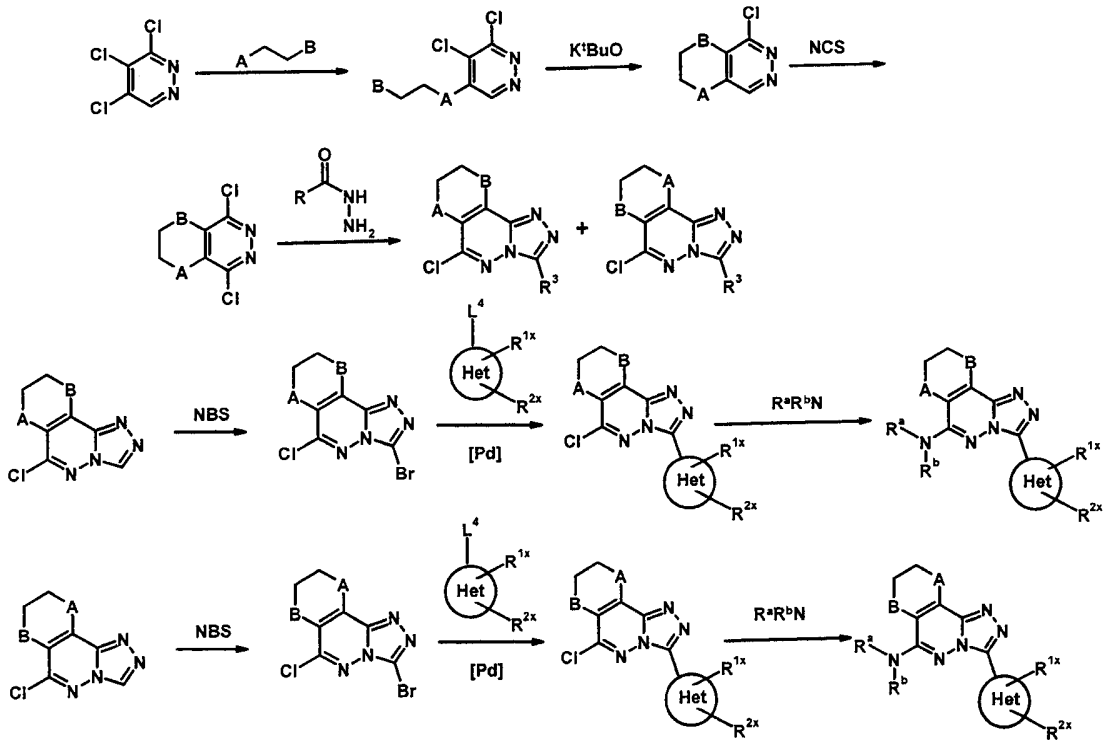
Combination assays were performed as described in:
"Pim 1 kinase inhibitor ETP-45299 suppresses cellular proliferation and synergizes with PI3K inhibition". Blanco-Aparicio, Carmen; Collazo, Ana Maria Garcia; Oyarzabal, Julen; Leal, Juan F.; Albaran, Maria Isabel; Lima, Francisco Ramos; Pequeno, Belen; Ajenjo, Nuria; Becerra, Mercedes; Alfonso, Patricia; Reymundo, Maria Isabel; Palacios, Irene; Mateos, Genoveva; Quinones, Helena; Corrionero, Ana; Carnero, Amancio; Pevarello, Paolo; Lopez, Ana Rodriguez;

Fominaya, Jesus; Pastor, Joaquin; Bischoff, James R. *Cancer Letters* (Shannon, Ireland) ***2011***, *300(2)*, 145-153.

The compound names given herein were generated with MDL ISIS/DRAW 2.5 SP 2, Autonom 2000.

The invention is illustrated by way of the following examples.

General scheme:



Experimental part:

Herein after, the term "DCM" means dichloromethane, "MeOH" means methanol, "THF" means tetrahydrofuran, "DMA" means dimethylacetamide, "DMF" means dimethylformamide, "DME" means 1,2-dimethoxyethane, "EtOAc" means ethyl acetate, "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium, "DIPEA" means diisopropylethylamine, "TEA" means triethylamine, "HATU" means O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,

"BINAP" means (R)/(+_)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, "min" means minutes, "h" means hours, "$Pd_2(dba)_3$" means tris(dibenzylideneacetone)dipalladium(0), "eq" means equivalents, "nBuOH" means n-butanol, "$Pd(dppf)Cl_2$.DCM" means 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, dichloromethane, "NCS" means n-chlorosuccinimide, "NBS" means n-bromosuccinimide "mw" means microwave, "RT" means room temperature, "CCTLC" means centrifugal circular thin-layer chromatography.

General Procedure

NMR spectra were recorded in 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.

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% to 100% of B within 8 min at 50 °C, DAD.

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: 5% to 40% of B within 8 min at 50 °C, DAD.

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: 0% to 30% of B within 8 min at 50 °C, DAD.

Method 4

Reversed phase HPLC was carried out on a Gemini C18 column (50 x 2 mm, 3 um).

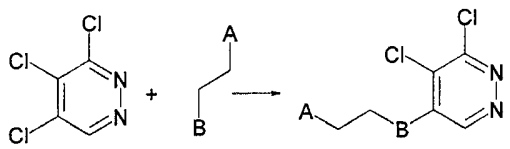
Solvent A: water with 0.1% formic acid; Solvent B: acetonitrile with 0.1% formic acid. Gradient: 10% to 95% of B within 4 min at 50°C, DAD.

Method 5

Reversed phase HPLC was carried out on a Gemini C18 column (50 x 2 mm, 3 um). Solvent A: water with 0.1% formic acid; Solvent B: acetonitrile with 0.1% formic acid. Gradient: 0% to 30% of B within 4 min at 50°C, DAD.

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

Bicyclic intermediates

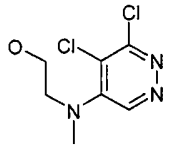


General procedure A

To a solution of 3,4,5-trichloropyridazine (1.0 eq) in MeOH (1 mL/mmol) was added dropwise a solution of the appropriate aminoalcohol (e.g. 2-methylamino-ethanol) (3.0 eq) in MeOH (1 mL/mmol) for 1h at RT. The solvent was removed in vacuo to give a brown oil which was purified by Biotage flash column chromatography (eluent: 70% EtOAc in cyclohexane to 100% EtOAc) to give the desired product (e.g. 2-[(5,6-Dichloro-pyridazin-4-yl)-methyl-amino]-ethanol).

Intermediate 1-01

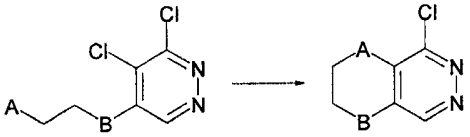
2-[(5,6-Dichloro-pyridazin-4-yl)-methyl-amino]-ethanol:



HPLC-MS (method 4): Rt =2.5 min, $[M+H]^+$ 222.1, 224.0.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 3.90 (t, J = 5.4 Hz, 2H), 3.72 (m, 2H), 3.20 (s, 3H).

Yield: 85%

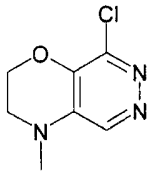


General procedure B

The appropriate dichloropyridazine (1.0 eq) was dissolved in THF (20 mL/mmol). When the solution reached reflux, ^{t}BuOK (1.2 eq) was added portionwise. The reaction mixture was refluxed for 2 h. On cooling, a saturated aqueous solution of NH_4Cl was added and the layers were separated. The aqueous phase was extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was triturated with Et_2O-DCM 9:1 and filtered off to afford the desired product (e.g. 8-Chloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b]-1,4-oxazine).

Intermediate 2-01

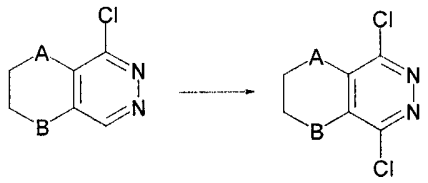
8-Chloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b]-1,4-oxazine:



HPLC-MS (method 4): Rt =0.98 min, $[M+H]^+$ 186.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 4.42 (m, 2H), 3.46 (m, 2H), 3.06 (s, 3H).

Yield: 90%

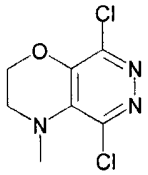


General procedure C

A mixture of the appropriate bicyclic chloropyridazines (1.0 eq) in acetonitrile (5 mL/mmol) was heated at 50°C. Then, NCS (1.2 eq) was added and the reaction mixture was heated at 50°C for 3h. The solvent was removed in vacuo. The residue was taken up into DCM and washed with a saturated solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and evaporated to give an orange solid which was purified by column chromatography (biotage, DCM/EtOAc 20%) to afford the desired product (e.g. 5,8-Dichloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b]-1,4-oxazine).

Intermediate 3-01

5,8-Dichloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b]-1,4-oxazine:



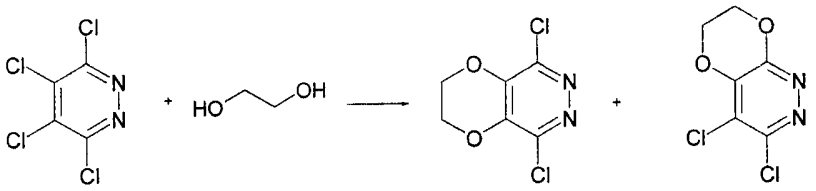
HPLC-MS (method 4): Rt =3.1min, $[M+H]^+$ 220.0, 222.0.

^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (m, 2H), 3.31 (m, 2H), 3.14 (s, 3H).

Yield: 60%

Synthesis of Intermediate 3-02

5,8-Dichloro-2,3-dihydro-[1,4]dioxino[2,3-d]pyridazine



3-02 3-03

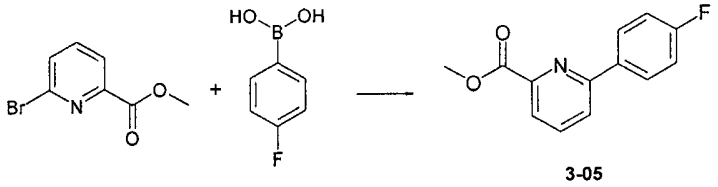
A mixture of 3,4,5,6-tetrachloropyridazine (5.0 g, 22.9 mmol), ethylene glycol (1.49 mL) and NaH (60% in mineral oil, 1.1 g) in dry DMF (250 mL) was stirred at RT for 18 h. Then, more NaH (60% in mineral oil, 1.1 g) was added and the mixture was heated at 60 °C for 3 h and stirred at RT for 18 h. The solvents were removed in vacuum and the residue was purified by column chromatography (EtOAc/hexanes 1:10 to 1:1) to give Intermediate **3-02** (758 mg, 16%) and compound **3-03** (1.31 g, 27%) as yellow solids.

Synthesis of Intermediate 3-04
(5-Chloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b][1,4]oxazin-8-yl)-hydrazine

3-01 3-04

A mixture of Intermediate **3-01** (200 mg, 0.91 mmol) and hydrazine hydrate (0.354 mL, 7.27 mmol) in ethanol (5 mL) was heated in a pressure tube at 70 °C overnight and at 78 °C for 6 h. More hydrazine hydrate (0.5 mL) was added and the reaction mixture was heated at 72 °C overnight. After cooling to RT, the mixture was evaporated and the residue was purified by column chromatography (Biotage, EtOAc: MeOH, 100:0 to 90:10) to afford Intermediate **3-04** (155 mg, 79%).

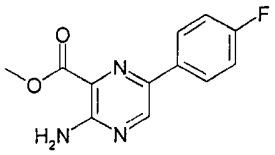
Synthesis of Intermediate 3-05
6-(4-Fluoro-phenyl)-pyridine-2-carboxylic acid methyl ester



3-05

A mixture of methyl 6-bromopicolinate (0.5 g, 2.31 mmol), 4-fluorophenylboronic acid (0.421 g, 3 mmol), sodium carbonate (4.1 mL, 2M aqueous solution) in 1,2-dimethoxyethane (12.5 mL) was degassed by bubbling argon for 15 min. Pd(dppf)Cl_2.DCM (0.287 g, 0.347 mmol) was added and the resulting mixture was heated under microwave irradiation at 75 °C for 80 min. On cooling, the mixture was evaporated and the residue was purified by column chromatography (Biotage, DCM) to afford Intermediate **3-05** (0.507 g, yield 95%) as colourless oil.

Intermediate **3-06** was prepared following an analogous procedure:

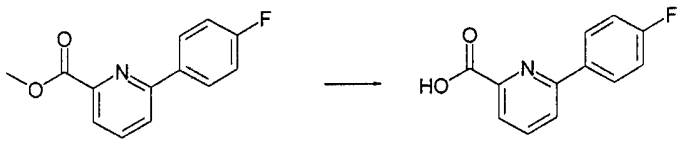


3-06

Yield: 100%.

Synthesis of Intermediate 3-07

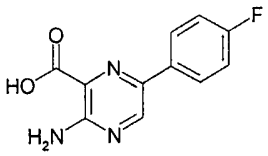
6-(4-Fluoro-phenyl)-pyridine-2-carboxylic acid



3-05 3-07

To a solution of Intermediate **3-05** (507 mg, 2.19 mmol) in H_2O:MeOH (6 mL, 1:1) was added lithium hydroxide monohydrate (469 mg, 10.96 mmol). The reaction mixture was heated at 80 °C for 3 h. After cooling to RT, the mixture was acidified by addition of HCl (1.6 M aqueous solution). The white solid was filtered off, washed with water and dried to afford Intermediate **3-07** (278 mg, 58%).

Intermediate **3-08** was prepared following an analogous procedure:

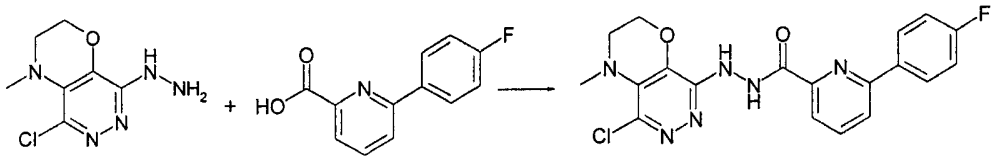


3-08

Yield: 83%.

Synthesis of Intermediate 3-09

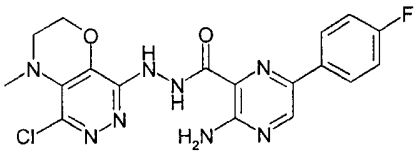
6-(4-Fluoro-phenyl)-pyridine-2-carboxylic acid N'-(5-chloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b][1,4]oxazin-8-yl)-hydrazide



3-04 3-07 3-09

A mixture of Intermediate **3-07** (156 mg, 0.72 mmol), HATU (394 mg, 1.0 mmol) and DIPEA (0.639 mL, 3.66 mmol) in DCM (6 mL) was stirred at RT for 15 min. A solution of Intermediate **3-04** (155 mg, 0.72 mmol) in DCM (4 mL) was added and the reaction mixture was stirred at RT for 14 h. The mixture was washed with water, and the organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (Biotage, cHex:EtOAc, 85:15 to 50:50) to afford Intermediate **3-09** (298 mg, 100%).

Intermediate **3-10** was prepared following an analogous procedure:

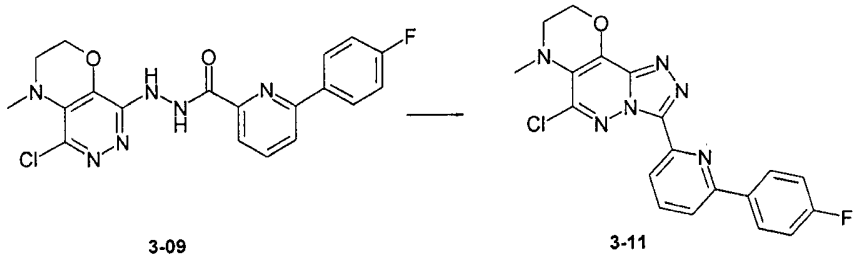


3-10

Yield: 51%.

Synthesis of Intermediate 3-11

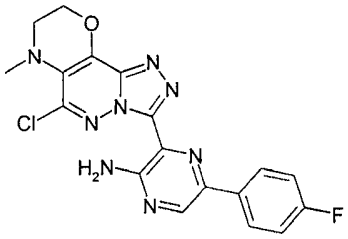
5-Chloro-3-[6-(4-fluoro-phenyl)-pyridin-2-yl]-6-methyl-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene



3-09 3-11

To a solution of Intermediate **3-09** (450 mg, 1.08 mmol) in acetonitrile (10 mL) was added DIPEA (0.567 mL, 3.25 mmol) followed by triphenylphosphine dibromide (620 mg, 1.41 mmol) portionwise at 0°C. The reaction mixture was stirred at 0°C for 1h and at RT for 12 h. The solvent was evaporated and the residue was purified by column chromatography (Biotage, DCM) to afford Intermediate **3-11** (430 mg, 100%).

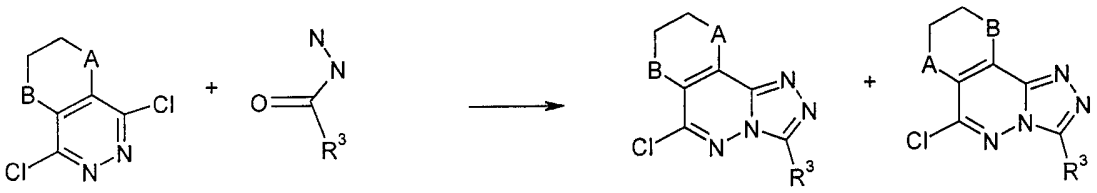
Intermediate **3-12** was prepared following an analogous procedure:



3-12

Yield: 63%.

Tricyclic intermediates

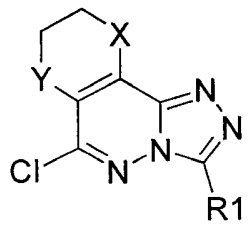


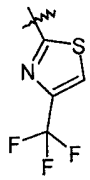
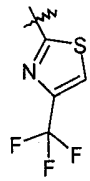
General procedure D

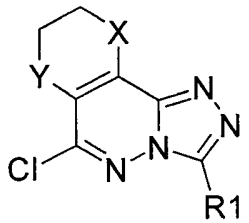
The appropriate bicyclic dichloropyridazines (e.g. 5,8-Dichloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b]-1,4-oxazine) (1 eq) and the appropriate hydrazide (e.g. formic acid hydrazide) (1.85 eq) were dissolved in n-butanol (7 mL/mmol). The mixture was heated at 155°C to 195°C in a sealed tube or in a Parr system for 2h to 40h. The solvent was evaporated under vacuum. The residue was purified by flash chromatography, eluent gradient: DCM-EtOAc 0-100% to give both regioisomers (e.g. 5-Chloro-6-methyl-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-benz[e]indene and 5-Chloro-9-methyl-8,9-dihydro-7H-6-oxa-1,2,3a,4,9-pentaaza-benz[e]indene).

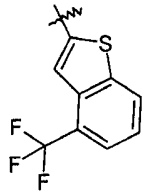
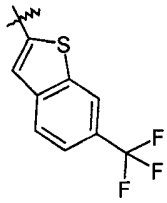
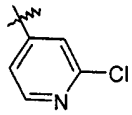
The intermediate compounds of Table 1 were prepared according to the general procedure D.

Table 1. 5-Chloro-tricycle Intermediates (**4-01** to **4-07**)



No.	--X--	--Y--	--R1	Yield %
4-01	--O--	--NMe--	H	42
4-02	--NMe--	--O--	H	23
4-03	--O--	--NMe--		18
4-04	--NMe--	--O--		14



No.	--X--	--Y--	--R1	Yield %
4-05	--O--	--NMe--		32
4-06	--O--	--NMe--		27
4-07	--O--	--O--		29

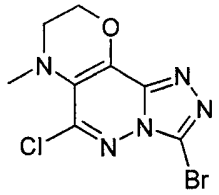
General procedure E

Bromide synthesis

To a solution of the appropriate 5-chloro-tricycle (**4-01** or **4-02**) (1 eq) in chloroform (4 mL/mmol), NBS (1.5 eq) was added. The reaction mixture was stirred at RT for 18h. A $NaHCO_3$ sat solution was added. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (Biotage, eluting with gradient DCM-EtOAc 0-100%) to yield the expected compounds.

Intermediate 5-01

3-Bromo-5-chloro-6-methyl-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-benz[e]indene



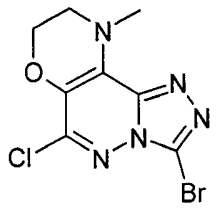
HPLC-MS (method 4): Rt=3.3 min, $[M+H]^+$ 304.0, 306.0.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (m, 2H), 3.48 (m, 2H), 3.03 (s, 3H).

Yield: 64%

Intermediate 5-02

3-Bromo-5-chloro-9-methyl-8,9-dihydro-7H-6-oxa-1,2,3a,4,9-pentaaza-benz[e]indene



HPLC-MS (method 4): Rt=3.7 min, $[M+H]^+$ 304.0, 306.0.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (m, 2H), 3.86 (s, 3H), 3. 59 (m, 2H).

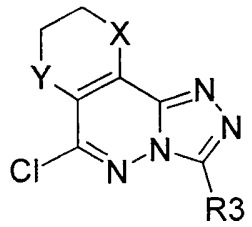
Yield: 57%

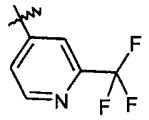
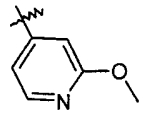
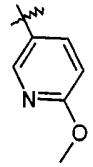
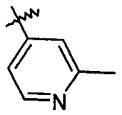
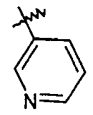
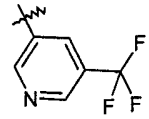
General procedure F

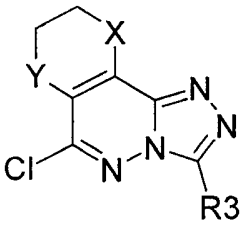
A mixture of the appropriate 3-Bromo-5-chloro-tricycle (**5-01** or **5-02**) (1.0 eq), the appropriate boronic acid or boronic acid pinacol ester (1.25 eq), Pd(dppf)Cl_2.DCM) (0.075 eq) and a saturated potassium carbonate solution (4.5 mL/mmol) in DME (6 mL/mmol) was heated under microwave irradiation at 100 to 120°C for 10 to 60 min. The reaction mixture was diluted with DCM and washed with water. The combined organic layers were dried (sodium sulphate), filtered and concentrated. The crude product was purified by flash chromatography Biotage eluting with DCM-EtOAc 0-100% or by CCTLC on a chromatotron (eluent: DCM/MeOH, 96/4) to give the desired product.

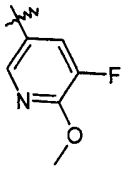
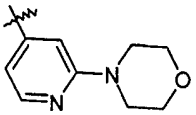
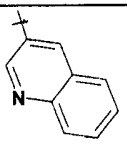
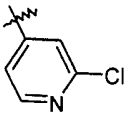
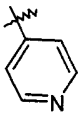
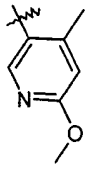
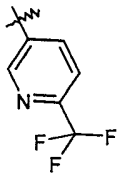
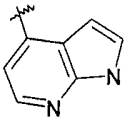
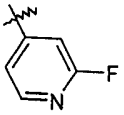
The intermediate compounds of Table 2 were prepared according to the general procedure F.

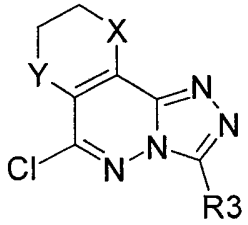
Table 2. 5-Chloro-tricycle Intermediates (**6-01** to **6-24**)

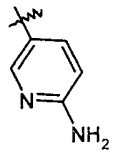
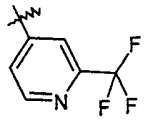
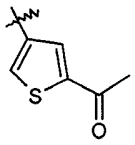
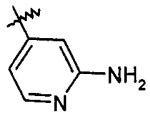
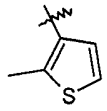
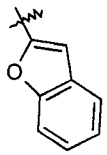
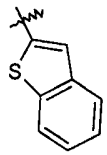
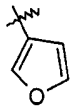


No.	--X--	--Y--	--R3	Yield %
6-01	--O--	--NMe--		50
6-02	--O--	--NMe--		64
6-03	--O--	--NMe--		64
6-04	--O--	--NMe--		92
6-05	--O--	--NMe--		42
6-06	--O--	--NMe--		35
6-07	--O--	--NMe--		37



No.	--X--	--Y--	--R3	Yield %
6-08	--O--	--NMe--		66
6-09	--O--	--NMe--		58
6-10	--O--	--NMe--		14
6-11	--O--	--NMe--		22
6-12	--O--	--NMe--		23
6-13	--O--	--NMe--		22
6-14	--O--	--NMe--		57
6-15	--O--	--NMe--		35
6-16	--O--	--NMe--		75



No.	--X--	--Y--	--R3	Yield %
6-17	--O--	--NMe--		48
6-18	--NMe--	--O--		36
6-19	--O--	--NMe--		69
6-20	--O--	--NMe--		25
6-21	--O--	--NMe--		39
6-22	--O--	--NMe--		54
6-23	--O--	--NMe--		39
6-24	--O--	--NMe--		52

Examples

General method I:

A solution of the appropriate chloride (e.g. 5-chloro-6-methyl-3-(2-trifluoromethyl-pyridin-4-yl)-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-benz[e]indene) and the appropriate amine (5 eq) (e.g. (1-methyl-4-piperidinyl)methanamine) in nBuOH was heated at 170°C under microwave irradiation for 6 h to 48 h. When the amine was a hydrochloride salt, DIPEA (5 eq.) was added. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (Isolute/Flash, SiII, 2.5% MeOH with 7N ammonia in DCM) followed by semi-preparative HPLC (Gemini C18 (150 10 mm; 5 m), Solvent A: water with 0.1% formic acid; Solvent B: acetonitrile with 0.1% formic acid. Gradient: 40% of A to 0% of A). Some compounds were isolated as their corresponding formic acid salts.

When the diamine was monoBoc-protected, deprotection of the Boc-protected compounds was achieved by treatment either with MeOH (10 mL/mmol) and HCl (4M in dioxane) (6 eq) at RT overnight (after evaporation, the final compounds were obtained as their corresponding hydrochloric salts) or with MeOH (10 mL/mmol) and Amberlyst (10 eq) at RT overnight and, after treatment with 7N NH_3 in MeOH, the final compounds were obtained in the free base form.

General method II:

A solution of the appropriate chloride (e.g. 5-Chloro-6-methyl-3-(2-trifluoromethyl-pyridin-4-yl)-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-benz[e]indene) and the appropriate monoBOC-protected amine (5 eq) (e.g. 2-amino-7-aza-spiro[3.5]nonane-7-carboxilic acid tert-butyl ester) in nBuOH was heated up to 180-185°C under microwave irradiation for 5 h to 10 h. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (Isolute/Flash, SiII, 2.5% MeOH with 7N ammonia in DCM) followed by semi-preparative HPLC (Gemini C18 (150 10 mm; 5 m), Solvent A: water with 0.1% formic acid; Solvent B: acetonitrile with 0.1% formic acid. Gradient: 40% of A to 0% of A) to yield the final compounds without the protecting group. In some cases, two compounds (regioisomers) were obtained in the reaction. Some compounds were isolated as their corresponding formic acid salts.

General method III

To a solution of the appropriate chloride (e.g. 5-Chloro-6-methyl-3-(2-trifluoromethyl-pyridin-4-yl)-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-benz[e]indene) in degassed dry 1,4-dioxane, sodium tertbutoxide (1.7 eq), BINAP (0.1 eq) or Xantphos (0.1 eq), $Pd_2(dba)_3$ (0.07 equiv) and the appropriate amine (e.g. 4-aminotetrahydropyran) were added at room temperature. When the amine was as hydrochloride, 3 eq. of sodium tertbutoxide were added. The mixture was heated in a mw oven at 120°C for 1h. The reaction mixture was filtered through a Celite pad and washed with DCM. The solvent was removed under vacuum to yield the crude mixture. The residue was purified by flash chromatography (Isolute/Flash, SiII, 2.5% MeOH with 7N ammonia in DCM) followed by semi-preparative HPLC (Gemini C18 (150 10 mm; 5 m), Solvent A: water with 0.1% formic acid; Solvent B: acetonitrile with 0.1% formic acid. Gradient: 40% of A to 0% of A). Some compounds were isolated as their corresponding formic acid salts.

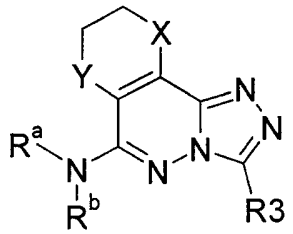
When the amine was Boc-protected, deprotection of the Boc-protected obtained compounds was achieved by treatment with dry MeOH (10 mL/mmol) and HCl (4M in dioxane) (6 eq) at room temperature overnight. After evaporation, the final compounds were obtained as their corresponding hydrochloric acid salts.

General method IV

To a solution of the appropriate chloride (e.g. 5-chloro-6-methyl-3-(2-trifluoromethyl-pyridin-4-yl)-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza cyclopenta[a]naphthalene) (1 eq) in DMA (10 mL/mmol) the appropriate amine (e.g. 2,8-diaza-spiro[4.5]decan-1-one) (3 eq) and TEA (3 eq) were added. The mixture was heated in a sealed tube at 100°C for 18h and at 125°C for 2h. On cooling, the solvent was removed under vacuum. Water and EtOAc were added, and the organic phase was separated, dried (Na_2SO_4), filtered and evaporated. The residue was purified by HPLC to give the desired product (e.g. 8-[6-methyl-3-(2-trifluoromethyl-pyridin-4-yl)-7,8-dihydro-6H-9-oxa-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalen-5-yl]-2,8-diaza-spiro[4.5]decan-1-one).

When the diamine was monoBoc-protected, deprotection of the Boc-protected obtained compounds was achieved by treatment either with MeOH (10 mL/mmol) and HCl (4M in dioxane) (6 eq) at RT overnight (after evaporation, the final compounds were obtained as their corresponding hydrochloric acid salts) or with MeOH (10 mL/mmol) and Amberlyst (10 eq) at RT overnight and, after treatment with 7N NH_3 in MeOH, the final compounds were obtained in the free base form.

Table 3: Final products



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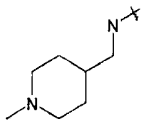
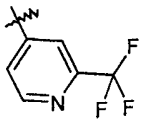
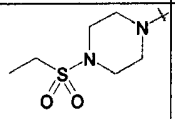
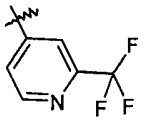
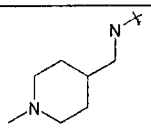
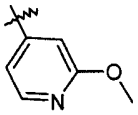
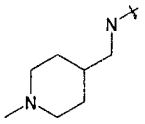
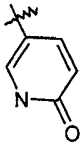
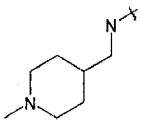
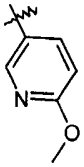
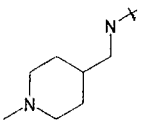
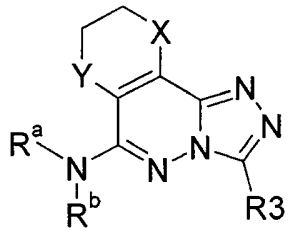
1		--O--	--NMe--		6-01	I	51
2		--O--	--NMe--		6-01	I	32
3		--O--	--NMe--		6-02	I	31
4		--O--	--NMe--		6-03	I	15
5		--O--	--NMe--		6-03	I	14
6		--O--	--NMe--		6-04	I	29



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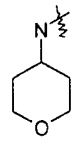
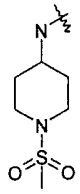
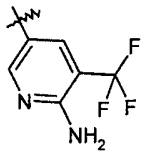
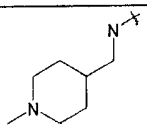
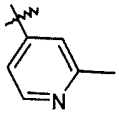
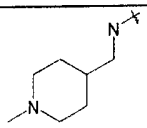
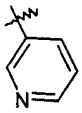
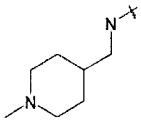
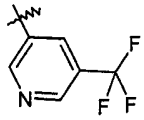
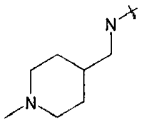
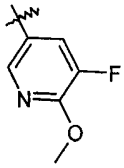
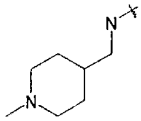
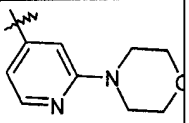
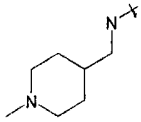
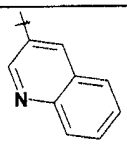
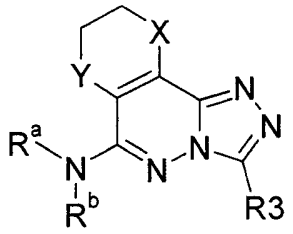
7		--O--	--NMe--		6-04	I	21
8		--O--	--NMe--		6-04	I	6
9		--O--	--NMe--		6-05	I	20
10		--O--	--NMe--		6-06	I	18
11		--O--	--NMe--		6-07	I	18
12		--O--	--NMe--		6-08	I	2
13		--O--	--NMe--		6-09	I	25
14		--O--	--NMe--		6-10	I	42



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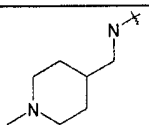
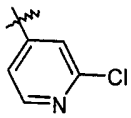
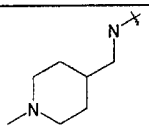
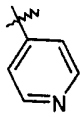
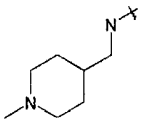
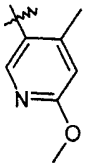
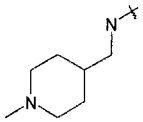
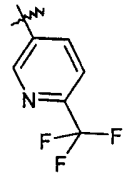
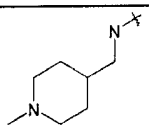
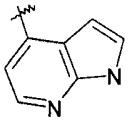
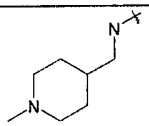
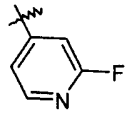
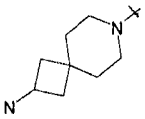
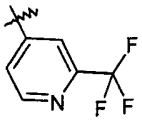
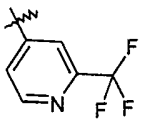
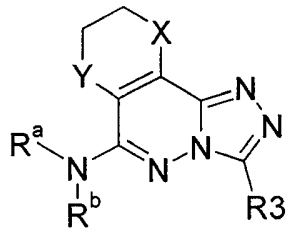
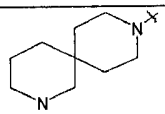
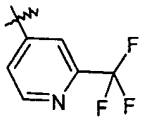
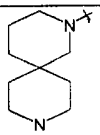
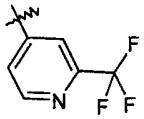
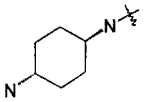
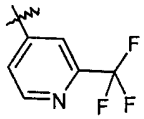
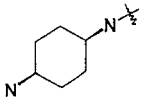
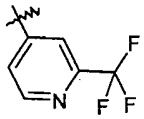
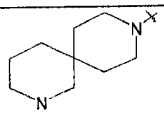
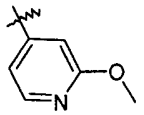
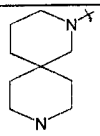
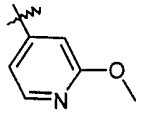
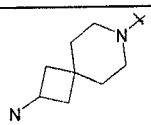
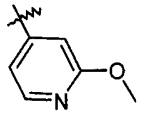
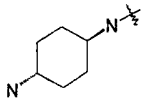
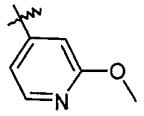
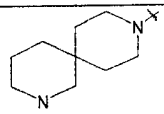
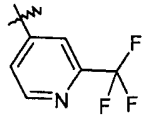
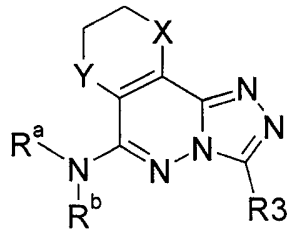
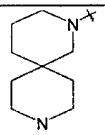
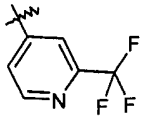
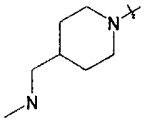
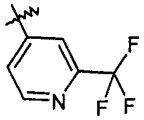
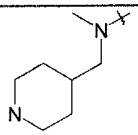
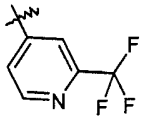
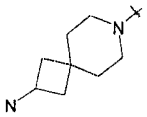
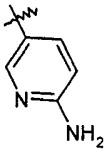
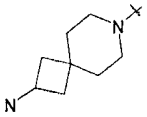
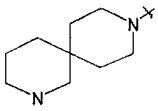
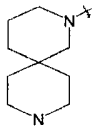
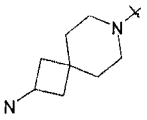
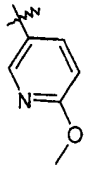
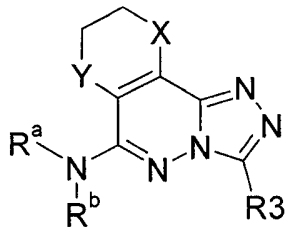
15		--O--	--NMe--		6-11	I	39
16		--O--	--NMe--		6-12	I	46
17		--O--	--NMe--		6-13	I	11
18		--O--	--NMe--		6-14	I	39
19		--O--	--NMe--		6-15	I	6
20		--O--	--NMe--		6-16	I	17
21		--O--	--NMe--		6-01	II	14
22		--O--	--NMe--		6-01	II	18

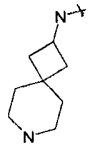
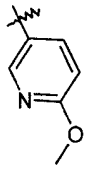
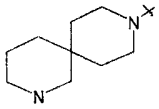
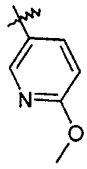
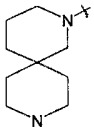
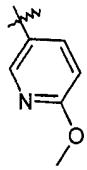
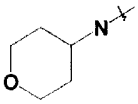
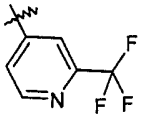
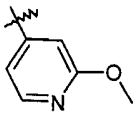
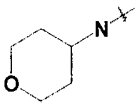
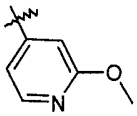
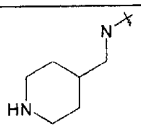
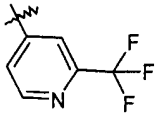
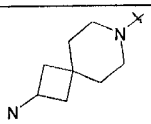
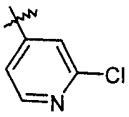


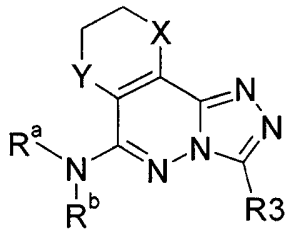
No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
23		--O--	--NMe--		6-01	II	7
24		--O--	--NMe--		6-01	II	22
25		--O--	--NMe--		6-01	II	19
26		--O--	--NMe--		6-01	II	19
27		--O--	--NMe--		6-02	II	6
28		--O--	--NMe--		6-02	II	21
29		--O--	--NMe--		6-02	II	3
30		--O--	--NMe--		6-02	II	13
31		--NMe--	--O--		6-18	II	12

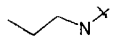
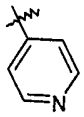
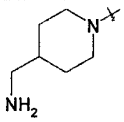
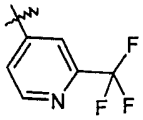
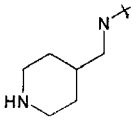
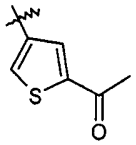
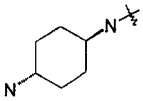
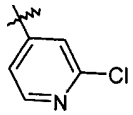
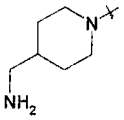
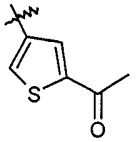
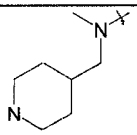
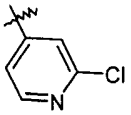
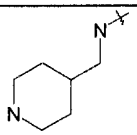
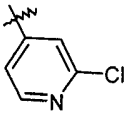
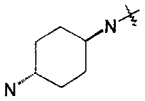
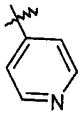
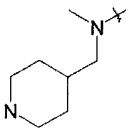
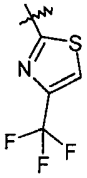


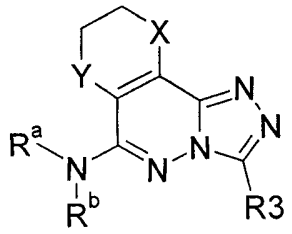
No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
32		--NMe--	--O--		6-18	II	31
33		--O--	--NMe--		6-01	II	22
34		--O--	--NMe--		6-01	II	22
35		--O--	--NMe--		6-17	II	9
36		--O--	--NMe--		6-04	II	6
37		--O--	--NMe--		6-04	II	9
38		--O--	--NMe--		6-04	II	17
39		--O--	--NMe--		6-03	II	16

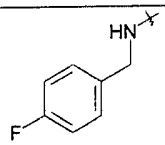
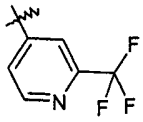
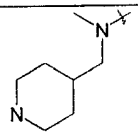
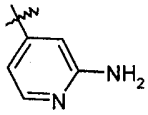
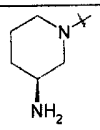
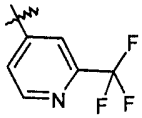
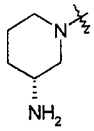
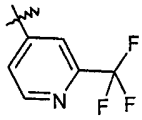
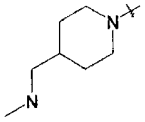
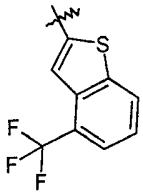
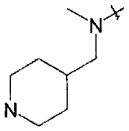
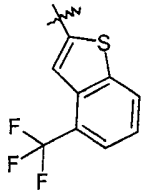
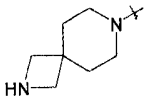
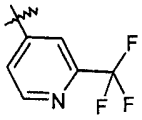
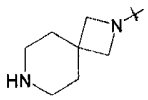
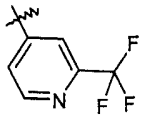


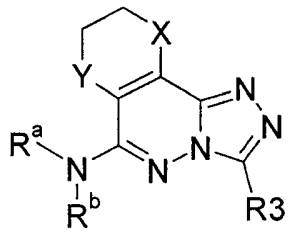
No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
40		--O--	--NMe--		6-03	II	14
41		--O--	--NMe--		6-03	II	4
42		--O--	--NMe--		6-03	II	5
43		--O--	--NMe--		6-01	III	13
44		--O--	--NMe--		6-02	III	81
45		--O--	--NMe--		6-02	III	4
46		--O--	--NMe--		6-01	I	26
47		--O--	--NMe--		6-11	I	11

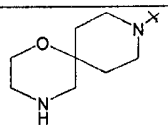
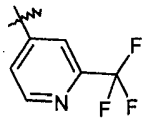
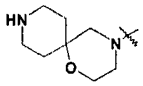
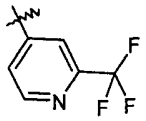
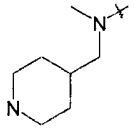
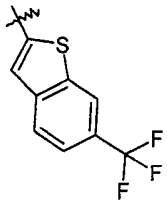
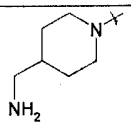
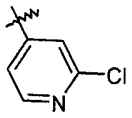
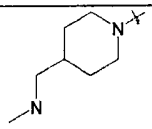
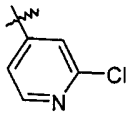
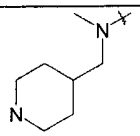
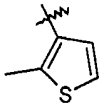
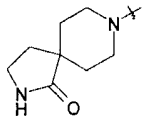
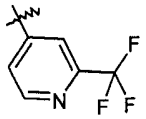
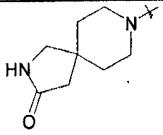
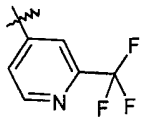


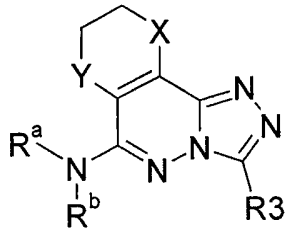
No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
48		--O--	--NMe--		6-12	I	74
49		--O--	--NMe--		6-01	I	10
50		--O--	--NMe--		6-19	I	15
51		--O--	--NMe--		6-11	I	15
52		--O--	--NMe--		6-19	I	9
53		--O--	--NMe--		6-11	I	80
54		--O--	--NMe--		6-11	I	82
55		--O--	--NMe--		6-12	I	3
56		--O--	--NMe--		4-03	I	66

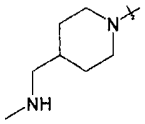
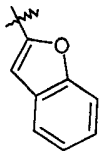
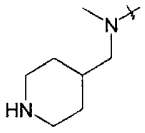
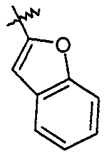
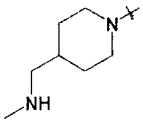
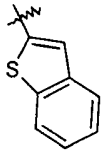
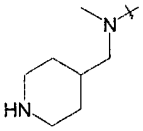
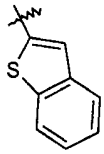
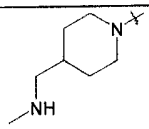
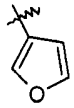
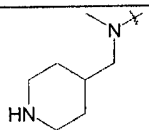
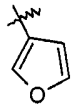
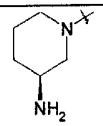
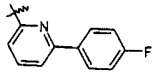
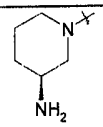
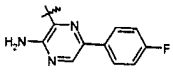


No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
57		--O--	--NMe--		6-01	I	47
58		--O--	--NMe--		6-20	I	39
59		--O--	--NMe--		6-01	I	60
60		--O--	--NMe--		6-01	I	73
61		--O--	--NMe--		4-05	I	22
62		--O--	--NMe--		4-05	I	23
63		--O--	--NMe--		6-01	I	45
64		--O--	--NMe--		6-01	I	41



No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
65		--O--	--NMe--		6-01	I	36
66		--O--	--NMe--		6-01	I	38
67		--O--	--NMe--		4-06	I	15
68		--O--	--O--		4-07	I	4
69		--O--	--O--		4-07	I	5
70		--O--	--NMe--		6-21	I	17
71		--O--	--NMe--		6-01	IV	20
72		--O--	--NMe--		6-01	IV	23



No.	--NR^{a}R^b	--X--	--Y--	--R3	Starting Material	General Method	Yield %
73		--O--	--NMe--		6-22	II	7
74		--O--	--NMe--		6-22	II	6
75		--O--	--NMe--		6-23	II	14
76		--O--	--NMe--		6-23	II	8
77		--O--	--NMe--		6-24	I	11
78		--O--	--NMe--		6-24	I	11
79		--O--	--NMe--		3-11	II	6
80		--O--	--NMe--		3-12	II	36

Example 81

Analytical data and PIM activity – R_t means retention time (in minutes), $[M+H]^+$ means the protonated mass of the compound, method refers to the method used for (LC)MS.

Biological activity in PIM1, PIM2 and PIM3 for certain examples is represented in Table 4 by semi-quantative results: IC50 >1μM (*), IC50 <100 nM (***), 100 nM < IC50 <1 μM (**). There are also some quantitative data, in parentheses, which depict the actual IC_{50} values (nM) for representative examples.

Table 4

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
1	3.99	463.0	2	*** (86)	*	**	$CDCl_3$ δ 9.03 (s, 1H), 8.86 (d, J = 5.2 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H), 8.50 (s, 1H), 5.36 (t, J = 5.8 Hz, 1H), 4.51 (m, 1H), 3.45 (t, J = 6.3 Hz, 1H), 3.33 (d, J = 11.8 Hz, 1H), 3.23 (m, 1H), 2.76 (s, 1H), 2.54 (s, 1H), 2.37 (td, J = 12.0, 2.5 Hz, 1H), 2.05 (s, 1H), 1.90 (d, J = 11.6 Hz, 1H), 1.75 (m, 1H).
2	4.84	513.2	1	**	*		$CDCl_3$ δ 8.92 (s, 1H), 8.88 (d, J = 5.1 Hz, 1H), 8.58 (d, J = 5.0 Hz, 1H), 4.44 (m, 2H), 3.72 (m, 4H), 3.54 (m, 4H), 3.30 (m, 2H), 3.04 (q, J = 7.4 Hz, 2H), 2.91 (s, 3H), 1.41 (t, J = 7.4 Hz, 3H).
3	5.2	425.2	3	**	*	**	$CDCl_3$ δ 8.55 (s, 1H), 8.25 (d, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.90 (dd, J = 5.5, 1.3 Hz, 1H), 5.56 (t, J = 5.7 Hz, 1H), 4.46 (m, 2H), 3.96 (s, 4H), 3.37 (m, 4H), 3.19 (m, 2H), 2.73 (s, 3H), 2.55 (s, 3H), 2.43 (td, J = 12.3, 2.2 Hz, 2H), 2.15 (ddd, J = 11.1, 8.1, 3.8 Hz, 1H), 1.93

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
							(m, 2H), 1.66 (m, 2H).
4	3.77	411.1	3	*	*		$CDCl_3$ δ 8.80 (d, *J* = 2.4 Hz, 1H), 8.52 (dd, *J* = 9.7, 2.5 Hz, 1H), 6.71 (d, *J* = 9.7 Hz, 1H), 5.20 (t, *J* = 5.8 Hz, 1H), 4.47 (m, 2H), 3.36 (t, *J* = 6.1 Hz, 2H), 3.20 (m, 2H), 2.95 (d, *J* = 11.1 Hz, 2H), 2.74 (s, 2H), 2.30 (s, 3H), 1.99 (t, *J* = 11.7 Hz, 3H), 1.82 (m, 3H), 1.52 (m, 2H).
5	5.0	425.1	3	**	*		$CDCl_3$ δ 9.30 (d, J = 1.9 Hz, 1H), 8.60 (dd, J = 8.7, 2.3 Hz, 1H), 8.51 (s, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.18 (t, J = 5.6 Hz, 1H), 4.47 (m, 2H), 4.01 (s, 3H), 3.40 (t, J = 6.0 Hz, 2H), 3.31 (d, J = 11.7 Hz, 2H), 3.0 (m, 2H), 2.74 (s, 3H), 2.53 (s, 3H), 2.39 (td, J = 12.0, 2.3 Hz, 2H), 2.01 (m, 1H), 1.90 (m, 2H), 1.73 (m, 2H).
6	2.6	478.1	1	**			$CDCl_3$ δ 9.32 (d, J = 1.7 Hz, 1H), 8.93 (d, J = 1.9 Hz, 1H), 8.50 (s, 1H), 5.27 (m, 1H), 4.46 (m, 2H), 3.37 (m, 4H), 3.20 (m, 2H), 2.73 (s, 3H), 2.56 (s, 3H), 2.43 (m, 2H), 2.03 (m, 1H), 1.88 (d, J = 11.3 Hz, 2H), 1.73 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
7	4.11	451.3	1	**		**	$CDCl_3$ δ 9.32 (s, 1H), 8.97 (s, 1H), 5.21 (s, 2H), 4.95 (d, J = 6.7 Hz, 1H), 4.48 (m, 2H), 4.04 (m, 3H), 3.59 (td, J = 11.7, 2.0 Hz, 2H), 3.21 (m, 2H), 2.75 (s, 3H), 2.15 (d, J = 12.3 Hz, 2H), 1.68 (m, 2H).
8	4.11	528.0	1	**	*	*	$CDCl_3$ δ 9.31 (s, 1H), 8.95 (s, 1H), 5.24 (s, 2H), 4.97 (d, J = 6.9 Hz, 1H), 4.49 (m, 2H), 3.87 (m, 3H), 3.21 (m, 2H), 2.90 (m, 2H), 2.84 (s, 3H), 2.73 (s, 3H), 2.29 (d, J = 10.9 Hz, 2H), 1.68 (m, 2H).
9	3.3	409.3	3	*	*		$CDCl_3$ δ 8.63 (d, J = 5.2 Hz, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 8.26 (d, J = 5.2 Hz, 1H), 5.26 (s, 1H), 4.49 (m, 2H), 3.43 (t, J = 6.1 Hz, 2H), 3.31 (m, 2H), 3.22 (m, 2H), 2.75 (s, 3H), 2.65 (s, 3H), 2.52 (s, 3H), 2.36 (m, 2H), 2.05 (m, 1H), 1.92 (s, 2H), 1.76 (s, 2H).
10	2.3	395.1	2	*	*		$CDCl_3$ δ 9.75 (d, J = 1.5 Hz, 1H), 8.73 (dt, J = 8.1, 1.8 Hz, 1H), 8.67 (dd, J = 4.8, 1.5 Hz, 1H), 8.50 (s, 1H), 7.44 (dd, J = 8.0, 4.9 Hz, 1H), 5.27 (t, J = 5.6 Hz, 1H), 4.48 (m, 2H), 3.42 (t, J = 6.1 Hz, 2H), 3.35 (m, 2H), 3.21 (m, 2H), 2.75 (s, 3H), 2.56 (s, 3H), 2.45 (t, J = 10.9 Hz, 2H), 2.05 (m, 1H), 1.91 (m, 2H), 1.76 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
11	2.85	463.1	1	*	*		$CDCl_3$ δ 9.91 (d, J = 1.6 Hz, 1H), 9.17 (s, 1H), 8.92 (s, 1H), 8.46 (s, 1H), 5.42 (t, J = 5.8 Hz, 1H), 4.50 (m, 2H), 3.43 (m, 4H), 3.22 (m, 2H), 2.76 (s, 3H), 2.62 (s, 3H), 2.52 (td, J = 11.8, 2.6 Hz, 2H), 2.09 (m, 1H), 1.85 (m, 4H).
12	2.74	443.2	1	*	*		DMSO-d_6 δ 8.99 (d, J = 1.6 Hz, 1H), 8.57 (dd, J = 11.9, 1.6 Hz, 1H), 8.25 (s, 1H), 6.94 (t, J = 5.2 Hz, 1H), 4.42 (m, 2H), 4.03 (s, 3H), 3.22 (m, 4H), 2.85 (m, 2H), 2.67 (s, 3H), 2.20 (s, 3H), 1.98 (m, 2H), 1.88 (m, 1H), 1.72 (m, 2H), 1.28 (m, 2H).
13	2.57	480.4	2	*	*		DMSO-d_6 δ 8.28 (d, J = 4.9 Hz, 1H), 8.18 (s, 1H), 7.92 (s, 1H), 7.66 (d, J = 5.3 Hz, 1H), 6.61 (t, J = 5.4 Hz, 1H), 4.44 (m, 2H), 3.75 (m, 4H), 3.53 (m, 4H), 3.28 (m, 2H), 3.21 (m, 2H), 2.81 (m, 2H), 2.70 (s, 3H), 2.18 (s, 3H), 1.90 (m, 2H), 1.79 (m, 1H), 1.71 (d, J = 12.5 Hz, 2H), 1.26 (m, 2H).
14	3.85	445.2	2	*	*		$CDCl_3$ δ 10.03 (d, J = 2.0 Hz, 1H), 9.33 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 7.1 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 5.20 (t, J = 5.5 Hz, 1H), 4.49 (m, 2H), 3.44 (t, J = 5.8 Hz, 2H), 3.22 (m, 2H), 3.00 (m, 2H), 2.77 (s, 3H), 2.33 (s, 3H), 2.06 (m, 2H), 1.86 (m, 3H), 1.54 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
15	2.52	429.2	1	*** (44)	*	**	$CDCl_3$ δ 8.59 (s, 1H), 8.45 (t, J = 5.3 Hz, 1H), 8.38 (s, 1H), 8.28 (dd, J = 5.3, 1.2 Hz, 1H), 5.30 (t, J = 5.6 Hz, 1H), 4.44 (m, 2H), 3.37 (t, J = 6.3 Hz, 2H), 3.29 (m, 2H), 3.16 (m, 2H), 2.69 (s, 3H), 2.49 (s, 3H), 2.35 (m, 2H), 1.90 (m, 2H), 1.71 (m, 2H).
16	3.20	395.2	3	*	*	**	DMSO-d_6 δ 8.74 (d, J = 5.6 Hz, 2H), 8.39 (d, J = 5.6 Hz, 2H), 8.25 (s, 1H), 6.97 (t, J = 5.5 Hz, 1H), 4.43 (m, 2H), 3.27 (m, 2H), 3.20 (m, 2H), 2.85 (m, 2H), 2.68 (s, 3H), 2.19 (s, 3H), 1.95 (m, 3H), 1.74 (m, 2H), 1.29 (m, 2H).
17	2.37	439.3	1	*	*		DMSO-d_6 δ 8.45 (s, 1H), 8.24 (s, 1H), 6.88 (s, 1H), 6.68 (t, J = 5.5 Hz, 1H), 4.41 (m, 2H), 3.90 (s, 3H), 3.19 (m, 2H), 3.05 (t, J = 6.0 Hz, 2H), 2.79 (m, 2H), 2.33 (s, 3H), 2.19 (s, 3H), 1.93 (m, 2H), 1.71 (m, 1H), 1.60 (m, 2H), 1.19 (m, 2H).
18	2.78	463.2	1	*	*		DMSO-d_6 δ 9.76 (s, 1H), 9.03 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 6.95 (t, J = 5.7 Hz, 1H), 4.44 (m, 2H), 3.26 (m, 2H), 3.21 (m, 2H), 2.78 (m, 2H), 2.68 (s, 3H), 2.14 (s, 3H), 1.85 (m, 3H), 1.71 (m, 2H), 1.28 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
19	2.40	434.4	1	*	*		DMSO-d_6 δ 11.93 (s, 1H), 9.21 (d, J = 1.6 Hz, 1H), 9.02 (d, J = 1.4 Hz, 1H), 8.30 (s, 1H), 7.58 (m, 1H), 6.89 (t, J = 5.3 Hz, 1H), 6.50 (m, 1H), 4.43 (m, 2H), 3.24 (m, 4H), 2.82 (d, J = 11.2 Hz, 2H), 2.69 (s, 3H), 2.16 (s, 3H), 1.91 (m, 3H), 1.76 (d, J = 11.7 Hz, 2H), 1.27 (m, 2H).
20	2.53	413.3	1	**	*		DMSO-d_6 δ 8.42 (d, J = 5.3 Hz, 1H), 8.29 (d, J = 5.3 Hz, 1H), 8.24 (s, 1H), 8.21 (s, 1H), 7.10 (t, J = 5.6 Hz, 1H), 4.44 (m, 2H), 3.24 (m, 4H), 2.82 (m, 2H), 2.68 (s, 3H), 2.18 (s, 3H), 1.92 (m, 3H), 1.74 (d, J = 12.5 Hz, 2H), 1.27 (m, 2H).
21	3.08	475.3	1	*** (3)	**	*** (33)	$CDCl_3$ δ 9.01 (s, 1H), 8.87 (d, J = 5.2 Hz, 1H), 8.62 (dd, J = 5.1, 0.7 Hz, 1H), 4.39 (m, 2H), 3.51 (m, 4H), 3.29 (m, 2H), 2.90 (s, 3H), 2.32 (m, 2H), 1.80 (m, 4H), 1.64 (m, 2H).
22	3.25	475.3	1	*** (5)	**	*** (17)	MeOD δ 9.05 (s, 1H), 8.84 (d, J = 4.9 Hz, 1H), 8.53 (m, 2H), 4.48 (m, 2H), 4.34 (m, 1H), 3.30 (m, 2H), 3.13 (m, 2H), 3.02 (m, 2H), 2.78 (s, 3H), 2.51 (m, 2H), 1.96 (m, 4H), 1.81 (m, 2H).
23	4.06	489.2	1	*** (26)	*	*** (75)	$CDCl_3$ δ 8.96 (s, 1H), 8.89 (d, J = 4.8 Hz, 1H), 8.62 (d, J = 4.5 Hz, 1H), 8.58 (s, 1H), 4.40 (t, J = 4.0 Hz, 2H), 3.57 (m, 4H), 3.28 (m, 2H), 3.08 (m, 2H), 2.99 (m, 2H), 2.89 (s, 3H), 1.84 (m, 6H), 1.68 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
24	3.32	489.3	1	*** (0.7)	**	*** (14)	$CDCl_3$ δ 9.05 (s, 1H), 8.87 (d, J = 5.3 Hz, 1H), 8.58 (m, 2H), 4.44 (m, 2H), 3.51 (m, 2H), 3.38 (m, 2H), 3.32 (m, 2H), 3.11 (s, 4H), 2.88 (s, 3H), 1.83 (m, 6H), 1.69 (m, 2H).
25	4.19	449.2	2	*** (2)	**	*** (29)	MeOD δ 8.96 (s, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.57 (d, J = 5.3 Hz, 1H), 8.54 (s, 1H), 4.51 (m, 2H), 3.87 (m, 1H), 3.30 (m, 2H), 3.20 (m, 1H), 2.77 (s, 3H), 2.36 (m, 2H), 2.17 (m, 2H), 1.62 (m, 4H).
26	4.28	449.2	2	*** (2)	**	*** (13)	CDCl3 δ 9.04 (s, 1H), 8.84 (d, J = 5.2 Hz, 1H), 8.57 (dd, J = 5.1, 1.1 Hz, 1H), 8.28 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 4.48 (m, 2H), 4.04 (m, 1H), 3.23 (m, 3H), 2.77 (s, 3H), 2.61 (s, 3H), 2.05 (m, 2H), 1.91 (m, 4H), 1.76 (m, 2H).
27	2.94	451.2	1	*** (94)	*	**	$CDCl_3$ δ 8.45 (s, 1H), 8.30 (d, J = 5.4 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.88 (s, 1H), 4.37 (m, 2H), 3.99 (s, 3H), 3.51 (m, 4H), 3.24 (m, 2H), 3.11 (m, 2H), 3.02 (m, 2H), 2.86 (s, 3H), 1.83 (m, 6H), 1.68 (m, 2H).
28	3.01	451.3	1	*** (3)	*	*** (33)	$CDCl_3$ δ 8.43 (s, 1H), 8.28 (d, J = 5.7 Hz, 1H), 7.91 (m, 2H), 4.40 (m, 2H), 3.98 (s, 3H), 3.46 (m, 2H), 3.35 (m, 2H), 3.28 (m, 2H), 3.15 (m, 4H), 2.84 (s, 3H), 1.84 (m, 6H), 1.66 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
29	2.89	437.3	2	*** (15)	*	**	$CDCl_3$ δ 8.30 (d, J = 5.7 Hz, 1H), 7.96 (d, J = 5.7 Hz, 1H), 7.91 (s, 1H), 4.38 (m, 2H), 4.00 (s, 3H), 3.74 (m, 1H), 3.33 (m, 2H), 3.27 (m, 4H), 2.88 (s, 3H), 2.28 (m, 2H), 1.94 (m, 2H), 1.55 (m, 4H).
30	3.42	411.2	2	*** (2)	*	*** (27)	MeOD δ 8.52 (s, 2H), 8.20 (d, J = 5.3 Hz, 1H), 7.86 (s, 1H), 7.81 (d, J = 4.5 Hz, 1H), 6.20 (d, J = 6.8 Hz, 1H), 4.48 (m, 2H), 3.96 (s, 3H), 3.79 (m, 1H), 3.27 (m, 2H), 3.06 (m, 1H), 2.74 (s, 3H), 1.52 (m, 8H).
31	3.32	489.2	1	**	*		$CDCl_3$ δ 8.98 (s, 1H), 8.88 (d, J = 5.0 Hz, 1H), 8.62 (d, J = 5.0 Hz, 1H), 8.50 (s, 1H), 4.31 (m, 2H), 3.80 (s, 3H), 3.53 (m, 2H), 3.42 (m, 4H), 3.08 (m, 2H), 2.99 (m, 2H), 1.80 (m, 6H), 1.66 (m, 2H).
32	3.49	489.2	1	**	*		$CDCl_3$ δ 9.06 (s, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.52 (s, 1H), 4.34 (m, 2H), 3.81 (s, 3H), 3.57 (m, 2H), 3.37 (m, 2H), 3.25 (m, 2H), 3.14 (m, 4H), 1.85 (m, 6H), 1.61 (m, 2H).
33	2.96	463.3	1	*** (26)	*	**	$CDCl_3$ δ 8.95 (s, 1H), 8.84 (d, J = 5.1 Hz, 1H), 8.57 (m, 2H), 4.39 (m, 2H), 4.29 (m, 2H), 3.27 (m, 2H), 2.91 (m, 7H), 2.66 (s, 3H), 2.06 (m, 3H), 1.55 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
34	3.11	463.2	1	*** (2)	*	*** (81)	$CDCl_3$ δ 8.96 (s, 1H), 8.85 (d, J = 5.1 Hz, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.47 (s, 1H), 4.41 (m, 2H), 3.59 (m, 2H), 3.30 (m, 4H), 3.14 (s, 3H), 2.79 (s, 3H), 2.74 (m, 2H), 2.02 (m, 1H), 1.74 (d, J = 12.3 Hz, 2H), 1.52 (s, 2H).
35	3.66	422.3	3	**	*		MeOD δ 9.06 (d, J = 2.1 Hz, 1H), 8.54 (s, 1H), 8.30 (dd, J = 8.8, 2.3 Hz, 1H), 6.72 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 4.2 Hz, 2H), 3.80 (m, 1H), 3.53 (m, 2H), 3.45 (m, 2H), 2.94 (s, 3H), 2.39 (m, 2H), 1.90 (m, 6H).
36	2.90	490.3	1	*** (36)	**	**	$CDCl_3$ δ 9.30 (s, 1H), 8.91 (s, 1H), 8.39 (s, 1H), 4.35 (m, 2H), 3.62 (m, 2H), 3.39 (m, 4H), 3.24 (m, 2H), 2.86 (s, 3H), 2.30 (m, 2H), 1.81 (m, 6H).
37	2.92	504.3	1	**	*	**	$CDCl_3$ δ 9.35 (s, 1H), 8.90 (s, 1H), 8.53 (s, 1H), 5.32 (s, 2H), 4.38 (m, 2H), 3.57 (m, 2H), 3.45 (m, 2H), 3.24 (m, 2H), 3.08 (m, 2H), 2.97 (m, 2H), 2.86 (s, 3H), 1.81 (m, 6H), 1.66 (m, 2H).
38	3.06	504.3	1	*** (32)	*	**	$CDCl_3$ δ 9.29 (s, 1H), 8.96 (d, J = 1.5 Hz, 1H), 8.53 (s, 1H), 5.38 (s, 2H), 4.40 (m, 2H), 3.44 (m, 2H), 3.28 (m, 4H), 3.11 (m, 4H), 2.85 (s, 3H), 1.82 (m, 6H), 1.64 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
39	2.89	437.3	1	*** (60)	*	*	$CDCl_3$ δ 9.28 (d, J = 2.1 Hz, 1H), 8.59 (dd, J = 8.8, 2.3 Hz, 1H), 8.49 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.36 (m, 2H), 4.00 (s, 3H), 3.73 (m, 1H), 3.39 (m, 4H), 3.23 (m, 2H), 2.87 (s, 3H), 2.36 (m, 2H), 1.98 (m, 2H), 1.81 (m, 4H).
40	2.74	437.2	1	**	*	*	$CDCl_3$ δ 9.24 (d, J = 1.9 Hz, 1H), 8.53 (m, 2H), 6.86 (d, J = 8.7 Hz, 1H), 5.12 (d, J = 5.3 Hz, 1H), 4.47 (m, 2H), 4.30 (m, 1H), 4.00 (s, 3H), 3.32 (m, 1H), 3.25 (m, 1H), 3.19 (m, 2H), 3.11 (m, 1H), 3.03 (m, 1H), 2.74 (s, 3H), 2.54 (m, 2H), 1.98 (m, 2H), 1.89 (m, 2H), 1.53 (m, 2H).
41	2.86	451.3	1	**	*	*	$CDCl_3$ δ 9.28 (d, J = 2.1 Hz, 1H), 8.60 (dd, J = 8.8, 2.4 Hz, 1H), 8.54 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.37 (m, 2H), 4.02 (s, 3H), 3.55 (m, 2H), 3.39 (m, 2H), 3.23 (m, 2H), 3.07 (m, 2H), 2.95 (m, 2H), 2.87 (s, 3H), 1.82 (m, 6H), 1.67 (m, 2H).
42	3.02	451.3	1	*** (25)	*	*** (89)	$CDCl_3$ δ 9.25 (d, J = 2.0 Hz, 1H), 8.58 (m, 2H), 6.88 (d, J = 8.7 Hz, 1H), 4.40 (m, 2H), 4.01 (s, 3H), 3.41 (m, 2H), 3.28 (m, 4H), 3.11 (m, 4H), 2.83 (s, 3H), 1.82 (m, 6H), 1.63 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
43	4.72	436.2	1	*** (47)	*	*	$CDCl_3$ δ 9.05 (s, 1H), 8.86 (d, J = 5.2 Hz, 1H), 8.58 (dd, J = 5.2, 1.2 Hz, 1H), 5.04 (d, J = 6.8 Hz, 1H), 4.51 (m, 2H), 4.07 (m, 3H), 3.62 (td, J = 11.7, 2.1 Hz, 2H), 3.24 (m, 2H), 2.77 (s, 3H), 2.19 (dd, J = 12.4, 2.2 Hz, 2H), 1.67 (m, 2H).
44	2.73	437.2	1	*** (14)	*	*** (35)	DMSO δ 8.85 (br s, 2H), 8.33 (d, J = 5.3 Hz, 1H), 8.07 (s, 1H), 7.87 (d, J = 5.0 Hz, 1H), 7.12 (d, J = 5.4 Hz, 1H), 4.44 (m, 2H), 4.24 (m, 1H), 3.93 (s, 3H), 3.22 (m, 2H), 3.08 (m, 2H), 2.94 (m, 2H), 2.70 (s, 3H), 2.39 (m, 2H), 1.98 (m, 2H), 1.85 (m, 2H), 1.76 (m, 2H).
45	4.30	398.2	1	*** (51)	*	**	$CDCl_3$ δ 8.28 (d, J = 5.5 Hz, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.94 (dd, J = 5.5, 1.4 Hz, 1H), 4.96 (d, J = 6.4 Hz, 1H), 4.48 (m, 2H), 4.07 (m, 3H), 3.99 (s, 3H), 3.65 (m, 2H), 3.22 (m, 2H), 2.76 (s, 3H), 2.20 (m, 2H), 1.66 (m, 2H).
46	2.80	449.3	1	*** (5)	**	*** (21)	DMSO δ 8.96 (m, 2H), 8.62 (d, *J* = 5.6 Hz, 1H), 7.10 (t, *J* = 5.6 Hz, 1H), 4.45 (m, 2H), 3.28 (m, 2H), 3.22 (m, 2H), 3.15 (m, 2H), 2.69 (s, 3H), 2.66 (m, 2H), 2.05 (m, 1H), 1.78 (m, 2H), 1.28 (m, 2H).
47	4.30	441.1	2	*** (2)	**	*** (32)	MeOD δ 8.54 (m, 2H), 8.34 (t, *J* = 4.7 Hz, 1H), 4.43 (m, 2H), 3.82 (m, 1H), 3.60 (m, 2H), 3.52 (m, 2H), 3.35 (m, 2H), 2.96 (s, 3H), 2.42 (m, 2H),

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
							1.95 (m, 6H).
48	3.22	326.2	1	**	**	*** (57)	$CDCl_3$ δ 8.75 (dd, *J* = 4.7, 1.6 Hz, 2H), 8.47 (dd, *J* = 4.7, 1.6 Hz, 2H), 5.08 (t, *J* = 5.1 Hz, 1H), 4.48 (m, 2H), 3.44 (m, 2H), 3.22 (m, 2H), 2.76 (s, 3H), 1.80 (h, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.4 Hz, 3H).
49	2.99	449.2	1	*** (12)	*	**	DMSO δ 8.97 (d, *J* = 5.1 Hz, 1H), 8.92 (s, 1H), 8.61 (d, *J* = 5.0 Hz, 2H), 4.39 (m, 2H), 4.24 (m, 2H), 3.30 (m, 2H), 2.84 (m, 5H), 2.71 (m, 2H), 1.90 (m, 2H), 1.77 (m, 1H), 1.43 (m, 2H).
50	3.46	428.3	2	*** (53)	*	*** (72)	DMSO δ 8.82 (d, *J* = 1.1 Hz, 1H), 8.64 (d, *J* = 1.1 Hz, 1H), 6.89 (t, *J* = 5.4 Hz, 1H), 4.44 (m, 2H), 3.20 (m, 6H), 2.70 (m, 2H), 2.68 (s, 3H), 2.64 (s, 3H), 2.02 (m, 1H), 1.81 (m, 2H), 1.31 (m, 2H).
51	0.36, 3.31	415.1	2	*** (2)	**	*** (15)	$CDCl_3$-MeOD 10:1 δ 8.55 (s, 1H), 8.41 (d, *J* = 5.3 Hz, 1H), 8.21 (dd, *J* = 5.3, 1.0 Hz, 1H), 5.15 (d, *J* = 6.5 Hz, 1H), 4.44 (m, 2H), 3.73 (m, 1H), 3.18 (m, 2H), 3.08 (m, 1H), 2.68 (s, 3H), 2.33 (m, 2H), 2.17 (m, 2H), 1.61 (m, 2H), 1.42 (m, 2H).
52	3.88	428.3	2	*** (93)	*	**	DMSO δ 8.84 (s, 1H), 8.63 (s, 1H), 4.37 (m, 2H), 4.22 (m, 2H), 3.28 (m, 2H), 2.85 (s, 3H), 2.80 (m, 2H), 2.70 (m, 2H), 2.66 (s, 3H), 1.89 (m,

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
							2H), 1.72 (m, 1H), 1.41 (m, 2H).
53	4.31	429.2	2	*** (10)	**	*** (28)	$CDCl_3$ δ 8.53 (s, 1H), 8.51 (d, *J* = 5.4 Hz, 1H), 8.31 (dd, *J* = 5.3, 1.3 Hz, 1H), 4.41 (m, 2H), 3.57 (d, *J* = 7.0 Hz, 2H), 3.32 (m, 4H), 3.16 (s, 3H), 2.80 (s, 3H), 2.76 (m, 2H), 2.07 (m, 1H), 1.81 (m, 2H), 1.53 (m, 2H).
54	3.45	415.1	2	*** (29)	**	*** (21)	MeOD δ 8.42 (m, 2H), 8.16 (d, *J* = 5.3 Hz, 1H), 6.99 (t, *J* = 5.6 Hz, 1H), 4.47 (m, 2H), 3.46 (m, 2H), 3.35 (m, 2H), 3.26 (m, 2H), 3.08 (m, 2H), 2.76 (s, 3H), 2.32 (m, 1H), 2.12 (m, 2H), 1.53 (m, 2H).
55	3.40	381.2	3	**	**	*** (46)	$CDCl_3$ δ 8.75 (dd, *J* = 4.7, 1.5 Hz, 2H), 8.46 (dd, *J* = 4.7, 1.6 Hz, 2H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.48 (m, 2H), 3.76 (m, 1H), 3.21 (m, 2H), 2.83 (m, 1H), 2.74 (s, 3H), 2.32 (m, 2H), 2.04 (m, 2H), 1.39 (m, 4H).
56	2.93	469.2	1	*** (37)	*	**	$CDCl_3$ δ 7.93 (s, 1H), 4.39 (m, 2H), 3.63 (d, *J* = 6.8 Hz, 2H), 3.38 (m, 2H), 3.31 (m, 2H), 3.20 (s, 3H), 2.89 (m, 2H), 2.80 (s, 3H), 2.19 (m, 1H), 1.82 (m, 2H), 1.58 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
57	5.58	460.2	1	*** (39)	*	*** (32)	$CDCl_3$ δ 8.95 (s, 1H), 8.84 (d, *J* = 5.1 Hz, 1H), 8.54 (d, *J* = 5.0 Hz, 1H), 7.39 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 5.47 (t, *J* = 5.1 Hz, 1H), 4.63 (d, *J* = 5.3 Hz, 2H), 4.53 (m, 2H), 3.24 (m, 2H), 2.80 (s, 3H).
58	3.22	410.4	3	**	*		MeOD δ 8.06 (d, *J* = 5.2 Hz, 1H), 7.59 (m, 2H), 4.44 (m, 2H), 3.66 (d, *J* = 7.1 Hz, 2H), 3.34 (m, 4H), 3.21 (s, 3H), 2.90 (m, 2H), 2.84 (s, 3H), 2.16 (m, 1H), 1.87 (m, 2H), 1.35 (m, 2H).
59	2.81	435.2	1	*** (30)	*	**	DMSO δ 8.97 (d, *J* = 5.2 Hz, 1H), 8.86 (s, 1H), 8.64 (m, 1H), 4.39 (m, 2H), 4.25 (m, 1H), 4.02 (m, 1H), 3.28 (m, 2H), 3.16 (m, 1H), 2.83 (m, 5H), 2.01 (m, 1H), 1.87 (m, 1H), 1.74 (m, 1H), 1.43 (m, 1H).
60	2.83	435.2	1	*** (44)	*	**	DMSO δ 8.97 (d, *J* = 5.1 Hz, 1H), 8.86 (s, 1H), 8.64 (m, 1H), 4.39 (m, 2H), 4.26 (m, 1H), 4.02 (m, 1H), 3.28 (m, 2H), 3.08 (m, 1H), 2.83 (m, 5H), 2.02 (m, 1H), 1.87 (m, 1H), 1.75 (m, 1H), 1.43 (m, 1H).
61	3.58	518.2	1	*** (9)	**	**	$CDCl_3$ δ 8.56 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.31 (m, 1H), 4.30 (m, 4H), 3.17 (m, 2H), 2.90 (m, 4H), 2.80 (s, 3H), 2.72 (s, 3H), 2.17 (m, 1H), 2.07 (m, 2H), 1.59 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
62	3.73	518.2	1	*** (1)	**	*** (8)	$CDCl_3$ δ 8.67 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.41 (m, 1H), 4.38 (m, 2H), 3.61 (m, 2H), 3.32 (m, 4H), 3.16 (s, 3H), 2.79 (m, 5H), 2.09 (m, 1H), 1.81 (m, 2H), 1.55 (m, 2H).
63	2.81	461.2	1	*** (30)	*	**	DMSO) δ 8.98 (d, *J* = 4.9 Hz, 1H), 8.89 (s, 1H), 8.61 (m, 1H), 4.39 (m, 2H), 3.69 (m, 4H), 3.49 (m, 4H), 3.29 (m, 2H), 2.83 (s, 3H), 1.98 (m, 4H).
64	2.86	461.2	1	*** (98)	*	*	DMSO δ 8.96 (d, *J* = 5.2 Hz, 1H), 8.88 (s, 1H), 8.66 (m, 1H), 4.41 (m, 2H), 3.96 (s, 4H), 3.21 (m, 2H), 2.92 (m, 4H), 2.70 (s, 3H), 1.88 (m, 4H).
65	3.00	491.2	1	*** (45)	*	*** (82)	DMSO δ 8.96 (m, 2H), 8.61 (d, *J* = 4.9 Hz, 1H), 4.38 (m, 2H), 3.85 (m, 2H), 3.60 (m, 2H), 3.29 (m, 4H), 2.85 (s, 3H), 2.71 (m, 2H), 2.66 (m, 2H), 2.04 (m, 2H), 1.71 (m, 2H).
66	3.0	491.2	1	*** (29)	*	*** (73)	DMSO δ 8.97 (m, 2H), 8.59 (m, 1H), 8.21 (s, 1H), 4.42 (m, 1H), 4.38 (m, 1H), 3.92 (m, 1H), 3.85 (m, 1H), 3.61 (m, 1H), 3.54 (m, 1H), 3.28 (m, 5H), 3.11 (m, 1H), 2.98 (m, 1H), 2.85 (s, 3H), 2.73 (m, 1H), 2.09 (m, 2H), 1.71 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
67	3.91	518.2	1	**	*	**	DMSO δ 8.56 (s, 1H), 8.41 (s, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 4.39 (m, 2H), 3.60 (d, *J* = 6.4 Hz, 2H), 3.29 (m, 2H), 3.15 (m, 5H), 2.71 (m, 5H), 2.07 (m, 1H), 1.70 (m, 2H), 1.32 (m, 2H).
68	2.55	402.2	1	*** (72)	*	**	DMSO δ 8.62 (d, *J* = 5.2 Hz, 1H), 8.49 (s, 1H), 8.40 (s, 1H), 8.34 (dd, *J* = 5.2, 1.1 Hz, 1H), 4.61 (s, 2H), 4.51 (s, 2H), 4.07 (m, 2H), 2.93 (m, 2H), 2.62 (m, 2H), 1.84 (m, 2H), 1.69 (m, 1H), 1.34 (m, 2H).
69	3.26	416.1	1	**	*		MeOD δ 8.57 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.46 (s, 1H), 8.29 (m, 1H), 4.66 (m, 2H), 4.58 (m, 2H), 4.24 (m, 2H), 3.05 (m, 2H), 2.88 (d, *J* = 6.9 Hz, 2H), 2.67 (s, 3H), 2.01 (m, 1H), 1.95 (m, 2H), 1.54 (m, 2H).
70	2.89	414.2	1	**	*		DMSO δ 7.81 (d, *J* = 5.4 Hz, 1H), 7.48 (d, *J* = 5.3 Hz, 1H), 4.38 (m, 2H), 3.46 (d, *J* = 6.6 Hz, 2H), 3.27 (m, 2H), 3.12 (m, 2H), 3.02 (s, 3H), 2.71 (m, 8H), 1.97 (m, 1H), 1.61 (m, 2H), 1.24 (m, 2H).
71	4.50	489.2	1	*** (53)	*	*	DMSO δ 8.97 (d, *J* = 5.1 Hz, 1H), 8.89 (s, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 7.65 (s, 1H), 4.39 (m, 2H), 4.15 (m, 2H), 3.30 (m, 2H), 3.22 (t, *J* = 6.8 Hz, 2H), 3.07 (m, 2H), 2.87 (s, 3H), 2.05 (t, *J* = 6.7 Hz, 2H), 1.92 (m, 2H), 1.54 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
72	4.32	489.2	1	*** (15)	*	**	DMSO δ 8.98 (d, *J* = 5.2 Hz, 1H), 8.90 (s, 1H), 8.64 (d, *J* = 5.0 Hz, 1H), 7.59 (s, 1H), 4.39 (m, 2H), 3.64 (m, 2H), 3.48 (m, 2H), 3.27 (m, 2H), 3.13 (s, 2H), 2.86 (s, 3H), 2.15 (s, 2H), 1.78 (m, 4H).
73	3.03	434.3	1	**	*		DMSO δ 7.84 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.44 (m, 1H), 7.35 (m, 1H), 4.38 (m, 2H), 4.24 (m, 2H), 3.29 (m, 2H), 2.86 (m, 5H), 2.65 (d, *J* = 6.3 Hz, 2H), 2.43 (s, 3H), 1.93 (m, 2H), 1.81 (m, 1H), 1.43 (m, 2H).
74	3.17	434.3	1	*** (74)	*	**	DMSO δ 7.83 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 4.40 (m, 2H), 3.61 (d, *J* = 6.9 Hz, 2H), 3.30 (m, 2H), 3.17 (s, 3H), 3.06 (m, 2H), 2.74 (s, 3H), 2.61 (m, 2H), 1.99 (m, 1H), 1.61 (m, 2H), 1.19 (m, 2H).
75	3.21	450.2	1	*** (92)	*	**	DMSO δ 8.42 (s, 1H), 8.07 (m, 1H), 8.01 (m, 1H), 7.45 (m, 2H), 4.38 (m, 2H), 4.27 (m, 2H), 3.29 (m, 2H), 2.87 (m, 5H), 2.72 (m, 2H), 2.47 (s, 3H), 1.90 (m, 3H), 1.46 (m, 2H).
76	3.32	450.2	1	*** (6)	*	*** (23)	DMSO δ 8.41 (s, 1H), 8.07 (m, 1H), 7.99 (m, 1H), 7.45 (m, 2H), 4.40 (m, 2H), 3.61 (d, *J* = 7.0 Hz, 2H), 3.30 (m, 2H), 3.19 (s, 3H), 3.12 (m, 2H), 2.75 (s, 3H), 2.67 (m, 2H), 2.05 (m, 1H), 1.68 (m, 2H), 1.25 (m, 2H).

Cpd. Nr.	R_t	$[M+1]^+$	Meth.	PIM1	PIM2	PIM3	^{1}H NMR (300 MHz; δ in ppm)
77	2.53	384.3	1	**	*		$CDCl_3$ δ 8.41 (s, 1H), 7.50 (s, 1H), 7.22 (s, 1H), 4.36 (m, 2H), 4.23 (d, *J* = 12.3 Hz, 2H), 3.21 (m, 2H), 2.94 – 2.75 (m, 7H), 2.67 (s, 3H), 2.05 (m, 3H), 1.54 (m, 2H).
78	2.71	384.3	1	**	*		$CDCl_3$ δ 8.41 (s, 1H), 7.55 (m, 1H), 7.25 (m, 1H), 4.39 (s, 2H), 3.57 (d, *J* = 7.1 Hz, 2H), 3.30 (m, 6H), 3.11 (s, 3H), 2.77 (s, 3H), 2.02 (m, 1H), 1.76 (m, 2H), 1.54 (m, 2H).
79	3.21	461.2	1	**	*	**	DMSO δ 8.31 (m, 3H), 8.10 (d, *J* = 4.0 Hz, 2H), 7.39 (t, *J* = 8.8 Hz, 2H), 4.40 (m, 2H), 4.20 (m, 1H), 3.96 (m, 1H), 3.29 (m, 3H), 2.86 (s, 3H), 2.83 (m, 2H), 2.02 (m, 1H), 1.78 (m, 2H), 1.46 (m, 1H).
80	3.17	477.2	1	*** (92)	*		DMSO δ 8.73 (s, 1H), 8.20 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.63 (s, 2H), 7.33 (t, *J* = 8.9 Hz, 2H), 4.39 (m, 2H), 4.09 (m, 1H), 3.88 (m, 1H), 3.29 (m, 2H), 3.05 (m, 1H), 2.88 (s, 3H), 2.83 (m, 1H), 2.65 (m, 1H), 1.91 (m, 1H), 1.74 (m, 2H), 1.28 (m, 1H).

Example 82

Combination assays

Representative compounds of the examples were shown to display a synergistic effect when combined with other therapeutic agents and tested in certain cell lines, as is demonstrated by Table 5.

Combination index (CI) calculated for the combination of representative compounds of the invention and various chemotherapeutic agents in the MTT *in vitro* cell proliferation assays [CI<0.1 (++++), 0.1<CI<0.3 (+++), 0.3<CI<0.7 (++), 0.7<CI<1.2 (+)]:

Table 5

Cell line	Tumor type	Chemotherapeutic	Chemoth. EC50 (uM)	Example number	Example EC50 (uM)	Combination index (CI)	Synergy
PC3	prostate	lapatinib	10	**29**	10	0,283	+++
MV4:11	leukemia (AML)	PD-0325901	8	**29**	2,5	0,481	++
MV4:11	leukemia (AML)	lapatinib	5	**29**	2,5	1,02	+
MV4:11	leukemia (AML)	PD-0332991	1,875	**29**	2,5	0,699	++
MV4:11	leukemia (AML)	GDC-0941	0,75	**29**	2,5	0,536	++
T47D	breast	PD-0325901	20	**29**	8	0,34	++
T47D	breast	lapatinib	40	**29**	20	0,0001	++++
HT29	colon	PD-0325901	1	**29**	5	0,84	+
HT29	colon	lapatinib	10	**29**	5	1,172	+
U87MG	glioblastoma	lapatinib	5	**29**	5	0,56	++
HTC116	colon	lapatinib	10	**29**	10	0,03	++++
HTC116	colon	GDC-0941	6	**29**	10	0,02	++++
JEKO-1	Mantle cell lymphoma	lapatinib	5	**29**	5	0,56	++
JEKO-1	Mantle cell lymphoma	GDC-0941	0,75	**29**	5	0,788	+
Raji	Burkitt lymphoma	lapatinib	10	**29**	10	0,34	++
MDAMB231	breast	lapatinib	10	**29**	10	0,008	++++
MDAMB231	breast	GDC-0941	12	**29**	10	1,08	+
MDAMB231	breast	GDC-0879	40	**29**	10	0,538	++
RPMI8226	Multiple myeloma	lapatinib	5	**29**	10	0,429	++
A549	lung adenocarcinoma	PD-0325901	2	**29**	10	0,3	+++
A549	lung adenocarcinoma	GDC-0941	3	**29**	10	0,784	+
SKMEL-19	melanoma	lapatinib	2,5	**29**	10	0,32	++
MiaPaca	pancreas	lapatinib	10	**29**	10	0,005	++++
MiaPaca	pancreas	GDC-0941	12	**29**	10	0,662	++
DU145	prostate	PD-0325901	8	**29**	20	0,19	+++
DU145	prostate	lapatinib	10	**29**	20	0,001	++++
NCIH1975	lung adenocarcinoma	PD-0325901	4	**29**	20	0,602	++
NCIH1975	lung adenocarcinoma	lapatinib	10	**29**	20	0,002	++++
NCIH1975	lung adenocarcinoma	GDC-0941	6	**29**	20	0,006	++++
T47D	breast	lapatinib	40	**47**	20	0,0001	++++
MDAMB231	breast	PD-0325901	1	**47**	10	0,922	+
MDAMB231	breast	lapatinib	10	**47**	10	0,279	+++
MDAMB231	breast	GDC-0941	12	**47**	10	1,08	+
MDAMB231	breast	GDC-0879	40	**47**	10	0,244	+++
HTC116	colon	PD-0325901	10	**47**	2	0,87	+
HTC116	colon	lapatinib	10	**47**	5	0,02	++++
HTC116	colon	GDC-0941	6	**47**	10	0,474	++
HT29	colon	lapatinib	10	**47**	5	0,58	++
HT29	colon	GDC-0941	3	**47**	5	0,11	+++
U87MG	glioblastoma	lapatinib	5	**47**	10	0,472	++
MV4:11	leukemia (AML)	GDC-0941	0,75	**47**	1,25	0,49	++
MV4:11	leukemia (AML)	PD-0332991	1,875	**47**	1,25	0,786	+
JEKO-1	Mantle cell lymphoma	PD-0325901	8	**47**	1,25	0,824	+
JEKO-1	Mantle cell lymphoma	GDC-0941	0,75	**47**	1,25	0,588	++
A549	lung adenocarcinoma	PD-0325901	2	**47**	10	0,36	++
A549	lung adenocarcinoma	lapatinib	10	**47**	10	0,219	+++
A549	lung adenocarcinoma	GDC-0941	3	**47**	10	0,716	+
NCIH1975	lung adenocarcinoma	PD-0325901	4	**47**	10	0,279	+++
NCIH1975	lung adenocarcinoma	lapatinib	10	**47**	10	0,174	+++
NCIH1975	lung adenocarcinoma	GDC-0941	6	**47**	10	0,394	++
SKMEL-19	melanoma	PD-0325901	0,5	**47**	1,25	0,674	++
MiaPaca	pancreas	lapatinib	10	**47**	5	0,024	+++
MiaPaca	pancreas	GDC-0941	12	**47**	5	0,699	++
DU145	prostate	lapatinib	10	**47**	5	0,34	++

Example 83

Cell Data: BadP S112 inhibition by cell ELISA in H1299Pim1 cells

The following table demonstrates that representative compounds of the examples inhibit PIM-1 in the cellular assay described hereinbefore.

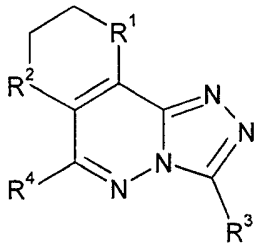
Efficacy to inhibit the Bad phosphorylation [EC_{50} values (nM)] for selected compounds of the examples is represented in Table 6.

Table 6

Cpd. Nr.	BadP H1299Pim1 EC_{50} (nM)
25	415
29	215
33	207
34	204
47	49
53	496
57	151
59	185
60	143
62	206
65	198
76	87

Claims

1. A compound of formula I,



I

wherein:

the ring containing R^1 and R^2 is non-aromatic, in which:

R^1 and R^2 are independently selected from -O-, -S-, -S(O)-, $-S(O)_2-$, $-C(R^6)(R^{6a})-$ and $-N(R^6)-$; and

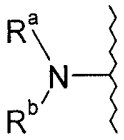
the $-CH_2-CH_2-$ moiety (between R^1 and R^2) is optionally substituted by one or more substituents selected from E^2;

each R^6 and R^{6a} independently represents, on each occasion when used herein, H, $-C(O)NHR^{d1}$, $-C(O)R^{d2}$ or R^{d3};

R^{d1}, R^{d2} and R^{d3} independently represent C_{1-12} alkyl optionally substituted by one or more substituents selected from E^1;

R^3 represents heteroaryl optionally substituted by one or more substituents selected from E^3;

R^4 represents a fragment of formula IA,



IA

R^a and R^b independently represent H, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from Q^1), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from Q^2); or

R^a and R^b are linked together, along with the requisite nitrogen atom to which they are necessarily attached, to form a 3- to 7-membered cyclic group, optionally containing one further heteroatom selected from nitrogen, sulfur and oxygen, and which ring optionally:

(a) is fused to a second ring that is either a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen, sulfur and nitrogen, a 3- to 12-membered saturated carbocyclic ring, or an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring;

(b) comprises a linker group $-(C(R^x)_2)_p-$ and/or $-(C(R^x)_2)_r-O-(C(R^x)_2)_s-$ (wherein p is 1 or 2; r is 0 or 1; s is 0 or 1; and each R^x independently represents hydrogen or C_{1-6} alkyl), linking together any two non-adjacent atoms of the first 3- to 7-membered ring (i.e. forming a bridged structure); or

(c) comprises a second ring that is either a 3- to 12-membered saturated carbocyclic ring or a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen and nitrogen, and which second ring is linked together with the first ring *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle),

all of which cyclic groups, defined by the linkage of R^a and R^b, are optionally substituted by one or more substituents selected from =O, $=N-OR^{7b}$ and E^4;

each Q^1 and Q^2 independently represents, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-C(=Y)N(R^{10a})-OR^{11c}$, $-OC(=Y)-R^{10a}$, $-OC(=Y)-OR^{10a}$, $-OC(=Y)N(R^{10a})R^{11a}$, $-OS(O)_2OR^{10a}$, $-OP(=Y)(OR^{10a})(OR^{11a})$, $-OP(OR^{10a})(OR^{11a})$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$,

$-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, =S, $=N(R^{10a})$ and E^5), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^6);

R^{7b} represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

each R^{11c} independently represents, on each occasion when used herein, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, =S, $=N(R^{20})$ and E^7), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^8);

each R^{10a}, R^{11a} and R^{12a} independently represent, 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 =O, =S, $=N(R^{20})$ and E^7), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^8); or

any relevant pair of R^{10a}, R^{11a} and R^{12a} may be linked together to form a 4- to 20-membered ring, optionally containing one or more heteroatoms, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from =O, =S, $=N(R^{20})$ and E^9;

each E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 and E^9 independently represents, on each occasion when used herein:
(i) Q^4;
(ii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^5; or

any two E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8 or E^9 groups may be linked together to form a 3- to 12-membered ring, optionally containing one or more unsaturations, and

which ring is optionally substituted by one or more substituents selected from =O and J^1;

each Q^4 and Q^5 independently represent, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y)-R^{20}$, $-C(=Y)-OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-C(=Y)N(R^{20})-OR^{21a}$, $-OC(=Y)-R^{20}$, $-OC(=Y)-OR^{20}$, $-OC(=Y)N(R^{20})R^{21}$, $-OS(O)_2OR^{20}$, $-OP(=Y)(OR^{20})(OR^{21})$, $-OP(OR^{20})(OR^{21})$, $-N(R^{22})C(=Y)R^{21}$, $-N(R^{22})C(=Y)OR^{21}$, $-N(R^{22})C(=Y)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{20})R^{21}$, $-SC(=Y)R^{20}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and J^2), 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, =O, =S, $=NR^{23}$ or =N-CN;

each R^{21a} independently represents, on each occasion when used herein, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from J^4 and =O), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from J^5);

each R^{20}, R^{21}, R^{22} and R^{23} independently represent, 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^4 and =O), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from J^5); or

any relevant pair of R^{20}, R^{21} and R^{22}, may be linked together to form a 4- to 20-membered ring, optionally containing one or more heteroatoms, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from J^6 and =O;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represents, on each occasion when used herein:

(i) Q^7;

(ii) C_{1-6} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^8;

each Q^7 and Q^8 independently represents, on each occasion when used herein: halo, $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2R^{50}$, $-SR^{50}$, $-S(O)R^{50}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

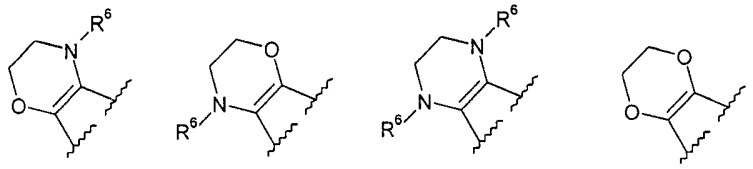
each Y^a independently represents, on each occasion when used herein, =O, =S, $=NR^{53}$ or =N-CN;

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, $-OR^{60}$ and $-N(R^{61})R^{62}$; or
any relevant pair of R^{50}, R^{51} and R^{52} may be linked together to form, a 3- to 8-membered ring, optionally containing one or more heteroatoms, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from =O and C_{1-3} alkyl;

R^{60}, R^{61} and R^{62} 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.

2. A compound as claimed in Claim 1, wherein:
the R^1 and R^2-containing ring of the compounds is a group selected from one of the following formulae:



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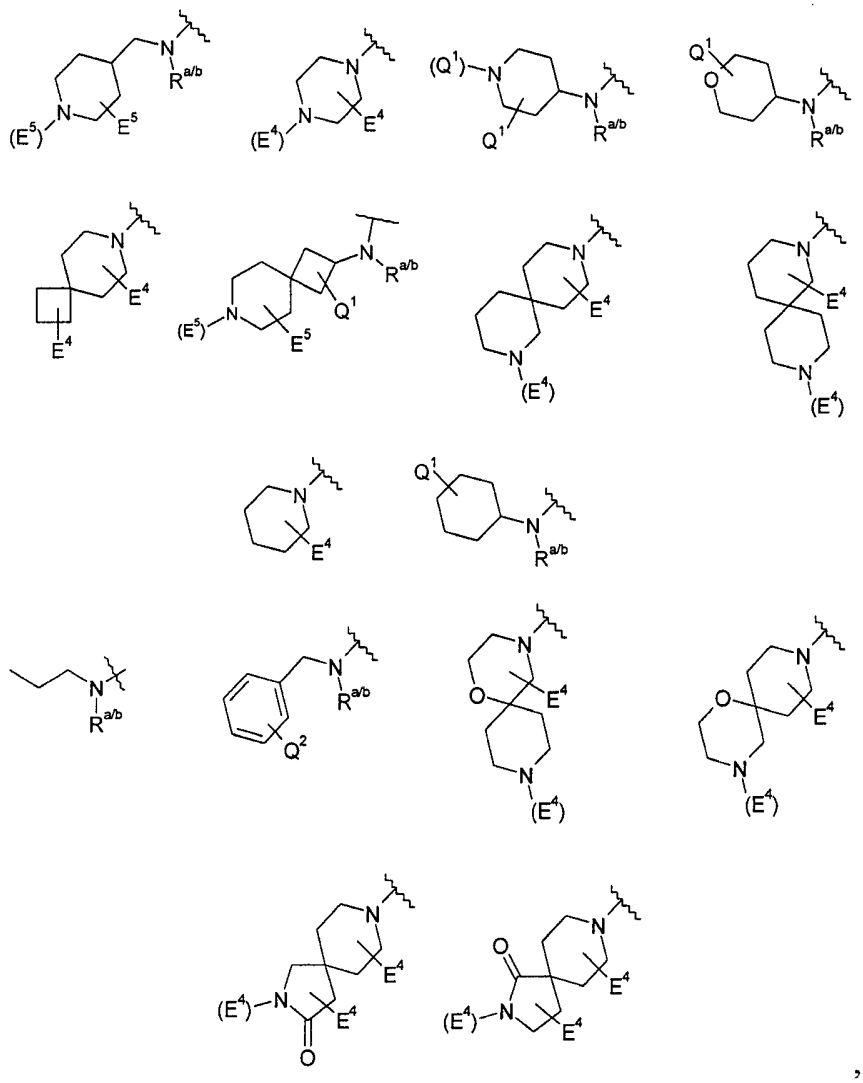
wherein the squiggly lines represent the point of attachment to the requisite triazolopyridazine of the compound of formula I, and R^6 is as defined in Claim 1;

R^3 represents a 5- or 6-membered monocyclic or a bicyclic 9- or 10-membered heteroaryl group, both of which are optionally substituted by one or more substituents selected from E^3;

R^4 represents a group of the following formulae:



,

wherein the squiggly line represents the point of attachment to the requisite triazolopyridazine of the compound of formula I, $R^{a/b}$ represents R^a or R^b, and E^4, E^5 and Q^1 are optional substituents and are as defined in Claim 1.

3. A compound as claimed in Claim 1 or Claim 2, wherein: each of R^1 and R^2 independently represents -O- or -NR^6-; R^6 represents hydrogen or R^{d3}; R^{d3} represents C_{1-3} alkyl; the -CH_2-CH_2- group linking R^1 and R^2 is unsubstituted; one of R^a and R^b represents H or C_{1-3} alkyl and the other represents (i) C_{1-6} alkyl

optionally substituted by one or more substituents selected from Q^1, (ii) heterocycloalkyl optionally substituted by one or more substituents selected from Q^1, or, R^a and R^b may be linked together to form a 3- to 6-membered ring, which ring may be linked to a further 4- to 6-membered ring *via* a single atom, wherein either ring may be optionally substituted by one or more substituents selected from =O and E^4; Q^1 may represent (for instance, when it is attached to a heterocycloalkyl group) C_{1-6} alkyl (optionally substituted by one or more substituents selected from E^5), $-N(R^{10a})R^{11a}$, $-OR^{10a}$ or $-S(O)_2R^{10a}$ or Q^1 may represent (for instance, when it is a substituent on an alkyl group) $-N(R^{10a})R^{11a}$, C_{1-6} alkyl optionally substituted by one or more substituents selected from =O and E^5, heterocycloalkyl (optionally substituted by one or more substituent selected from =O and E^5, and which heterocyclalkyl group may further be bridged by two non-adjacent atoms being linked together with $-(CH_2)-$), aryl or heteroaryl both of which latter two groups are optionally substituted by one or more substituents selected from E^6; E^3 represents Q^4 or C_{1-3} alkyloptionally substituted by one or more substituents selected from =O and Q^5; E^4 represents Q^4, or, C_{1-3} alkyl optionally substituted by one or more Q^5 substituents; E^5 represents Q^4 or C_{1-6} alkyl; E^6 represents Q^4; Q^4 represents aryl (optionally substituted by a substitutent selected from J^3), halo, -CN, $-OR^{20}$, $-N(R^{20})R^{21}$, $-C(=Y)R^{20}$, $-C(=Y)OR^{20}$ or $-S(O)_2R^{20}$; Q^5 represents C_{1-6} alkyl or, preferably, halo, $-N(R^{20})R^{21}$ or $-N(R^{22})C(=Y)R^{21}$; and/or R^{10a} and R^{11a} independently represent H or C_{1-3} alkyl.

4. A compound as claimed in any one of the preceding claims, wherein: R^{20} represents H or C_{1-4} alkyl optionally substituted by one or more J^4; R^{21} represents hydrogen or C_{1-4} alkyl; R^{22} represents hydrogen; Y and Y^a independently represent =O; J^4 represents Q^7; and/or Q^7 represents halo.

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, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use in the treatment of a disease in which inhibition of PIM-1, PIM-2 and/or PIM-3 is desired and/or required.

8. Use of 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 the manufacture of a medicament for the treatment of a disease in which inhibition of PIM-1, PIM-2 and/or PIM-3 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 PIM-1, PIM-2 and/or PIM-3 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, 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, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof; and

(B) another therapeutic agent that is useful in the treatment of 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. The combination product of Claim 11, which comprises 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, another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and a pharmaceutically-acceptable adjuvant, diluent or carrier.

13. The combination product of Claim 11, which comprises a kit of parts comprising components:

(a) 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 thereo, 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.

14. A kit of parts as claimed in Claim 13, wherein components (a) and (b) are suitable for sequential, separate and/or simultaneous use in the treatment of cancer and/or a proliferative disease.

15. A combination product as claimed in any one of Claims 11 to 14, wherein the other therapeutic agent is selected from:

(i) a targeted kinase inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(ii) a receptor tyrosine kinase (RTK) inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(iii) an Akt or PI3-K inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(iv) an Flt-3 inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(v) an EGFR or HER2 inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(vi) a therapeutic monoclonal antibody, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(vii) a MEK inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(viii) a B-Raf inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(ix) an anthracyclin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(x) a taxane, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xi) a platin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xii) a nucleotide analog, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xiii) an alkylating agent, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xiv) a hormone therapeutic agent, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xv) an anti-tumour compound that has potential radiosensitising and/or chemosensitising effects, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xvi) an mTOR inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xvii) a JAK inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xviii) a cyclin dependent kinase inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof; and/or

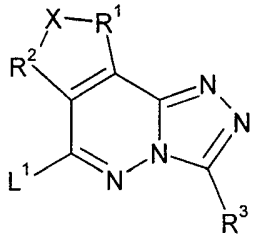
(xix) an agent that modulates the DNA damage response mechanism and/or the stress signaling pathway, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof.

16. Use according to Claim 8 or Claim 9, wherein the medicament is for the treatment of a disease as defined in Claim 8 or Claim 9 in a patient who is also administered one or more therapeutic agents as defined in Claim 15.

17. A method according to Claim 10, wherein the administration of the compound of formula I or a pharmaceutically-acceptable ester, amide, solvate or salt thereof, is to a patient suffering from, or susceptible to, a condition as defined in Claim 10 or Claim 9, which patient is also administered one or more therapeutic agents as defined in Claim 15.

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

(i) reaction of a compound of formula II,



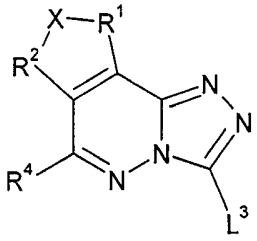
II

wherein L^1 represents a suitable leaving group, and R^1, R^2 and R^3 are as defined in Claim 1 and X is $-CH_2CH_2-$ optionally substituted as defined in Claim 1, with a compound of formula III,

$$R^4\text{-}H \qquad \text{III}$$

wherein R^4 is as defined in Claim 1;

(ii) reaction of a compound of formula IV,



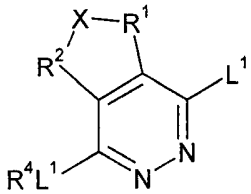
IV

wherein L^3 represents a suitable leaving group, and R^1, R^2 and R^4 are as defined in Claim 1 and X is $-CH_2CH_2-$ optionally substituted as defined in Claim 1, with a compound of formula V,

$$R^3\text{-}L^4 \qquad \text{V}$$

wherein L^4 represents a suitable group, and R^3 is as defined in Claim 1;

(iii) reaction of a compound of formula VI,



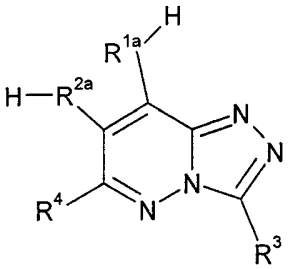
VI

wherein R^4L^1 represents either L^1 or R^4, and R^1, R^2, R^4 and each L^1 are as defined in Claim 1 or above, and X is $-CH_2CH_2-$ optionally substituted as defined in Claim 1, with a compound of formula VII,

$$R^3\text{-}C(O)\text{-}N(H)NH_2 \qquad \text{VII}$$

wherein R^3 is as defined in Claim 1;

(iv) for compounds of formula I in which R^1 and R^2 are independently selected from -O-, -S- and $-NR^6-$, reaction of a compound of formula VIII,



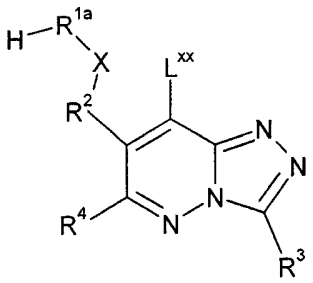
VIII

wherein R^{1a} and R^{2a} independently represent -O-, -S- and $-NR^6-$, and R^3 and R^4 are as defined in Claim 1, with a compound of formula IX,

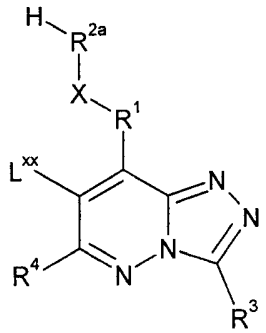
$$L^5\text{-}X\text{-}L^6 \qquad \text{IX}$$

wherein L^5 and L^6 independently represent a suitable leaving group and X is $-CH_2CH_2-$ optionally substituted as defined in Claim 1;

(v) for compounds of formula I in which one of R^1 and R^2 represents -O-, -S- or $-NR^6-$, reaction of a compound of formula IXA or IXB,



IXA



IXB

wherein L^{xx} represents a suitable leaving group, R^{1a} and R^{2a} are as defined above and R^1, R^2, R^3 and R^4 are as defined in Claim 1, and X is $-CH_2CH_2-$ optionally substituted as defined in Claim 1.

19. A process for the preparation of 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.

20. A process for the preparation of a combination product as defined in Claim 11, which process comprises bringing into association 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 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

International application No
PCT/GB2012/050091

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/14 A61K31/5365 A61P5/00 A61P3/00 A61P9/00
A61P17/00 A61P19/00 A61P21/00 A61P25/00 A61P31/00
A61P35/00 A61P37/00

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)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TINA MORWICK: "Pim kinase inhibitors: a survey of the patent literature", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 20, 1 January 2010 (2010-01-01), pages 193-212, XP009146911, ISSN: 1354-3776 page 197; table 1 page 198; figure 1; compound 2 page 205; table 4 page 207; figure 5; compound 19 page 194, paragraph 2.1 - page 200 -----	1-20
A	WO 2004/058769 A2 (VERTEX PHARMA [US]; GREEN JEREMY [US]; GREY RONALD JR [US]; PIERCE ALB) 15 July 2004 (2004-07-15) page 7, paragraph 29 - paragraph 30 claims 1-50 -----	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2012	11/04/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marzi, Elena

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/050091

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/67245 A1 (MERCK SHARP & DOHME [GB]; CARLING WILLIAM ROBERT [GB]; CASTRO PINEIRO) 29 December 1999 (1999-12-29) claims 1-9 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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