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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 February 2012 (16.02.2012)

PCT

(10) International Publication Number
WO 2012/020217 A1

(51) International Patent Classification:
C07D 513/04 (2006.01) *A61P 35/00* (2006.01)
C07D 519/00 (2006.01) *A61P 35/02* (2006.01)
A61K 31/438 (2006.01) *A61P 3/00* (2006.01)
A61K 31/454 (2006.01) *A61P 5/00* (2006.01)
A61K 31/5377 (2006.01) *A61P 9/00* (2006.01)
A61K 31/433 (2006.01) *A61P 11/00* (2006.01)
A61K 31/55 (2006.01) *A61P 17/00* (2006.01)
A61K 31/496 (2006.01)

(21) International Application Number:
PCT/GB2011/001189

(22) International Filing Date:
9 August 2011 (09.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10380102.3 9 August 2010 (09.08.2010) GB

(71) Applicant *(for all designated States except US)*: **CENTRO NACIONAL DE INVESTIGACIONES ONCOLÓGICAS (CNIO)** [ES/ES]; Melchor Fernández, Almagro 3, E-28029 Madrid (ES).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PASTOR FERNÁNDEZ, Joaquín** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **GARCÍA COLLAZO, Ana, María** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **NOYA MARIÑO, Beatriz** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **GONZÁLEZ CANTALAPIEDRA, Esther** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES).

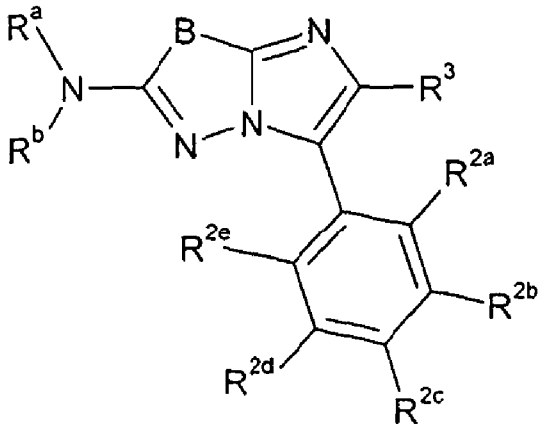
(74) Agent: **MCNEENEY, Stephen, Phillip**; Potter Clarkson LLP, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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

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

[Continued on next page]

(54) Title: AMINO- IMIDAZOLOTHIADIAZOLES FOR USE AS PROTEIN OR LIPID KINASE INHIBITORS



(I)

(57) Abstract: There is provided compounds of formula (I), wherein R^a, R^b, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e} and R^3 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, and/or Flt-3) is desired and/or required, and particularly in the treatment of cancer or a proliferative disease.

WO 2012/020217 A1

Published:

— *with international search report (Art. 21(3))*

AMINO- IMIDAZOLOTHIADIAZOLES FOR USE AS PROTEIN OR LIPID KINASE 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, or Flt3 inhibitors). The compounds may also be useful as inhibitors of Flt3. 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 sl., 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.

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

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

There is a constant need to provide alternative and/or more efficacious inhibitors of protein or lipid kinases, and particularly inhibitors of PIM-1, PIM-2 and/or PIM-3, and/or inhibitors of Flt3. 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.

For the treatment of cancer, targeted therapies are becoming more important. That is, therapy that has the effect of interfering with specific target molecules that are linked to tumor growth and/or carcinogenesis. Such therapy may be more effective than current treatments (e.g. chemotherapy) and less harmful to normal cells (e.g. because chemotherapy has the potential to kill normal cells as well as cancerous cells). This, and also the fact that targeted therapies may be selective (i.e. it may inhibit a certain targeted molecule more selectively as compared to other molecular targets, e.g. as described hereinafter), may have the benefit of reducing side effects and may also have the benefit that certain

specific cancers can be treated (also selectively). The latter may in turn also reduce side effects.

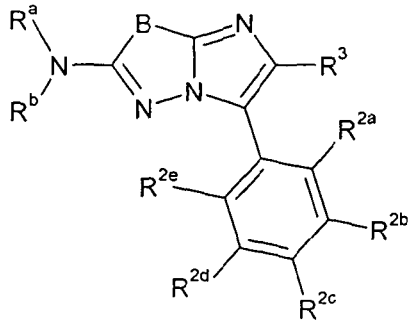
Hence, it is a clear goal of current oncologists to develop targeted therapies (e.g. ones that are selective). In this respect, it should be pointed out that several different molecular targets may exist that are linked to certain diseases (e.g. cancer). However, one simply cannot predict if a therapy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

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.

International patent applications WO 2009/040552 and WO 2010/112874 disclose various imidazothiadiazole derivatives for use as certain kinase inhibitors. International patent application WO 2010/012345 discloses various imidazothiadiazoles for use as e.g. TGF-beta receptor kinase inhibitors. However, these documents predominantly relate to imidazothiadiazoles, for instance those with certain substituents attached to the core bicyclic ring, e.g. certain amino groups at the 2-position and certain aromatic groups (with specific substitution) at the 5-position.

Disclosure of the Invention

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



I

wherein:

B represents -S-, -S(O)- or -SO_2-;

R^{2a}, R^{2b}, R^{2c}, R^{2d} and R^{2e} independently represent hydrogen or a substituent selected from E^1;

R^a and R^b are defined as follows:

(I) 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 contains a further (second) ring as defined by Z^1, all of which cyclic groups, defined by the linkage of R^a and R^b (with the optional second ring defined by Z^1), are optionally substituted by one or more substituents selected from =O, =NOR^{7a} and E^2 (preferably from =O and E^2); or

(II) one of R^a and R^b represents T^1, and the other represents hydrogen or C_{1-12} (e.g. C_{1-6}) alkyl optionally substituted by one or more halo (e.g. fluoro) atoms;

T^1 represents:

(i) heterocycloalkyl (e.g. 3- to 7-membered heterocycloalkyl), which optionally comprises a further ring as defined by Z^2, and which ring(s) (i.e. heterocycloalkyl and optional further ring) is/are optionally substituted by one or more substituents selected from =O, =NOR^{7a} and Q^1;

(ii) acyclic C_{1-12} (e.g. C_{1-8}) alkyl substituted by:

(a) -$N(R^{5a})$-T-R^{5b} (in which T represents a direct bond, -C(O)-, -$S(O)_2$-, -C(O)$N(R^{5c})$- or -C(O)O-; and R^{5a}, R^{5b} and R^{5c} are independently hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro atoms, or, R^{5b} and R^{5c} are linked together to form a 5- or 6-membered heterocycloalkyl group);

(b) one or more (e.g. one) heterocycloalkyl group(s) (in which the heteroatoms are selected from sulfur and, preferably, nitrogen and/or in which the heterocycloalkyl group is attached to the acyclic alkyl group *via*

a single carbon atom), which heterocycloalkyl group may comprise a further ring as defined by Z^3; and/or

(c) one or more (e.g. one) C_{3-12} cycloalkyl group, which is substituted by Q^2 or comprises a further ring as defined by Z^{3a},

and which acyclic C_{1-12} alkyl group, heterocycloalkyl group (and optional further ring, defined by Z^3) and cycloalkyl group (and requisite further ring system, defined by Z^{3a}) is/are (further) optionally substituted by one or more substituents selected from $=NOR^{7b}$ and Q^2;

(iii) C_{3-12} cycloalkyl, which comprises a further ring as defined by Z^4 (and which cycloalkyl group and further ring are optionally substituted by one or more substituents selected from =O, $=NOR^{7c}$ and Q^3);

(iv) C_{3-12} cycloalkyl, which is substituted by at least one W^1 substituent, and may be further optionally substituted by one or more substituents selected from =O, $=NOR^{7d}$ and Q^4, provided that at least one (e.g. one) of R^{2a} to R^{2e} (e.g. R^{2b}) represents a substituent selected from -CN, $-OR^{5d}$, $-N(R^{5e})R^{5f}$, $-C(O)R^{5g}$ and C_{1-6} alkyl (optionally, and preferably, substituted by one or more fluoro atoms, e.g. C_{1-3} perfluoroalkyl, such as $-CF_3$) (and the others (e.g. R^{2a}, R^{2c}, R^{2d} and R^{2e}) may represent hydrogen or a substituent defined by E^1);

W^1 represents $-N(R^{1a})-T^{1a}-R^{1b}$, $=NOR^{1c}$, $-C(O)N(H)R^{1d}$, $-C(O)N(R^{1e})-OR^{1f}$, $-O-C(O)-R^{1h}$ or $-OR^{1i}$;

T^{1a} represents a direct bond, $-C(O)-$, $-S(O)_2-$, $-C(O)N(R^{1g})-$ or $-C(O)O-$;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} independently represent hydrogen or C_{1-6} alkyl (optionally substituted by one or more substituents selected from halo (e.g. fluoro), -CN, $-OR^{6a}$ and $-N(R^{6b})R^{6c}$) or aryl or heteroaryl (both of which are optionally substituted by one or more substituents selected from halo, -CN and C_{1-6} alkyl); or

any pair of R^{1a} and R^{1b} (for instance when T^{1a} represents a direct bond) or R^{1a} and R^{1g} may be linked together to form a 4- to 8- (e.g. a 5- or 6-) membered ring optionally containing one or two further heteroatoms (in addition to the requisite N atom and any heteroatom contained within the definition of T^{1a}) preferably selected from nitrogen and oxygen, and optionally containing one or two double

bonds, which ring is optionally substituted by one or more substituents selected from =O, =NOR^{7e} and Q^5;

R^{1h} and R^{1i} independently represent C$_{1-6}$ alkyl optionally substituted by one or more substituents selected from halo, -N(R^{2h})R^{3h} and -OR^{4h};

R^{2h}, R^{3h}, R^{4h}, R^{6a}, R^{6b} and R^{6c} independently represent hydrogen or C$_{1-6}$ alkyl;

R^{5d}, R^{5e}, R^{5f}, R^{5g}, R^{7a}, R^{7b}, R^{7c}, R^{7d} and R^{7e} independently represent hydrogen or C$_{1-6}$ alkyl optionally substituted by one or more fluoro atoms;

Z^1, Z^2, Z^3, Z^{3a} and Z^4 each independently represent a moiety that results in a further ring sytem (that is present in addition to the "first ring" i.e. in addition to the monocyclic cycloalkyl or heterocycloalkyl groups, to which that Z^1 to Z^4 group is attached) that is formed by that Z^1 to Z^4 group representing:

(a) 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) that is fused to the first ring;

(b) 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 ring (i.e. forming a bridged structure); or

(c) a second ring that is either a 3- to 12-membered saturated carbocyclic ring or 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);

R^3 represents hydrogen or halo;

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

halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-C(=Y)N(R^{10a})-OR^{11a}$, $-OC(=Y)-R^{10a}$, $-OC(=Y)-OR^{10a}$, $-OC(=Y)N(R^{10a})R^{11a}$, $-OS(O)_2OR^{10a}$, $-OP(=Y)(OR^{10a})(OR^{11a})$, $-OP(OR^{10a})(OR^{11a})$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, 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^3), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^4);

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^5), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^6); 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^7;

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

(i) Q^{20};

(ii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^{21}; or

any two E^1, E^2, E^3, E^4, E^5, E^6 or E^7 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^6 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^{20} and Q^{21} independently represent, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y)-R^{20}$, $-C(=Y)-OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-OC(=Y)-R^{20}$, $-OC(=Y)-OR^{20}$, $-OC(=Y)N(R^{20})R^{21}$, $-OS(O)_2OR^{20}$, $-OP(=Y)(OR^{20})(OR^{21})$, $-OP(OR^{20})(OR^{21})$, $-N(R^{22})C(=Y)R^{21}$, $-N(R^{22})C(=Y)OR^{21}$, $-N(R^{22})C(=Y)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{20})R^{21}$, $-SC(=Y)R^{20}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$, 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^{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^{30};
(ii) C_{1-6} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^{31};

each Q^{30} and Q^{31} independently represents, on each occasion when used herein: halo, $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2N(R^{50})R^{51}$, $-N(R^{52})-C(O)-N(R^{50})R^{51}$, $-S(O)_2R^{50}$, $-SR^{50}$, $-S(O)R^{50}$ 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.

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.

For instance, certain compounds of the invention, including, but not limited to compounds of formula I in which there is a W^1 group present (i.e. T^1 represents C_{3-12} cycloalkyl substituted by at least one W^1 substituent), which represents -O-C(O)-R^{1h} (e.g. -O-C(O)-CH_2-NH_2) may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds (which may or may not be other compounds of the invention) that do possess pharmacological activity as such (e.g. corresponding compounds in which W^1 represents -OH).

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 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_{2-q} heterocycloalkenyl (where q is the upper limit of the range) group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo-[3.2.1]octanyl, aziridinyl, azetidinyl, dihydropyranyl, 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 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-tetrahydro-naphthyl. The point of attachment of aryl groups may be *via* any atom of the ring system. For example, when the aryl group is polycyclic the point of attachment may be *via* atom including an atom of a non-aromatic ring. However, when aryl groups are polycyclic (e.g. bicyclic or tricyclic), they are preferably linked to the rest of the molecule *via* 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 between 5 and 20 members (e.g. 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). When the heteroaryl group is polycyclic the point of attachment may be *via* atom including an atom of a non-aromatic ring. However, when heteroaryl groups are polycyclic (e.g. bicyclic or tricyclic), they are preferably linked to the rest of the

molecule *via* an aromatic ring. Heteroaryl groups that may be mentioned include 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^7 (such as E^6) substituent present, then those Q^1 or Q^2, or, E^1 to E^7 (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^7 (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^7*" 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 and E^7, inclusively. Similarly, R^{2a} to R^{2e} will be understood to mean R^{2a}, R^{2b}, R^{2c}, R^{2d} and R^{2e} inclusively, Z^1 to Z^4 will be understood to mean Z^1, Z^2, Z^3, Z^{3a} and Z^4 inclusively, and Q^1 to Q^5 will be understood to mean Q^1, Q^2, Q^3, Q^4 and Q^5, 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.

Compounds of the invention that may be mentioned include those in which:
when two E^1 groups (e.g. when any two adjacent R^{2a}, R^{2b}, R^{2c}, R^{2d} and R^{2e}) are linked together, the linkage preferably forms a 3- to 12-membered (e.g. 5 or 6-membered) carbocyclic ring (i.e. one that contains no heteroatoms), which may contain one to three double bonds, and which is optionally substituted as defined herein, i.e. by one or more substituents selected from =O and J^1;
any two E^1 groups may not be linked together; and/or
any two E^1, E^2, E^3, E^4, E^5, E^6 or E^7 groups may not be linked together.

When W^1 represents -O-C(O)-R^{1h}, then preferred R^{1h} groups that may be mentioned include esters e.g. in which R^{1h} represents methyl or ethyl or aminoesters, i.e. in which R^{1h} represents -CH_2-NH_2. Such compounds may be prodrugs of corresponding compounds in which W^1 represents -OH.

In an (e.g. preferred) embodiment of the invention, R^a and R^b are linked together as hereinbefore defined. In an (e.g. separate) embodiment of the invention, one of R^a and R^b represents T^1 and the other is as hereinbefore defined.

For compounds of the invention in which one of R^a and R^b represents T^1 and the other represents hydrogen or C_{1-12} alkyl optionally substituted by one or more halo atoms (i.e. embodiment (II) above), the following compounds (depicted by embodiments (A) and (B) below) represent (a) further specific (preferred) embodiment(s):

(A) compounds of the invention in which T^1 represents:

(i) heterocycloalkyl (as defined herein);

(ii) substituted acyclic C_{1-12} (e.g. C_{1-8}) alkyl (as defined herein):

(iii) C_{3-12} cycloalkyl, comprising a further ring (as defined herein),

all of which groups defined by (i), (ii), (iii) above are, for the avoidance of doubt, optionally substituted as defined herein; or

(B) compounds of the invention in which T^1 represents C_{3-12} cycloalkyl, which is substituted by one W^1 substituent (in which W^1 is as hereinbefore defined, but preferably represents $-N(R^{1a})-T^{1a}-R^{1b}$ (in which T^{1a}, R^{1a} and R^{1b} are as defined herein)), provided that at least one (e.g. one) of R^{2a} to R^{2e} (e.g. R^{2b}) represents a substituent selected from -CN, $-OR^{5d}$, $-N(R^{5e})R^{5f}$, $-C(O)R^{5g}$ and C_{1-6} alkyl (as defined herein; i.e. the alkyl group is optionally substituted by one or more fluoro atoms).

In a preferred embodiment, when one of R^a and R^b represents T^1 and the other represents hydrogen or optionally substituted C_{1-12} alkyl, then the specific embodiment (A) above is preferred, for instance embodiment (A) in which T^1 represents:

(i) heterocycloalkyl (which preferably does not comprise a further ring) optionally substituted by one or more substituents selected from =O and Q^1;

(ii) acyclic C_{1-12} (e.g. C_{1-8}) alkyl substituted by:

(a) $-N(R^{5a})-T-R^{5b}$ (in which T, R^{5a} and R^{5b} are as defined herein);

(b) one heterocycloalkyl group (in which the heteroatoms are selected from nitrogen; and in which the heterocycloalkyl group is preferably not attached to the acyclic alkyl group *via* a single carbon atom), which heterocycloalkyl group may comprise a further ring as defined herein by Z^3 (but preferably does not comprise such a further ring); or

(c) one C_{3-12} cycloalkyl group, which comprises a further ring as defined by Z^{3a},

and which acyclic C_{1-12} alkyl group, heterocycloalkyl group (and optional further ring, defined by Z^3) and cycloalkyl group (and requisite further ring system, defined by Z^{3a}) is/are (further) optionally substituted by one or more substituents selected from Q^2;

(iii) C_{3-12} cycloalkyl, which comprises a further ring as defined by Z^4 (and which cycloalkyl group and further ring are optionally substituted by one or more substituents selected from =O and Q^3).

Preferably (e.g. for the specific embodiment (A) defined herein), there are further preferred embodiments of the invention in which:

T^1 represents (i) heterocycloalkyl (optionally substituted as defined herein) or (iii) cycloalkyl (which comprises a further Z^4 ring and is optionally substituted, as defined herein) (either embodiments (i) or (iii) may be preferred); and

T^1 represents substituted acyclic C_{1-12} alkyl as defined herein (most preferably, when T^1 represents acyclic C_{1-12} alkyl, then it is substituted with a heterocycloalkyl group as the requisite substituent).

It is preferred that when T^1 represents acyclic C_{1-12} alkyl, then it is preferably substituted by (a) one $-N(R^{5a})-T-R^{5b}$ substituent; (b) one 4- to 8- (e.g. 5- or 6-) membered heterocycloalkyl group (containing one or two nitrogen heteroatoms) and which does not comprise a further ring (as defined by Z^3; or (c) one C_{3-12} (e.g. C_{3-7}) cycloalkyl group, which comprises a further ring as defined by Z^{3a}, which acyclic C_{1-12} alkyl group, 4- to 8-membered heterocycloalkyl group and C_{3-12} cycloalkyl group (and further Z^{3a} ring) are optionally substituted by one or more substituents selected from Q^2. Any of the foregoing embodiments (a), (b) and (c) may be preferred, however, it is particularly preferred that when T^1 represents acyclic C_{1-12} alkyl, then it is preferably substituted by (a) or, especially, (c).

When one of R^a and R^b represents T^1 and the other represents hydrogen or optionally substituted C_{1-12} alkyl, then, for the specific embodiment (B), it is preferred that:

T^1 represents C_{3-12} cycloalkyl substituted by one W^1 substituent;

W^1 represents $-N(R^{1a})-T^{1a}-R^{1b}$ (in which T^{1a}, R^{1a}, R^{1b} and R^{1c} are as defined herein); and

at least one (e.g. one) of R^{2a} to R^{2e} (e.g. R^{2b}) represents a substituent selected from -CN, $-OR^{5d}$, $-N(R^{5e})R^{5f}$, $-C(O)R^{5g}$ and optionally substituted C_{1-6} alkyl (all of which are as defined herein; preferred substituents in this regard include -CN, $-OCH_3$, $-OCF_3$, -OH, $-N(CH_3)_2$, $-CF_3$ and $-C(O)CH_3$, and especially preferred is the $-OR^{5d}$ substituent, in which R^{5d} represents a C_{1-6} (e.g. C_{1-3}) perfluoroalkyl group, so forming e.g. a $-OCF_3$ substituent) (and those remaining represent hydrogen or a substituent selected from E^1; for instance two or, preferably, one may represent a substituent selected from E^1 and the others represent hydrogen).

When one of R^a and R^b represents T^1 and the other represents hydrogen or optionally substituted C_{1-12} alkyl, then, for the specific embodiment (B), it may also be preferred that W^1 represents $-O-C(O)-R^{1h}$, which compounds may metabolise to corresponding compounds in which W^1 represents -OH (hence, compounds in which W^1 represents $-O-C(O)-R^{1h}$ may be prodrugs).

Further preferred compounds of the invention include those in which:

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

halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, 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^3), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^4);

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^5); 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);

each of E^1, E^2, E^3, E^4, E^5, E^6 and E^7 independently represent, on each occasion when used herein, Q^{20} or C_{1-6} alkyl (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from =O and Q^{21};

each Q^{20} and Q^{21} independently represent 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^{20} or, particularly, Q^{21} more preferably represents halo, such as fluoro);

any two E^1, E^2, E^3, E^4, E^5, E^6 and/or E^7 groups may be linked together (e.g. any two E^3 substituents may also be linked together as defined herein, for 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 and/or E^7) 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;

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^{31}, or, such groups independently represent a substituent selected from Q^{30};

each Q^{30} and Q^{31} 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 the requisite phenyl ring bearing R^{2a} to R^{2e} (or on any cyclic group that R^a and R^b may form or bear) 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 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 $-OR^{z1}$, $-C(O)R^{z2}$, $-C(O)OR^{z3}$, $-N(R^{z4})R^{z5}$, $-S(O)_2R^{z6}$, $-S(O)_2N(R^{z7})R^{z8}$; $-N(R^{z9})-C(O)-R^{z10}$, $-C(O)-N(R^{z11})R^{z12}$, $-N(R^{z9})-C(O)-N(R^{z10})$ and/or $-N(R^{z9})-S(O)_2-N(R^{z10})$ substituents);

aryl (e.g. phenyl) (e.g. which substitutent may also be present on an alkyl group, thereby forming e.g. a benzyl group);

$-OR^{z1}$;

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

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

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

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

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

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

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

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

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

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.

More preferred compounds of the invention include those in which:

Z^1, Z^2, Z^3, Z^{3a} and Z^4 independently represent either: (a) a 4- to 7- (e.g. 5- or 6-) membered saturated heterocycloalkyl group fused to the first ring (so forming e.g. a 5,5-fused bicycle); or (b) a 4- to 7- (e.g. 4- to 6-)-membered saturated

carbocyclic group or a 4- to 7- (e.g. 4- to 6-)-membered saturated heterocycloalkyl group linked together with the first 4- to 7- (e.g. 5-, 6- or 7-)-membered ring *via* a single common carbon atom to form a spiro-cycle;

each Q^1, Q^2, Q^3, Q^4 and Q^5 independently represents, on each occasion when used herein, halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, C_{1-12} alkyl or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and E^3);

more preferably, each Q^1, Q^2, Q^3, Q^4 and Q^5 independently represents, on each occasion when used herein, $-C(=Y)OR^{10a}$, $-C(=Y)R^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-S(O)_2R^{10a}$ or C_{1-6} alkyl (e.g. methyl, ethyl or part-cyclic alkyl such as cyclopropylmethyl; optionally substituted by one or more substituents selected from E^3) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

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;

any relevant pair of R^{10a}, R^{11a} and R^{12a} is preferably not linked together;

each E^1, E^2, E^3, E^4, E^5, E^6 and E^7 independently represents Q^{20} or C_{1-6} (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from =O and Q^{21} (more preferably E^1 to E^7 preferably represent Q^{20});

any two E^1, E^2, E^3, E^4, E^5, E^6 or E^7 groups are preferably not linked together;

each Q^{20} and Q^{21} independently represent, on each occasion when used herein halo, -CN, $-NO_2$, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y)-R^{20}$, $-C(=Y)-OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-N(R^{22})-C(=Y)-OR^{21}$ or C_{1-6} alkyl (optionally substituted by one or more substituents selected from =O and J^2);

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

each R^{20}, R^{21}, R^{22} and R^{23} independently represent, on each occasion when used herein, hydrogen or C_{1-6} alkyl (optionally substituted by one or more substituents selected from =O and, preferably, J^4);

any relevant pair of R^{20}, R^{21} and R^{22} is preferably not linked together;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represents Q^{30};

each Q^{30} and Q^{31} independently represents, on each occasion when used herein: halo, $-N(R^{50})R^{51}$, $-OR^{50}$ or C_{1-3} (e.g. C_{1-2}) alkyl optionally substituted by one or more fluoro atoms;

each Y^a independently represents, on each occasion when used herein, =O;

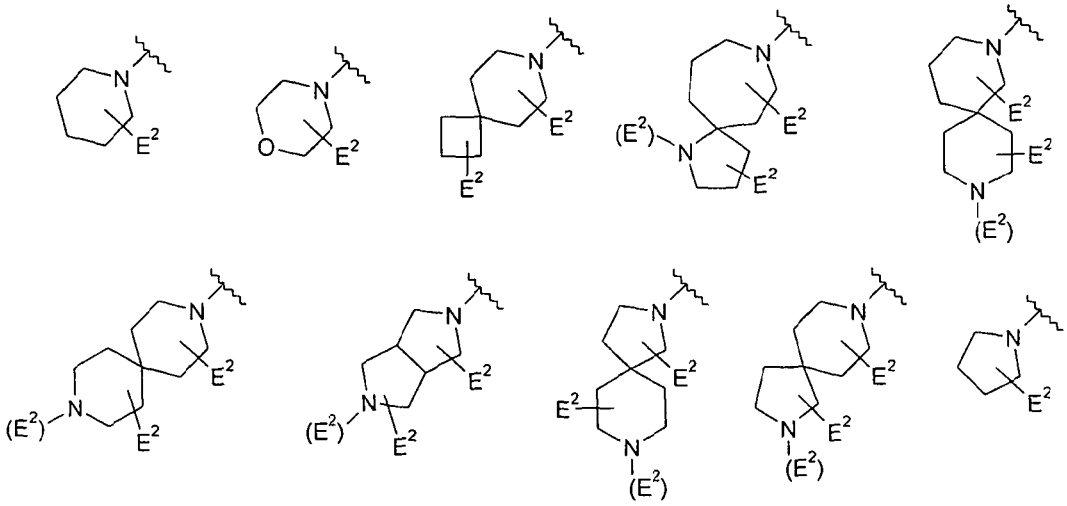
each R^{50}, R^{51}, R^{52} and R^{53} independently represents, on each occasion when used herein, hydrogen or C_{1-3} (e.g. C_{1-2}) alkyl optionally substituted by one or more substituents selected from fluoro and $-OR^{60}$ (preferably, fluoro);

any relevant pair of R^{50}, R^{51} and R^{52} is preferably not linked together;

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

Preferred values of R^a and R^b include those in which:

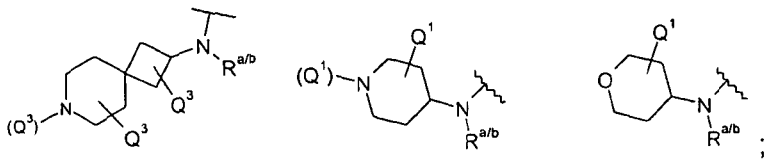
(I) when R^a and R^b are linked together, they form one of the following:



;

(II) one of R^a and R^b represents hydrogen (or C_{1-3} alkyl (e.g. methyl), but preferably represents hydrogen) and the other represents T^1, in which T^1 may represent:

(i) optionally substituted C_{3-12} (e.g. C_{4-7}) cycloalkyl, which comprises a further (optionally substituted) ring as defined by Z^4, or optionally substituted heterocycloalkyl (optionally comprising a further ring defined by Z^2), which may represent one of the following:



;

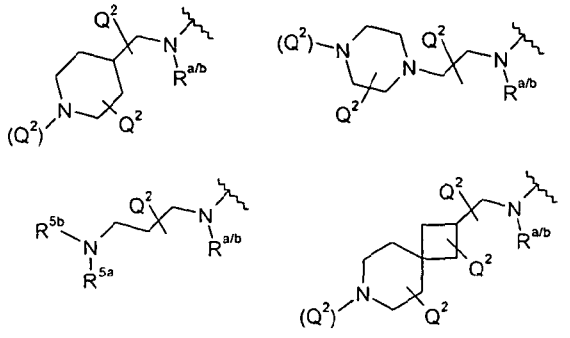
(ii) acyclic C_{1-12} (e.g. C_{1-3}) alkyl (e.g. methyl, ethyl or propyl) substituted by:

(A) one optionally substituted monocyclic heterocycloalkyl group (e.g. 3- to 8-membered, preferably, 5- or 6-membered) containing one nitrogen heteroatom (which heterocycloalkyl group may comprise a further ring as defined by Z^3);

(B) one optionally substituted C_{4-7} cycloalkyl group comprising a further ring defined by Z^{3a}; or

(C) $-N(R^{5a})-T-R^{5b}$,

which may therefore be represented by any one of the following:



; or

(iii) C_{3-12} cycloalkyl substituted by W^1 (e.g. $-N(R^{1a})-T^{1a}-R^{1b}$), provided that at least one of R^{2a} to R^{2e} represents a substituent as hereinbefore defined, which may represent C_{4-7} (e.g. C_{4-6}) cycloalkyl (e.g. cyclohexyl) substituted by $-N(R^{1a})-R^{1b}$ (e.g. $-NH_2$) for instance at the 4-position of a cyclohexyl group,

wherein in the relevant cases above, the squiggly line represents the point of attachment to the requisite imidazodiathiazole of the compound of formula I, $R^{a/b}$ (if present) represents R^a or R^b, and E^2, Q^1, Q^2 and Q^3 each independently represent one or more optional E^2, Q^1, Q^2 and/or Q^3 substituents (where they are depicted as 'floating') or the depiction of those substituents in brackets signifies that that substituent is optionally present, and may therefore be absent (i.e. $N-(E^2)$ may signify $N-E^2$ or N-H). Further, the cyclic groups depicted (i.e. the cyclic groups formed by the linage of R^a and R^b, or cyclic substituents on those R^a or R^b groups, or any further rings) above may also be further substituted e.g. with one or more (e.g. one) =O group (as indicated hereinbefore).

Particularly preferred compounds of the invention include those in which:

B represents -S-;

at least two (e.g. at least three) of R^{2a} to R^{2e} represent hydrogen;

two or, preferably, one of R^{2a} to R^{2e} represents a substituent selected from E^1;

at least one of R^{2b}, R^{2c} and R^{2d} represent a substituent other than hydrogen, i.e. there is at least one *meta* or *para* substituent (preferably, *meta* substituent) present on the relevant phenyl ring;

either R^{2b}, R^{2b} and R^{2c} or R^{2c} represent a substituent other than hydrogen;

R^{2b} and/or R^{2d} represents a substituent selected from E^1 (preferably one of R^{2b} and R^{2d} represents such a substituent and the other represents hydrogen), i.e. it is preferred that there is at least one (e.g. one) *meta* substituent present on the phenyl ring bearing the R^{2a} to R^{2e} moieities;

R^{2a} and R^{2e} independently represent hydrogen, i.e. it is preferred that the *ortho* positions of the relevant phenyl ring are unsubstituted;

R^{2c} may represent hydrogen or a substituent selected from E^1, i.e. in addition to the preferred *meta* substituent of the relevant phenyl ring, there is also present an optional *para*-substituent;

E^1 represents Q^{20} or C_{1-3} alkyl (e.g. methyl) optionally substituted by one or more Q^{21} groups (so forming e.g. a $-CF_3$ group);

when E^1 represents Q^{20}, then Q^{20} preferably represents halo or, more preferably, -CN, $-OR^{20}$, $-N(R^{20})R^{21}$ or $-C(O)R^{20}$ (in which instances, R^{20} and R^{21} may represent hydrogen or C_{1-3} alkyl optionally substituted by one or more fluoro atoms);

Q^{21} represents halo (e.g. fluoro);

specific preferred E^1 groups include -CN, $-CF_3$, $-OCF_3$, -OH, $-OCH_3$, $-N(CH_3)_2$, and $-C(O)-CH_3$.

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

R^3 represents hydrogen;

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

when R^a and R^b are linked together, they preferably:

form a 4- to 7- (e.g. a 5-, 6- or 7-) membered ring, optionally containing one further heteroatom (e.g. oxygen or nitrogen; so forming e.g. a piperidinyl, morpholinyl, pyrrolidinyl, or azepanyl group), optionally containing a further ring defined by Z^1, and all of which rings are optionally substituted by one or more E^2 substituents;

Z^1 represents either: (a) a 4- to 7- (e.g. 5- or 6-) membered saturated heterocycloalkyl group fused to the first ring (so forming e.g. a 5,5-fused bicycle, e.g. octahydro-pyrrolo[3,4-c]pyrrole); or (b) a 4- to 7- (e.g. 4- to 6-)-membered saturated carbocyclic group (e.g. cyclobutyl) or a 4- to 7- (e.g. 4- to 6-)-membered saturated heterocycloalkyl group (e.g. pyrrolidinyl or piperidinyl) linked together with the first 4- to 7- (e.g. 5-, 6- or 7-)-membered ring *via* a single common carbon atom to form a spiro-cycle (e.g. a [5.3], [3.5], [5.5], [4.5], [5.4], [6.4] or [4.6] spiro-cycle, such as 7-aza-spiro-[3.5]nonane-7-yl), 2,9-diaza-spiro-[5.5]undecane-2-yl, 3,9-diaza-spiro-[5.5]undecane-3-yl, 2,8-diaza-spiro-[4.5]decane-8-yl, 2,8-diaza-spiro-[4.5]decane-2-yl or 1,8-diaza-spiro-[4.6]undecane-8-yl);

E^2 represents Q^{20} or C_{1-6} (e.g. C_{1-3}) alkyl (e.g. methyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^{21};

when E^2 represents Q^{20}, then Q^{20} represents $-C(=Y)-OR^{20}$ or $-N(R^{20})R^{21}$;

when E^2 represents C_{1-12} (e.g. C_{1-6}) alkyl substituted by Q^{21}, then Q^{21} represents $-N(R^{22})-C(=Y)-OR^{21}$ or $-N(R^{20})R^{21}$;

when one of R^a and R^b represents hydrogen or C_{1-3} alkyl (e.g. methyl) and the other represents T^1, then T^1 may represent:

(i) heterocycloalkyl (e.g. a 4- to 6-membered group, containing one or two heteroatoms preferably selected from nitrogen and oxygen, so forming e.g. piperidinyl or tetrahydropyranyl) optionally substituted by one or more (e.g. one) Q^1 substituent(s);

(ii) C_{4-7} (e.g. C_{4-6}) cycloalkyl (e.g. cyclobutyl) comprising a further ring as defined by Z^4, which rings are optionally substituted by one or more (e.g. one) Q^3 substituent(s);

(iii) acyclic C_{1-4} alkyl (e.g. methyl, ethyl or *n*-propyl) substituted by either: a 5- or preferably 6-membered heterocycloalkyl group containing one or two heteroatoms preferably selected from nitrogen (so forming e.g. piperidinyl or piperazinyl) optionally substituted by one or more (e.g. one) Q^2 substituent(s); C_{4-6} cycloalkyl (e.g. cyclobutyl) comprising a further ring as defined by Z^{3a}, which rings are optionally substituted by one or more (e.g. one) Q^2 substituent(s); or $-N(R^{5a})-T-R^{5b}$ (in which T preferably represents a direct bond; and R^{5a} and R^{5b} preferably and independently represent hydrogen); or

(iv) (e.g. in a separate embodiment of the invention), C_{4-7} (e.g. C_{4-6}) cycloalkyl (e.g cyclohexyl) substituted by one or more (e.g. one) W^1

substituent, in which W^1 preferably represents $-N(R^{1a})-T^{1a}-R^{1b}$ (e.g. $-NH_2$), provided that at least one of R^{2a} to R^{2e} represents a certain substituent as defined hereinbefore;

Z^{3a} and Z^4 independently represent a 4- to 7- (e.g. 4- to 6-) membered saturated heterocycloalkyl group (e.g. piperidinyl) that is attached to the first ring *via* a common carbon atom to form, together with the first ring to which these second rings are attached, a spiro-cycle (e.g. a [3.5] or [5.3] spiro-cycle, such as 7-aza-spiro[3.5]nonane-2-yl);

Q^1 represents $-S(O)_2R^{10a}$ or C_{1-3} alkyl (e.g. unsubstituted methyl) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

Q^2 represents $-C(=Y)OR^{10a}$, $-C(=Y)R^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-S(O)_2R^{10a}$ or C_{1-6} alkyl (e.g. methyl, ethyl or part-cyclic alkyl such as cyclopropylmethyl; optionally substituted by one or more substituents selected from E^3) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

Q^3 represents $-C(=Y)OR^{10a}$, $-C(=Y)R^{10a}$, $-S(O)_2R^{10a}$ or C_{1-6} alkyl (e.g. methyl, ethyl or part-cyclic alkyl such as cyclopropylmethyl; optionally substituted by one or more substituents selected from E^3) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

each R^{10a} independently represents hydrogen or, preferably, C_{1-6} (e.g. C_{1-4}) alkyl (e.g. *tert*-butyl, methyl, ethyl);

R^{11a} represents hydrogen;

E^3 and E^4 independently represent Q^{20};

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

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

Q^{21} represents $-N(R^{22})-C(=Y)-OR^{21}$ or $-N(R^{20})R^{21}$;

Y (and Y^a) represents =O;

R^{20} represents hydrogen or C_{1-6} (e.g. C_{1-4}) alkyl (e.g. ethyl or methyl);

R^{21} represents hydrogen or C_{1-6} (e.g. C_{1-4}) alkyl (e.g. *tert*-butyl or methyl);

R^{22} represents hydrogen;

specific E^2 substituents that are preferred include -C(O)O-ethyl, $-CH_2$-N(H)-C(O)-O-*tert*-butyl, $-NH_2$, -C(O)OH and $-CH_2-NH_2$;

specific Q^1, Q^2 and Q^3 substituents that are preferred include -C(O)O-*tert*-butyl, $-S(O)_2CH_3$, $-CH_3$, $-CH_2-CH_2-F$, $-CH_2-CH_2-OCH_3$, $-CH_2-C(O)-N(CH_3)_2$, $-CH_2$-cyclopropyl, $-C(O)-CH_3$ and -C(O)N(H)-ethyl (all of which substituents may be attached to a nitrogen atom).

Especially preferred compounds of the invention (e.g. particularly active inhibitors of a PIM family kinase (such as PIM-1 or PIM-3) or Flt3) include those in which:

B represents -S-;

at least three (e.g. three or four) of R^{2a} to R^{2e} represent hydrogen;

one of R^{2a} to R^{2e} (e.g. R^{2b}, R^{2c} or R^{2d}) represents a substituent selected from E^1;

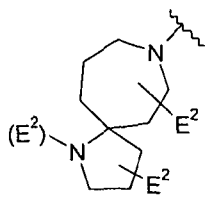
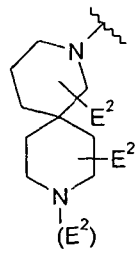
E^1 represents Q^{20} or C_{1-3} (e.g. C_{1-2}) alkyl optionally, and preferably, substituted by Q^{21} (preferably, Q^{21} is fluoro and the alkyl group is perfluorinated, so forming e.g. a $-CF_3$ group);

Q^{21} preferably represents halo (especially fluoro);

when E^1 represents Q^{20}, then Q^{20} preferably represents -CN, $-OR^{20}$ or $-N(R^{20})R^{21}$ (in which instances, R^{20} and R^{21} may represent hydrogen or C_{1-3} alkyl optionally substituted by one or more fluoro atoms);

specific preferred E^1 groups include -CN, $-CF_3$, $-OCF_3$, -OH and $-N(CH_3)_2$;

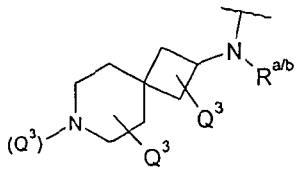
R^a and R^b are linked together to form one of the following:

; or

one of R^a and R^b represents hydrogen (or C_{1-3} alkyl (e.g. methyl), but preferably represents hydrogen) and the other represents T^1, in which T^1 may represent:

(i) optionally substituted C_{3-12} (e.g. C_{4-7}) cycloalkyl, which comprises a further (optionally substituted) ring as defined by Z^4, which may represent:



; or

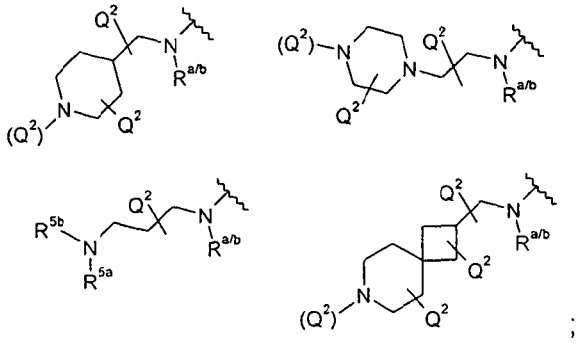
(ii) acyclic C_{1-12} (e.g. C_{1-3}) alkyl (e.g. methyl) substituted by:

(A) $-N(R^{5a})-T-R^{5b}$; or, preferably,

(B) one optionally substituted monocyclic heterocycloalkyl group containing one nitrogen heteroatom (which heterocycloalkyl group may comprise a further ring as defined by Z^3); or

(C) one optionally substituted C_{4-7} cycloalkyl group comprising a further ring defined by Z^{3a},

which may therefore be represented by any one of the following:



;

R^3 represents hydrogen;

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

when R^a and R^b are linked together, they preferably:

form a 6- or 7-membered ring, preferably containing no further heteroatoms (e.g. piperidinyl or azepanyl group), optionally containing a further ring defined by Z^1, and all of which rings are optionally substituted by one or more E^2 substituents (but preferably unsubstituted);

Z^1 represents: a 4- to 7- (e.g. 5- or 6-)-membered saturated heterocycloalkyl group (e.g. pyrrolidinyl or piperidinyl) linked together with the first 6- to 7-membered ring *via* a single common carbon atom to form a spiro-cycle (e.g. a [5.5], [6.4] or [4.6] spiro-cycle, such as 2,9-diaza-spiro-[5.5]undecane-2-yl or 1,8-diaza-spiro-[4.6]undecane-8-yl);

when one of R^a and R^b represents hydrogen or C_{1-3} alkyl (e.g. methyl) and the other represents T^1, then T^1 may represent:

(i) heterocycloalkyl (e.g. a 6-membered group, preferably containing one heteroatom preferably selected from nitrogen, so forming e.g. piperidinyl) optionally substituted by one or more (e.g. one) Q^1 substituent(s); or, preferably

(ii) C_{4-7} (e.g. C_{4-6}) cycloalkyl (e.g. cyclobutyl) comprising a further ring as defined by Z^4, which rings are optionally substituted by one or more (e.g. one) Q^3 substituent(s); or

(iii) acyclic C_{1-4} alkyl (e.g. methyl or ethyl) substituted by either: $-N(R^{5a})-T-R^{5b}$ (in which T preferably represents a direct bond); or, preferably, a 6-membered heterocycloalkyl group containing one or two heteroatoms preferably selected from nitrogen (so forming e.g. piperidinyl or piperazinyl) optionally substituted by one or more (e.g. one) Q^2 substituent(s); or C_{4-6} cycloalkyl (e.g. cyclobutyl) comprising a further ring as defined by Z^{3a}, which rings are optionally substituted by one or more (e.g. one) Q^2 substituent(s);

Z^{3a} and Z^4 independently represent a 4- to 6-membered saturated heterocycloalkyl group (e.g. piperidinyl) that is attached to the first ring *via* a common carbon atom to form, together with the first ring to which these second rings are attached, a spiro-cycle (e.g. a [3.5] spiro-cycle, such as 7-aza-spiro[3.5]nonane-2-yl);

Q^1 represents C_{1-3} alkyl (e.g. unsubstituted methyl) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

Q^2 represents $-C(=Y)R^{10a}$ or C_{1-6} alkyl (e.g. methyl, ethyl or part-cyclic alkyl such as cyclopropylmethyl; optionally substituted by one or more substituents selected from E^3) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

Q^3 represents $-C(=Y)R^{10a}$ or C_{1-6} alkyl (e.g. methyl, ethyl or part-cyclic alkyl such as cyclopropylmethyl; optionally substituted by one or more substituents selected from E^3) (which substituent(s) may be attached to a nitrogen heteroatom, e.g. one that is a part of a heterocycloalkyl ring);

each R^{10a} independently represents hydrogen or, preferably, C_{1-6} (e.g. C_{1-4}) alkyl (e.g. methyl);

R^{11a} represents hydrogen;

E^3 and E^4 independently represent Q^{20};

when E^3 or E^4 represents Q^{20}, then Q^{20} preferably represents $-C(=Y)N(R^{20})R^{21}$;

Q^{20} represents $-C(=Y)N(R^{20})R^{21}$;

Y (and Y^a) represents =O;

R^{20} represents hydrogen or C_{1-4} alkyl (e.g. methyl);

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

R^{22} represents hydrogen;

specific Q^1, Q^2 and Q^3 substituents that are preferred include $-CH_3$, $-CH_2-C(O)-N(CH_3)_2$, $-CH_2$-cyclopropyl and $-C(O)-CH_3$ (all of which substituents may be attached to a nitrogen atom).

In a further embodiment of the invention, preferred compounds of the invention include those in which one of R^a and R^b represents T^1 (the remainder of the substituents, e.g. R^{2a} to R^{2e} and R^3 with any relevant proviso, are as hereinbefore defined, and) and T^1 represents:

C_{3-12} cycloalkyl substituted by one W^1 substituent (and further optionally substituted as hereinbefore defined), in which W^1 is preferably $-N(R^{1a})-T^{1a}-R^{1b}$, provided that at least one of R^{2a} to R^{2e} represents a substituent as hereinbefore defined, and hence T^1 may (in such instances) represent C_{4-7} (e.g. C_{4-6}) cycloalkyl (e.g. cyclohexyl) substituted by $-N(R^{1a})-R^{1b}$ (e.g. $-NH_2$) for instance at the 4-position of a cyclohexyl group; or, more specifically,

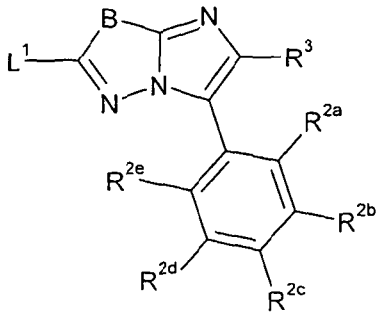
C_{4-7} (e.g. C_{4-6}) cycloalkyl (e.g cyclohexyl) substituted by one or more (e.g. one) $-N(R^{1a})R^{1b}$ (e.g. $-NH_2$) substituent, provided that at least one of R^{2a} to R^{2e} represents a certain substituent as defined hereinbefore.

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,



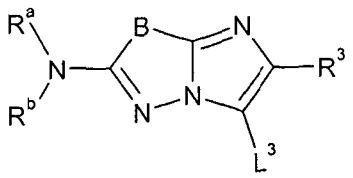
II

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 B, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e} and R^3 are as hereinbefore defined, with a compound of formula III,

$$R^b(R^a)N\text{-}H \qquad \text{III}$$

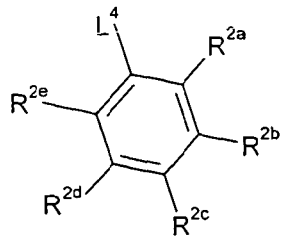
wherein R^a and R^b are as hereinbefore defined, under standard conditions, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as Cu, $Cu(OAc)_2$, CuI (or CuI/diamine complex), copper tris(triphenyl-phosphine)bromide, $Pd(OAc)_2$, tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) 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, ethanol, isopropanol, dimethylformamide, ethylene glycol, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or a mixture thereof). This reaction may be carried out under microwave irradiation reaction conditions or, alternatively, the reaction may be performed in the absence of other reagents such as catalyst, base and even solvent. 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 there is a 1-aza-bicyclo[2.2.1]hept-4-ylmethyl-amino moiety present;

(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^a, R^b, B and R^3 are as hereinbefore defined, with a compound of formula V,



V

wherein L^4 represents a suitable group, such as $-B(OH)_2$, $-B(OR^{wx})_2$ 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^{2a} to R^{2e} are as hereinbefore defined. The reaction may be performed, for example in the presence of a suitable catalyst system, e.g. a metal (or a salt or complex thereof) such as 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*-butylphosphino)-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).

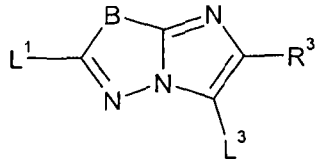
Alternative reaction conditions include microwave irradiation conditions, for example at elevated temperature of about 130°C;

(iii) for compounds of formula I in which there is a Q substituent (e.g. Q^1 to Q^5, Q^{20}, Q^{21}, Q^{30}, Q^{31}) present, in which such groups represent $-OR^{10a}$ or $-OR^{20}$ (or $-OR^{50}$), as appropriate, in which R^{10a} and R^{20} (or R^{50}) do not represent hydrogen (and most preferably represent optionally substituted alkyl as defined herein, e.g. C_{1-12} or C_{1-6} alkyl optionally substituted as defined herein), reaction of a corresponding compound of formula I in which there is a Q substituent present, which represents $-OR^{10a}$ and $-OR^{20}$ (or $-OR^{50}$; as appropriate), in which R^{10a} and R^{20} (or R^{50}) do represent hydrogen, with a compound of formula VI,

$$R^x\text{-}L^5 \qquad \text{VI}$$

wherein L^5 represents a suitable leaving group, such as one hereinbefore defined in respect of the L^1 definition (e.g. chloro or, preferably, bromo), and R^x represents R^{10a} or R^{20} (or R^{50}; as appropriate), provided that they do not represent hydrogen (and preferably represent C_{1-12} or C_{1-6} alkyl optionally substituted as defined herein), under reaction conditions known to those skilled in the art, the reaction may be performed at around room temperature or above (e.g. up to 40-180°C), optionally in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, *N*-ethyldiisopropylamine, *N*-(methylpolystyrene)-4-(methylamino)pyridine, potassium bis(trimethylsilyl)-amide, sodium bis(trimethylsilyl)amide, potassium *tert*-butoxide, lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidine or mixtures thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, trifluoromethylbenzene, dioxane, triethylamine, water or mixtures thereof).

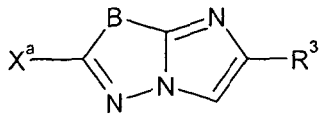
Compounds of formula II may be prepared by reaction of a compound of formula VII,



VII

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

Compounds of formula IV or VII in which L^3 represents halo, may be prepared by reaction of a compound of formula VIII,

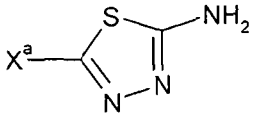


VIII

wherein X^a represents $-N(R^a)R^b$ (in the case of preparation of compounds of formula IV) or L^1 (in the case of preparation of compounds of formula VII) and L^1, R^a, R^b and R^3 are as hereinbefore defined, with a source of halide ions, for instance an electrophile that provides a source of iodide ions includes iodine, diiodoethane, diiodotetrachloroethane or, preferably, *N*-iodosuccinimide, a source of bromide ions includes *N*-bromosuccinimide and bromine, and a source of chloride ions includes *N*-chlorosuccinimide, chlorine and iodine monochloride.

Other compounds of formula IV (or VII) may also be prepared under standard conditions, for instance such as those described herein. For example, for the synthesis of compounds of formula IV in which L^3 represents a sulfonate group, reaction of a compound corresponding to a compound of formula IV but in which L^3 represents -OH with an appropriate sulfonyl halide, under standard reaction conditions, such as in the presence of a base (e.g. as hereinbefore described in respect of preparation of compounds of formula I (process step (iii)).

Compounds of formula VIII (e.g. those in which R^3 represents hydrogen) may be prepared by reaction of a compound of formula IX,



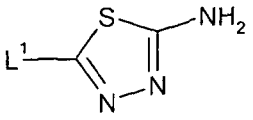
IX

wherein X^a is hereinbefore defined, with a compound of formula X,

$$Cl\text{-}CH_2\text{-}C(O)\text{-}R^{3a} \qquad X$$

wherein R^{3a} preferably represents hydrogen, under standard conditions known to those skilled in the art. For example, the compound of formula X may already be present in water, and hence, the reaction may be performed in the presence of water as a solvent, optionally in the presence of a further solvent, such as an alcohol (e.g. *n*-butanol), for example at room temperature or, preferably, elevated temperature such as at reflux.

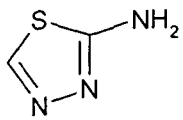
Compounds of formula IX in which X^a represents $-N(R^a)R^b$ may be prepared by reaction of a corresponding compound of formula XI,



XI

wherein L^1 is as hereinbefore defined, with a compound of formula III as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of preparation of compounds of formula I (process step (i)).

Compounds of formula IX in which X^a represents halo, may be prepared by reaction of a corresponding compound of formula XII,



XI

in the presence of a source of halide ions (e.g. in the case of bromide ions, bromine), such as those described hereinbefore in respect of preparation of

compounds of formula IV (or VII), for instance, in the presence of a suitable solvent, such as an alcohol (e.g. methanol) optionally in the presence of a suitable base, such as a weak inorganic base, e.g. sodium bicarbonate.

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 R^2 represents -C(O)OH (or an ester thereof), it may be converted to a $-C(O)N(R^{10b})R^{11b}$ group (in which R^{10b} and R^{11b} are as hereinbefore defined, and may be linked together, e.g. as defined above), and which reaction may (e.g. when R^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-$S(O)_2Cl$) and the like);

(x) formation of a urea functional group by reaction of an amine (e.g. a secondary amine, such as a -NH moiety that is a part of a heterocyclic group) with an alkyl isocyanate (e.g. ethyl isocyanate) to form a -N-C(O)-N(H)-alkyl (e.g. -N-C(O)-N(H)-CH_2CH_3 moiety), which transformation may be performed in the presence of a suitable solvent (e.g. acetonitrile) and base (e.g. *N*,*N*-diisopropylethylamine);

(xi) specific deprotection steps, such as deprotection of an *N*-Boc protecting group by reaction in the presence of an acid (or another suitable method known to those skilled in the art or a specific method described in the experimental hereinafter), 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 (e.g. from Sigma Aldrich, Wuxi and other similar sources), 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^a, R^b, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^3 and B 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/dimethyl-formamide 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.

According to a further aspect of the invention there is provided a compound of the invention, as hereinbefore defined, for use as a pharmaceutical and/or in isolated (i.e. *ex vivo*) form.

Compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity (as described hereinbefore).

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, and may also inhibit Flt3, 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, and/or Flt3) is desired and/or required. Advantageously, the compounds of the invention may inhibit both a PIM family kinase and Flt3 (and therefore may act as dual inhibitors).

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, and/or Flt3) activity. The reduction and/or prevention of kinase activity may be measured by comparing the kinase activity in a sample containing a compound of the invention and an equivalent sample of kinase (e.g. a PIM family kinase, such as PIM-1, PIM-2 and/or PIM-3, and/or Flt3) in the absence of a compound of the invention, as would be apparent to those skilled in the art. The measurable change may be objective (e.g. measurable by some test or marker, for example in an *in vitro* or *in vivo* assay or test, such as one described hereinafter, or otherwise another suitable assay or test known to those skilled in the art) or subjective (e.g. the subject gives an indication of or feels an effect).

Compounds of the invention may be found to exhibit 50% inhibition of a protein or lipid kinase (e.g. a PIM family kinase, such as PIM-1, PIM-2 and/or PIM-3, and/or Flt3) at a concentration of 100 μM or below (for example at a concentration of below 50 μM, or even below 10 μM, such as below 1 μM), when tested in an assay (or other test), for example as described hereinafter, or otherwise another suitable assay or test known to the skilled person.

Compounds of the invention are thus expected to be useful in the treatment of a disorder in which a protein or lipid kinase (e.g. a PIM family kinase, such as PIM-1, PIM-2 and/or PIM-3, and/or Flt3) 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).

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, and/or Flt3). Such conditions/disorders include cancer, immune disorders, cardiovascular diseases, viral infections, inflammation (e.g. airway inflammation and asthma), metabolism/endocrine function disorders and neurological disorders. In particular, excessive Flt3 activity is associated with refractory AML, so dual inhibitors of a PIM family kinase and Flt3 such as compounds of the invention are useful to treat refractory AML.

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 airway inflammation, 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, and/or Flt3), i.e. where such inhibition 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, and/or Flt3), which method comprises administration of a therapeutically effective amount of a compound of the invention, as hereinbefore defined, to a patient suffering from, or susceptible to, such a condition.

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

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

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

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

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

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

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

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

The invention further provides a process for the preparation of a pharmaceutical formulation, as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be combined with other therapeutic agents that are inhibitors of protein or lipid kinases (e.g. a PIM family kinase, such as PIM-1, PIM-2 and/or PIM-3, and/or Flt3) 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).

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.

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, and/or Flt3). Advantageously, the compounds of the invention may inhibit both a PIM family kinase and Flt3 (and may therefore be classed as "dual inhibitors").

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.

Compounds of the invention may also benefit from improved metabolic stability or improved activity. This is particularly so for compounds of the invention in which one of R^a and R^b represents T^1, and the other represents hydrogen or C_{1-12} alkyl optionally substituted by one or more halo atoms (i.e. embodiment (II) described hereinbefore), in which T^1 represents C_{3-12} cycloalkyl, which is substituted by at least one (e.g. one) W^1 substituent, in which W^1 is preferably $-N(R^{1a})-T^{1a}-R^{1b}$, in which T^{1a} is preferably a direct bond and R^{1a} and R^{1b} are as hereinbefore defined, but are preferably hydrogen (with the proviso specified hereinbefore; i.e. embodiment (B) described hereinbefore). Such metabolic stability may be tested in standard methods known to those skilled in the art and may constitute an improvement over the known compounds in this respect.

Compounds of the invention may be beneficial as they are medicaments with targeted therapy, i.e. which target a particular molecular entity by inferring or inhibiting it (e.g. in this case by inhibiting one or more protein or lipid kinases as hereinbefore described). Compounds of the invention may therefore also have the benefit that they have a new effect (for instance as compared to known

compounds in the prior art), for instance, the new effect may be a particular mode of action or another effect resultant of the targeted therapy. Targeted therapies may be beneficial as they may have the desired effect (e.g. reduce cancer, by reducing tumor growth or carcinogenisis) but may also have the advantage of reducing side effects (e.g. by preventing the killing of normal cells, as may occur using e.g. chemotherapy).

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

Compounds of the invention may also have the advantage that they may exhibit multiple kinase inhibitory activity. In this respect, advantageously, compounds of the invention may be considered as multi-targeted kinase inhibitors. Compounds of the invention that exhibit single selectivity for a kinase may have the additional benefit that they exhibit less side effects, whereas compounds of the invention that exhibit multiple kinase selectivity may have the additional benefit that they exhibit better potency and/or efficacy.

Compounds of the invention may therefore additionally act on other key kinases, thereby allowing single-agent administration (or, potentially, combination products with reduced dosages) and providing the associated benefits, e.g. reducing the risk of drug-drug interactions, etc.

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.

FLT3 biochemical assay

The biochemical assay to measure FLT3 activity relies on the ADP Hunter assay kit (DiscoveRx Corp., Cat. # 90-0077), that determines the amount of ADP as direct product of the kinase enzyme activity.

Assay conditions were as indicated by the kit manufacturers with the following adaptations for the kinase activity step:

- Kinase assay buffer and assay volume stay as recommended (15 mM HEPES, pH 7.4, 20 mM NaCl, 1 mM EGTA, 0.02% Tween 20, 10 mM MgCl2 and 0.1 mg/ml bovine gamma-globulins/25 uL assay volume)
- Incubation time and temperature: 60 min at 37°C
- FLT3 final concentration: 0.4 ug/ml (0.6 ug/ml; 12 nM)
- ATP final concentration: 100 uM

ABLtide substrate peptide: EAIYAAPFAKKK

- Peptide final concentration: 100 uM
- Positive control for kinase activity inhibition: 1 uM Staurosporine
- DMSO concentration below 2% during the kinase reaction

Assays were performed in either 96 or 384-well plates (corning 3575 or 3573). The final outcome of the coupled reactions provided by the kit is the release of

the fluorescent product Resorufin and has been measured with a multilabel HTS counter VICTOR V or ENVISION (PerkinElmer) using an excitation filter at 544 nm and an emission filter at 580 nm.

The compound names given herein were generated in accordance with IUPAC with MDL ISIS DRAW.

The invention is illustrated by way of the following examples.

Experimental

Hereinafter, the term "DCM" means dichloromethane, "EtOH" means ethanol, "MeOH" means methanol, "THF" means tetrahydrofuran, "DMF" means dimethylformamide, "DME" means 1,2-dimethoxyethane, "EtOAc" means ethyl acetate, "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium, "DIPEA" means diisopropylethylamine, "min" means minutes, "h" means hours, "rt" means room temperature, "$Pd_2(dba)_3$" means tris(dibenzylideneacetone)dipalladium(0) , "equiv" means equivalents, "aq" means aqueous, "Et_2O" diethylether, "Et_3N" means triethylamine, "$Pd(dppf)Cl_2.DCM$" means 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, dichloromethane, "MeCN" means acetonitrile, "mCPBA" means meta-chloroperoxybenzoic acid, "Na_2SO_4" means sodium sulphate, "$PdCl_2(PPh_3)_2$" means dichlorobis(triphenylphosphine)palladium.

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% of B 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: 50% of B to 100% 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: 5% of B to 40% 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: 10-95 % of B within 4 min at a flow rate of 0.5 mL/min followed by 2 min of 100 % of B at 0.8 mL/min, controlled temperature at 50 °C, DAD.

Method 5

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

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

Intermediate 1

2-bromo-5-iodo-imidazo[2,1-b][1,3,4]thiadiazole

To a solution of 2-bromo-imidazo[2,1-b][1,3,4]thiadiazole (11.2 g, 54.89 mmol) in DMF (180 mL) was added N-iodosuccinimide (14.3 g, 60.38 mmol). The reaction mixture was stirred at rt for 3 h. The mixture was poured into a 10% sodium thiosulphate solution and diluted with EtOAc. The resulting suspension was

filtered off and rinsed with water to give the desired product (2-bromo-5-iodo-imidazo[2,1-b][1,3,4]thiadiazole). The organic layer was dried, filtered and evaporated. The residue was suspended in water and filtered to give the same desired product (15.5 g, 85% yield).

^{1}H NMR (300 MHz, DMSO) δ 7.43 (s, 1H).

General method A

A mixture of 2-bromo-5-iodo-imidazo[2,1-b][1,3,4]thiadiazole (1 equiv), the appropriate amine (ex: 2-amino-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester) (1.5 equiv) and Et_3N (2 equiv) in MeCN (5 mL/mmol) in a sealed tube was heated at 110 °C (sand bath) for 18 h to 36 h. The solvent was evaporated under vacuum, and the residue was partitioned between DCM and water. The combined organic layers were dried (sodium sulphate), filtered and concentrated. The residue was purified by column chromatography (Isolute/Flash, SiII, 0% to 2% MeOH in DCM) to give the desired product (ex: 2-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester).

Intermediate 4

2-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.74 min, $[M+1]^+$ m/z 490.0.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.69 (d, J = 6.1 Hz, 1H), 4.26 – 4.09 (m, 1H), 3.42 – 3.24 (m, 4H), 2.51 – 2.35 (m, 2H), 1.87 – 1.72 (m, 2H), 1.68 – 1.49 (m, 4H), 1.45 (s, 9H).

Yield: 86%.

Intermediate 5

2-[(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-methyl]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.80 min, $[M+1]^+$ m/z 504.1.

Yield: 99%.

Intermediate 6

5-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.49 min, $[M+1]^+$ m/z 462.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1H), 3.81 – 3.60 (m, 4H), 3.47 – 3.20 (m, 4H), 3.15 – 2.98 (m, 2H), 1.45 (s, 9H).

Yield: 99%.

Intermediate 7

2-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-2,9-diaza-spiro[5.5]undecane-9-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.80 min, $[M+1]^+$ m/z 504.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 3.58 – 3.28 (m, 8H), 1.74 (m, 2H), 1.57 (m, 2H), 1.49 (m, 4H), 1.46 (s, 9H).

Yield: 97%.

Intermediate 8

9-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-3,9-diaza-spiro[5.5]undecane-3-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.92 min, $[M+1]^+$ m/z 504.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 3.55 – 3.29 (m, 8H), 1.64 (m, 4H), 1.49 (m, 4H), 1.45 (s, 9H).

Yield: 92%.

Intermediate 9

[1-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-piperidin-4-ylmethyl]-carbamic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.50 min, $[M+1]^+$ m/z 464.1.

Yield: 76%.

Intermediate 10

1-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-piperidine-3-carboxylic acid ethyl ester

HPLC-MS (method 4): Rt= 4.44 min, $[M+1]^+$ m/z 407.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 13.2, 4.1 Hz, 1H), 3.67 (dt, *J* = 12.9, 4.1 Hz, 1H), 3.37 (dd, *J* = 13.1, 9.6 Hz, 1H), 3.23 (m, 1H), 2.64 (m, 1H), 2.09 (m, 1H), 1.74 (m, 3H), 1.25 (m, 3H).

Intermediate 11

[1-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.30 min, $[M+1]^+$ m/z 436.1.

Yield: 99%.

Intermediate 12

[1-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-piperidin-3-yl]-carbamic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.48 min, $[M+1]^+$ m/z 450.0.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.60 (s, 1H), 3.47 (m, 4H), 1.80 (m, 4H), 1.39 (s, 9H).

Yield: 1.35 g, 90%.

Intermediate 13

(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-(1-methanesulfonyl-piperidin-4-yl)-amine

HPLC-MS (method 4): Rt= 3.53 min, $[M+1]^+$ m/z 428.0.

Yield: 1.13 g, 58%.

Intermediate 14

4-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 5.31 min, $[M+1]^+$ m/z 450.1.

Yield: 22%.

Intermediate 15

(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-(1-methyl-piperidin-4-yl)-amine

HPLC-MS (method 4): Rt= 2.2 min, $[M+1]^+$ 364 m/z .

Yield: 14 % (crude product after aqueous workup).

Intermediate 16

4-[(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.45 min, $[M+1]^+$ m/z 464.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 4.25 (m, 2H), 3.80 (m, 1H), 2.95 (s, 3H), 2.76 (m, 2H), 174 (m, 4H), 1.45 (s, 9H).

Yield: 68%.

Intermediate 17

4-[(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 3.4 min, $[M+1]^+$ 463.4 m/z .

Yield: 68 %.

Intermediate 18

(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-(1-methyl-piperidin-4-yl-methyl)-amine

HPLC-MS (method 4): Rt= 0.68 min, $[M+1]^+$ m/z 378.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 5.39 (s, 1H), 3.20 (t, J = 5.9 Hz, 2H), 2.81 (m, 2H), 2.21 (s, 3H), 1.87 (m, 2H), 1.67 (m, 2H), 1.56 (m, 1H), 1.30 (m, 2H).

Yield: 66%.

Intermediate 20

4-[2-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester

^{1}H NMR (300 MHz, DMSO) δ 7.99 (m, 1H), 7.03 (s, 1H), 3.39 (m, 2H), 3.37 (s, 4H), 2.54 (q, J = 6.3 Hz, 2H), 2.39 (m, 4H), 1.39 (s, 9H).

Yield: 48%.

Intermediate 21

[3-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-propyl]-carbamic acid tert-butyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.17 (m, 1H), 4.81 (m, 1H), 3.47 (m, 2H), 3.25 (m, 2H), 1.79 (m, 2H), 1.45 (s, 9H).

Yield: 99%.

Intermediate 22

(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-(tetrahydro-pyran-4-yl)-amine

HPLC-MS (method 4): Rt= 3.40 min, $[M+1]^+$ m/z 351.0.

Yield: quantitative

Intermediate 23

8-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-1,8-diaza-spiro[4.6]undecane

HPLC-MS (method 4): Rt= 0.79 min, $[M+1]^+$ m/z 404.0.

Yield: 93.5%.

Intermediate 24

7-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-7-aza-spiro[3.5]non-2-ylamine

HPLC-MS (method 4): Rt= 1.70 min, $[M+1]^+$ m/z 390.0.

Yield: quantitative

Intermediate 25

5-Iodo-2-morpholin-4-yl-imidazo[2,1-b][1,3,4]thiadiazole

A mixture of 2-bromoimidazo[2,1-b][1,3,4]thiadiazole (1.2 g, 5.88 mmol) and morpholine (2.05 mL, 23.52 mmol) was heated under microwave irradiation at 135 °C for 5 min. On cooling, DCM was added and the suspension was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (Isolute Flash Si II, DCM:MeOH, 100:0 to 98:2) to give 2-morpholin-4-yl-imidazo[2,1-b][1,3,4]thiadiazole (93% yield).

HPLC-MS (method 4): Rt= 0.56 min, $[M+1]^+$ m/z 211.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.4 Hz, 1H), 7.09 (d, *J* = 1.5 Hz, 1H), 3.81 (m, 4H), 3.44 (dd, *J* = 17.2, 12.2 Hz, 4H).

2-Morpholin-4-yl-imidazo[2,1-b][1,3,4]thiadiazole (1.146 g, 5.45 mmol) was dissolved in DMF (22 mL) and N-iodosuccinimide (1.348 g, 5.99 mmol) was added. The reaction mixture was stirred at rt for 3 h. The mixture was poured into a 10% aq. solution of sodium thiosulfate (47 mL) and chloroform (47 mL). The organic layer was washed with water (x 3) and with sat. aq. solution of ammonium chloride (x3), dried (Na_2SO_4), filtered and evaporated. The residue

was triturated with Et_2O to give the desired product (5-iodo-2-morpholin-4-yl-imidazo[2,1-b][1,3,4]thiadiazole) (67% yield).

HPLC-MS (method 4): Rt= 3.74 min, $[M+1]^+$ m/z 337.1.

^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 3.85 (m, 4H), 3.49 (m, 4H).

Intermediate 26

(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-piperidin-4-yl-amine

To a solution of 4-[(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (250 mg, 0.54 mmol) in 1,4-dioxane (3 mL) HCl (4 M in 1,4-dioxane, 0.5 mL) was added. The reaction mixture was heated at 45 °C for 3 h. The solvent was removed to give the desired product (5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-piperidin-4-yl-amine). It was used in the next reaction step without further purification.

HPLC-MS (method 4): Rt= 0.43 and 0.80 min, $[M+1]^+$ m/z 364.1.

Intermediate 27

(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-(1-methanesulfonyl-piperidin-4-yl)-methyl-amine

To a suspension of (5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-piperidin-4-yl-amine (196 mg, 0.54 mmol) in acetonitrile (5 mL), Et_3N (0.76 mL, 5.40 mmol) and MsCl (0.084 mL, 1.08 mmol) were added. The reaction mixture was stirred at rt overnight. The mixture was quenched with saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and evaporated to give the desired product (5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-(1-methanesulfonyl-piperidin-4-yl)-methyl-amine). This was used in the next reaction step without further purification.

HPLC-MS (method 4): Rt= 3.70 min, $[M+1]^+$ m/z 442.1.

Yield: 74%

Intermediate 28

[4-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester

^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 5.31 (m, 1H), 4.50 (m, 1H), 3.72 (m, 1H), 3.59 (m, 1H), 1.81 (m, 6H), 1.55 (m, 2H), 1.43 (s, 9H).

Yield: 67%.

General method B

Suzuki coupling

A mixture of the appropriate iodide (ex: 2-(5-iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester) (1 equiv), the appropriate boronic reagent (ex: 3-(trifluoromethoxy)phenylboronic acid) (1.3 equiv), the palladium catalyst (0.2 equiv) and a saturated sodium carbonate solution (5 mL/mmol) in 1,4-dioxane (10 mL/mmol) was heated under reflux for 2 h to 8 h (in some cases DME and microwave irradiation at 120 °C was used). DCM and water were added and the mixture was extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the solvent evaporated under vacuum.

In some cases the residue was purified by column chromatography (Isolute/Flash, SiII, 0% to 2% MeOH in DCM) to give the desired product (ex: 2-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester). In other cases the residue was precipitated with MeOH and filtered to give the desired product.

Intermediate 29

(3aS,6aR)-5-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 6.70 min, $[M+1]^+$ m/z 496.2.

^1H NMR (300 MHz, MeOD) δ 8.02 (s, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 3.81 (dd, J = 10.4, 7.2 Hz, 2H), 3.67 (m, 2H), 3.52 – 3.42 (m, 2H), 3.36 (m, 2H), 3.12 (m, 2H), 1.46 (s, 9H).

Yield: 68%.

Intermediate 30

2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 7.06 min, $[M+1]^+$ m/z 524.2.

^{1}H NMR (300 MHz, MeOD) δ 8.10 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 4.26 (p, *J* = 7.8 Hz, 1H), 3.41 (m, 2H), 3.33 (m, 2H), 2.45 (m, 2H), 1.86 (m, 2H), 1.63 (m, 2H), 1.55 (m, 2H), 1.43 (s, 9H).

Yield: 90%.

Example 1

2-[5-(3-Cyano-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

Boronic reagent: 3-cyanophenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 6.22 min, $[M+1]^+$ m/z 465.2.

^{1}H NMR (300 MHz, MeOD) δ 8.38 (s, 1H), 8.18 (m, 1H), 7.66 – 7.47 (m, 3H), 4.24 (p, J = 7.9 Hz, 1H), 3.48 (m, 2H), 3.38 (m, 2H), 3.35 (m, 2H), 2.44 (m, 2H), 1.97 (m, 2H), 1.83 (m, 2H), 1.47 (s, 9H).

Yield: 70%.

Example 2

2-[5-(3-Trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethyl)phenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 6.92 min, $[M+1]^+$ m/z 508.2.

^{1}H NMR (300 MHz, MeOD) δ 8.46 (s, 1H), 8.10 (m, 1H), 7.55 (m, 3H), 4.24 (m, 1H), 3.43 (m, 2H), 3.32 (m, 2H), 2.45 (m, 2H), 1.86 (m, 2H), 1.70 (m, 2H), 1.53 (m, 2H), 1.47 (s, 9H).

Yield: 41%.

Intermediate 31

2-[5-(3-Dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

Boronic reagent: 3-(dimethylamino)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt = 5.35min, $[M+H]^+$ m/z 457.

^1H NMR (300 MHz, $CDCl_3$) δ 7.39 - 7.25 (m, 1H), 7.15 (d, J = 7.7 Hz, 1H), 6.67 (dd, J = 8.1, 2.1 Hz, 1H), 5.66 (s, 1H), 4.11 (s, 1H), 3.32 (t, J = 6.4 Hz, 1H), 2.98 (s, 2H), 2.70 (dd, J = 23.2, 10.6 Hz, 1H), 2.04 - 1.66 (m, 2H), 1.44 (s, 3H), 1.18 (ddd, J = 16.6, 12.5, 4.6 Hz, 1H).

Yield: 94%.

Intermediate 32

2-{[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 4): Rt= 5.20 min, $[M+1]^+$ m/z 538.1.

Yield: 65%.

Intermediate 33

2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2,9-diaza-spiro[5.5]undecane-9-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 7.39 min, $[M+1]^+$ m/z 538.3.

^1H NMR (300 MHz, MeOD) δ 8.04 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.51 (s, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 3.61 – 3.42 (m, 6H), 3.36 (m, 2H), 1.75 (m, 2H), 1.66 – 1.48 (m, 4H), 1.37 (m, 2H), 1.43 (s, 9H).

Yield: 69%.

Intermediate 34

9-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-3,9-diaza-spiro[5.5]undecane-3-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 7.49 min, $[M+1]^+$ m/z 538.2.

^{1}H NMR (300 MHz, MeOD) δ 7.99 (s, 1H), 7.88 (d, J = 7.4 Hz, 1H), 7.53 (s, 1H), 7.48 (t, J = 8.1 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 3.54 (m, 4H), 3.44 (m, 4H), 1.70 (m, 4H), 1.54 (m, 4H), 1.45 (s, 9H).

Yield: 89%.

Intermediate 35

{1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidin-3-yl}-carbamic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $PdCl_2(PPh_3)_2$.

HPLC-MS (method 1): Rt= 6.60 min, $[M+1]^+$ m/z 484.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.34 (m, 2H), 7.03 (d, *J* = 7.9 Hz, 1H), 4.65 (s, 1H), 3.69 (m, 2H), 3.35 (m, 3H), 1.75 (m, 4H), 1.38 (s, 9H).

Yield: 21%

Intermediate 36

4-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-piperidine-1-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 2): Rt= 2.84 min, $[M+1]^+$ m/z 484.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 5.64 (s, 1H), 4.01 (m, 2H), 3.89 (m, 1H), 2.96 (m, 2H), 2.14 (m, 2H), 1.53 (m, 2H), 1.45 (s, 9H).

Yield: 17%.

Example 3

1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidine-3-carboxylic acid ethyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 6.59 min, $[M+1]^+$ m/z 441.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.74 (m, 1H), 7.40 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.97 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.70 (dt, *J* =

12.9, 4.0 Hz, 1H), 3.41 (dd, *J* = 13.2, 9.7 Hz, 1H), 3.27 (ddd, *J* = 13.1, 10.0, 3.2 Hz, 1H), 2.68 (m, 1H), 2.12 (m, 1H), 1.77 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H).
Yield: 26%.

Example 4

{1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidin-4-ylmethyl}-carbamic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.
Palladium catalyst: $PdCl_2(PPh_3)_2$.
HPLC-MS (method 1): Rt= 6.71 min, $[M+1]^+$ m/z 498.2.
^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.41 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 4.67 (s, 1H), 3.94 (d, *J* = 12.9 Hz, 2H), 3.12 (m, 4H), 1.86 (d, *J* = 12.7 Hz, 2H), 1.79 (m, 1H), 1.60 (s, 1H), 1.45 (s, 9H), 1.35 (m, 1H).
Yield: 48%.

Example 5

3-(2-Morpholin-4-yl-imidazo[2,1-b][1,3,4]thiadiazol-5-yl)-phenol

Boronic reagent: 3-Hydroxyphenylboronic acid.
Palladium catalyst: $Pd(PPh_3)_4$.
HPLC-MS (method 1): Rt= 8.09 min, $[M+1]^+$ m/z 303.1.
^1H NMR (300 MHz, DMSO) δ 8.13 (s, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 6.8 Hz, 1H), 3.76 (m, 4H), 3.49 (m, 4H).
Yield: 42%.

Example 6

5-(3,4-Dimethoxy-phenyl)-2-morpholin-4-yl-imidazo[2,1-b][1,3,4]thiadiazole

Boronic reagent: 3,4-Dimethoxyphenylboronic acid.
Palladium catalyst: $Pd(PPh_3)_4$.
HPLC-MS (method 1): Rt= 5.42 min, $[M+1]^+$ m/z 347.1.
^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.30 (s, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.83 (m, 4H), 3.48 (m, 4H).
Yield: 16%.

Example 7

[5-(3,4-Dimethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-(1-methanesulfonyl-piperidin-4-yl)-amine

Boronic reagent: 3,4-Dimethoxyphenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 1): Rt= 3.56 min, $[M+1]^+$ m/z 438.2.

^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 6.93 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (m, 1H), 3.76 (m, 2H), 2.91 (m, 2H), 2.80 (s, 3H), 2.29 (m, 2H), 1.80 (m, 2H).

Yield: 15%.

Example 8

(1-Methyl-piperidin-4-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 3.04 min, $[M+1]^+$ m/z 398.3.

^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.95 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.39 (m, 2H), 7.07 (d, *J* = 7.7 Hz, 1H), 3.90 (s, 1H), 3.44 (m, 2H), 2.70 (m, 2H), 2.68 (s, 3H), 2.35 (m, 2H), 2.04 (m, 2H).

Yield: 5%

Example 9

4-{[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $PdCl_2(dppf)$.

HPLC-MS (method 2): Rt= 2.97 min, $[M+1]^+$ m/z 498.2.

^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.71 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.40 (t, *J* = 8.1Hz, 1H), 7.37 (s, 1H), 7.04 (m, 1H), 6.49 (s, 1H), 4.14 (m, 2H), 3.35 (t, *J* = 6.1 Hz, 2H), 2.68 (m, 2H), 1.93 (m, 1H), 1.78 (d, *J* = 12.6 Hz, 2H), 1.43 (s, 9H), 1.23 (m, 2H).

Yield: 2%.

Example 10

4-{[5-(3-Cyano-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester

Boronic reagent: 3-cyanophenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 5.82 min, $[M+1]^+$ m/z 439.3.

^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.2 Hz, 1H), 8.02 (dt, *J* = 7.0, 1.9 Hz, 1H), 7.51 (m, 2H), 7.42 (s, 1H), 6.12 (m, 1H), 4.15 (m, 2H), 3.34 (t, *J* = 6.1 Hz, 2H), 2.71 (m, 2H), 1.89 (m, 1H), 1.76 (m, 2H), 1.40 (s, 9H), 1.23 (ddd, *J* = 24.8, 12.6, 4.5 Hz, 2H).

Yield: 45%.

Example 11

4-{[5-(3-Dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester

Boronic reagent: 3-(N,N-Dimethylamino)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 5.35 min, $[M+1]^+$ m/z 457.3.

^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 1H), 7.33 (s, 1H), 7.29 (m, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.67 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.66 (s, 1H), 4.11 (m, 2H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.97 (s, 6H), 2.70 (m, 2H), 1.88 (m, 1H), 1.75 (d, *J* = 12.9 Hz, 2H), 1.44 (s, 9H), 1.18 (ddd, *J* = 16.6, 12.5, 4.6 Hz, 2H).

Yield: 10%.

Example 12

4-{[5-(3-Trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethyl)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 4): Rt= 4.98 min, $[M+1]^+$ m/z 480.3.

Yield: 67%.

Example 13

(1-Methyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 3.25 min, $[M+1]^+$ m/z 412.2.

^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 5.92 (t, *J* = 5.8 Hz, 1H), 3.33 (t, *J* = 6.1 Hz, 2H), 2.87 (d, *J* = 11.5 Hz, 2H), 2.25 (s, 3H), 1.99 – 1.86 (m, 2H), 1.86 – 1.67 (m, 3H), 1.45 – 1.29 (m, 2H).

Yield: 9%.

Example 14

4-{2-[(1-Methyl-piperidin-4-ylmethyl)-amino]-imidazo[2,1-b][1,3,4]thiadiazol-5-yl}-phenol

Boronic reagent: 4-hydroxyphenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 0.68 min, $[M+1]^+$ m/z 344.2.

^1H NMR (300 MHz, MeOD) δ 8.29 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.21 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 3.51 (d, *J* = 11.9 Hz, 2H), 3.42 (d, *J* = 5.9 Hz, 2H), 3.02 (t, *J* = 11.9 Hz, 2H), 2.84 (s, 3H), 2.07 (m, 3H), 1.61 (m, 2H).

Yield: 13%.

Example 15

(1-Methyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

Boronic reagent: 3-(trifluoromethyl)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 3.07 min, $[M+1]^+$ m/z 396.2.

^1H NMR (300 MHz, DMSO) δ 8.42 (s, 1H), 8.20 (m, 2H), 7.64 (m, 3H), 3.24 (m, 2H), 2.75 (d, *J* = 11.1 Hz, 2H), 2.12 (s, 3H), 1.81 (t, *J* = 11.6 Hz, 2H), 1.68 (d, *J* = 10.5 Hz, 3H), 1.23 (m, 2H).

Yield: 50%.

Example 16

1-(3-{2-[(1-Methyl-piperidin-4-ylmethyl)-amino]-imidazo[2,1-b][1,3,4]thiadiazol-5-yl}-phenyl)-ethanone

Boronic reagent: 3-acetylphenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 2.44 min, $[M+1]^+$ m/z 370.3.

^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 6.5, 4.8 Hz, 1H), 8.03 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.83 (m, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 6.03 (s, 1H), 3.34 (t, *J* = 6.0 Hz, 2H), 2.90 (m, 2H), 2.61 (s, 3H), 2.30 (s, 3H), 2.02 (m, 2H), 1.79 (m, 3H), 1.44 (m, 2H).

Yield: 10%.

Example 17

1-(3-{2-[Methyl-(1-methyl-piperidin-4-ylmethyl)-amino]-imidazo[2,1-b][1,3,4]thiadiazol-5-yl}-phenyl)-ethanone

Secondary product isolated when synthesising example 15 due to a contamination of the amine.

HPLC-MS (method 1): Rt= 2.45min, $[M+1]^+$ m/z 370.0.

^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (t, J = 1.6 Hz, 1H), 8.03 (ddd, J = 7.8, 1.6, 1.1 Hz, 1H), 7.86 - 7.79 (m, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.43 (s, 1H), 6.03 (s, 1H), 3.34 (t, J = 6.0 Hz, 2H), 2.94 (d, J = 11.5 Hz, 3H), 2.63 (s, 3H), 2.30 (s, 3H), 2.13 - 1.94 (m, 3H), 1.79 (t, J = 10.4 Hz, 3H), 1.44 (q, J = 13.2 Hz, 2H).

Yield: 9.1%.

Example 18

3-{2-[(1-Methyl-piperidin-4-ylmethyl)-amino]-imidazo[2,1-b][1,3,4]thiadiazol-5-yl}-benzonitrile

Boronic reagent: 3-cyanophenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 2.56 min, $[M+1]^+$ m/z 353.2.

^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.2 Hz, 1H), 8.02 (ddd, *J* = 9.9, 6.1, 4.0 Hz, 1H), 7.51 (m, 3H), 5.94 (m, 1H), 3.38 (t, *J* = 5.7 Hz, 2H), 3.08 (d, *J* = 11.7 Hz, 2H), 2.37 (s, 3H), 2.17 (m, 3H), 1.85 (m, 2H), 1.62 (m, 2H).

Yield: 3%.

Example 20

(Tetrahydro-pyran-4-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 5.39 min, $[M+1]^+$ m/z 385.0.

^1H NMR (300 MHz, DMSO) δ 8.22 (d, J = 6.2 Hz, 1H), 8.10 (s, 2H), 7.90 (d, J = 7.6 Hz, 2H), 7.59 (ddd, J = 16.0, 13.1, 9.0 Hz, 8H), 7.31 (dt, J = 17.3, 7.8 Hz, 3H), 7.03 (d, J = 51.6 Hz, 1H), 3.96 - 3.75 (m, 7H), 3.69 - 3.37 (m, 17H), 2.04 (d, J = 11.5 Hz, 4H), 1.53 (dd, J = 19.5, 10.5 Hz, 4H), 1.23 (s, 3H), 0.85 (s, 1H).

Yield: 2.2%.

Example 21

7-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-7-aza-spiro[3.5]non-2-ylamine

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 3.61 min, $[M+1]^+$ m/z 424.0.

^1H NMR (300 MHz, MeOD) δ 8.55 (s, 1H), 7.99 (d, J = 16.5 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.58 - 7.44 (m, 2H), 7.18 (d, J = 8.2 Hz, 1H), 3.86 - 3.70 (m, 1H), 3.53 (dd, J = 20.5, 4.7 Hz, 4H), 2.46 - 2.30 (m, 2H), 2.06 - 1.72 (m, 6H), 1.41 - 1.11 (m, 1H), 0.90 (t, J = 6.9 Hz, 1H).

Yield: 1.1%.

Example 22

8-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-1,8-diaza-spiro[4.6]undecane

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 1): Rt= 3.50 min, $[M+1]^+$ m/z 438.0.

^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.89 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.47 - 7.33 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 4.04 - 3.43 (m, 8H), 3.27 (d, J = 6.9 Hz, 2H), 2.39 - 2.20 (m, 1H), 1.97 (tt, J = 14.0, 10.4 Hz, 9H)

Yield: 38%.

Intermediate 37

{4-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester

Boronic reagent: 3-(trifluoromethoxy)phenylboronic acid.

Palladium catalyst: $Pd(PPh_3)_4$.

HPLC-MS (method 4): Rt= 4.99 min, $[M+1]^+$ m/z 496.2.

Intermediate 38

2-Methylsulfanyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole

A mixture of 5-Iodo-2-methylsulfanyl-imidazo[2,1-b][1,3,4]thiadiazole (1 g, 3.365 mmol), 3-(trifluoromethoxy)phenylboronic acid (832 mg, 4.069 mmol), $PdCl_2$(dppf) (472 mg, 0.673 mmol) and 2M aq sodium carbonate (8 mL) in 1,4-dioxane (37 mL) was heated at 110°C for 6 h. DCM and water were added and the organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (Biotage/Flash, silica, 0% to 8% MeOH in DCM) to give the desired product (650 mg, 58% yield) (2-methylsulfanyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole).

HPLC-MS (method 4): Rt= 4.86 min, $[M+1]^+$ m/z 332.0.

^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 2.80 (s, 3H).

Intermediate 39

2-Methanesulfinyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole

To a solution of 2-methylsulfanyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole (100 mg, 0.302 mmol) in chloroform (4.5 mL) was added mCPBA (130 mg, 0.755 mmol) at 0°C. The reaction was stirred at 0 °C for 2 h. DCM was added and the mixture was washed with a 10% sodium thiosulphate solution, saturated sodium bicarbonate solution and with brine. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The residue was used in the next reaction step without further purification (96 mg, 92% yield).

HPLC-MS (method 1): Rt= 4.31 min, $[M+1]^+$ m/z 348.1.

^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (m, 3H), 7.49 (t, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 5.4 Hz, 1H), 3.18 (s, 3H).

Intermediate 40

2-Methanesulfonyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole

A mixture of 2-methanesulfinyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole (236 mg, 0.679 mmol) and mCPBA (117 mg, 0.679 mmol) in chloroform (10 mL) was stirred at 0 °C for 1 h and at rt for 4 h. More mCPBA (1 eq) was added and the mixture was for 1 h. mCPBA (1 equiv) was added and stirring was continued for 5 h. DCM was added and the mixture was washed with a 10% sodium thiosulphate solution (x2), a saturated sodium bicarbonate solution (x2) and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was used in the next reaction step without further purification (226 mg, 92% yield).

HPLC-MS (method 4): Rt= 4.55 min, $[M+1]^+$ m/z 364.2.

General method C

BOC deprotection.

A mixture of the appropriate amine BOC-protected product (ex: 2-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]nonane-7-carboxylic acid tert-butyl ester) (1 eq) and HCl (4N in dioxane, 10 eq) in MeOH (10 mL/mmol) was stirred at room temperature for 18 h. The solvent was evaporated under vacuum.

In some cases the residue was diluted with water and neutralized with a saturated sodium bicarbonate solution. The mixture was extracted with DCM (x3) and the combinated organic layers were concentrated. The residue was purified by column chromatography (Isolute/Flash, NH_2, 0% to 10% MeOH in DCM) to give the desired product as the free base (ex: (7-Aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine).

In other cases the residue was triturated from Et_2O to give the desired final compound as the hydrochloric salt.

Example 23

(7-Aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 3.36 min, $[M+1]^+$ m/z 424.2.

^{1}H NMR (300 MHz, MeOD) δ 8.12 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.28 (p, J = 7.9 Hz, 1H), 2.90 (m, 2H), 2.81 (m, 2H), 2.44 (m, 2H), 1.85 (m, 2H), 1.79 (m, 2H), 1.61 (m, 2H).

Yield: 48%.

Example 24

2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2,9-diaza-spiro[5.5]undecane, hydrochloride

HPLC-MS (method 1): Rt= 3.62 min, $[M+1]^+$ m/z 348.2.

^{1}H NMR (300 MHz, DMSO) δ 8.96 (m, 2H), 8.00 (m, 2H), 7.65 (m, 1H), 7.32 (m, 1H), 3.54 (m, 2H), 3.43 (m, 2H), 3.05 (m, 4H), 1.66 (m, 8H).

Yield: 74%.

Example 25

3-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-3,9-diaza-spiro[5.5]undecane, hydrochloride

HPLC-MS (method 1): Rt= 3.50 min, $[M+1]^+$ m/z 438.2.

^{1}H NMR (300 MHz, MeOD) δ 7.89 (m, 3H), 7.48 (s, 1H), 7.13 (s, 1H), 3.52 (m, 4H), 3.24 (m, 4H), 1.78 (m, 8H).

Yield: 41%.

Example 26

2-(Hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole, hydrochloride

HPLC-MS (method 1): Rt= 3.18 min, $[M+1]^+$ m/z 396.3.

^{1}H NMR (300 MHz, D_2O) δ 7.56 (m, 1H), 7.43 (m, 2H), 7.24 (m, 1H), 7.07 (m, 1H), 3.45 (m, 4H), 3.28 (m, 2H), 3.18 (m, 2H), 3.02 (m, 2H).

Yield: 78%.

Example 27

2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2,8-diaza-spiro[4.5]decane, hydrochloride

HPLC-MS (method 1): Rt= 3.46 min, $[M+1]^+$ m/z 424.2.

^{1}H NMR (300 MHz, D_2O) δ 7.59-7.09 (m, 6H), 3.33 (m, 2H), 3.15 (m, 2H), 3.00 (m, 4H), 1.93 (m, 2H), 1.21 (m, 4H).

Yield: 64%.

Example 28

3-[2-(7-Aza-spiro[3.5]non-2-ylamino)-imidazo[2,1-b][1,3,4]thiadiazol-5-yl]-benzonitrile, hydrochloride

HPLC-MS (method 1): Rt= 2.70 min, $[M+1]^+$ m/z 365.2.

^{1}H NMR (300 MHz, D_2O) δ 8.01 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.55 (m, 1H), 7.47 (m, 1H), 3.95 (m, 1H), 3.11 (m, 4H), 2.36 (m, 2H), 1.83 (m, 6H).

Yield: 85%.

Example 29

(7-Aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine, hydrochloride

HPLC-MS (method 1): Rt= 3.27 min, $[M+1]^+$ m/z 408.1.

^{1}H NMR (300 MHz, D_2O) δ 8.08 (s, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 7.47 (t, J = 7.6 Hz, 1H), 3.81 (p, J = 8.2 Hz, 1H), 3.10 (m, 2H), 3.03 (m, 2H), 2.27 (m, 2H), 1.75 (m, 6H).

Yield: 59%.

Example 30

1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidin-3-ylamine

HPLC-MS (method 1): Rt= 3.24 min, $[M+1]^+$ m/z 384.1.

^{1}H NMR (300 MHz, DMSO) δ 8.41 (s, 3H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.89 (s, 1H), 7.61 (t, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 3.98 (m, 1H), 3.62 (m, 2H), 3.45 (m, 2H), 2.03 (m, 1H), 1.86 (m, 1H), 1.70 (m, 2H).

Yield: 84%.

Example 31

1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-pyrrolidin-3-ylamine

HPLC-MS (method 1): Rt= 3.72 min, $[M+1]^+$ m/z 370.3.

^{1}H NMR (300 MHz, DMSO) δ 8.49 (s, 3H), 8.10 (s, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.89 (s, 1H), 7.61 (t, *J* = 8.1 Hz, 1H), 7.32 (m, 1H), 4.05 (m, 1H), 3.73 (m, 4H), 2.39 (m, 1H), 2.25 (m, 1H).

Yield: 60%.

Example 32

C-{1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidin-4-yl}-methylamine

HPLC-MS (method 1): Rt= 3.32 min, $[M+1]^+$ m/z 398.1.

^{1}H NMR (300 MHz, MeOD) δ 8.09 (s, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 4.07 (d, *J* = 13.0 Hz, 2H), 3.34 (m, 2H), 2.94 (d, *J* = 6.6 Hz, 2H), 2.00 (m, 3H), 1.51 (m, 2H).

Yield: 94%.

Example 33

Piperidin-4-yl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine Hydrochloride

HPLC-MS (method 1): Rt= 3.08 min, $[M+1]^+$ m/z 384.2.

^{1}H NMR (300 MHz, DMSO) δ 9.22 (d, *J* = 6.2 Hz, 1H), 9.08 (s, 2H), 8.10 (s, 1H), 8.01 (m, 2H), 7.62 (t, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 3.94 (m, 1H), 3.30 (m, 2H), 3.05 (m, 2H), 2.22 (m, 2H), 1.85 (m, 2H).

Yield: 99%.

Example 34

Piperidin-4-ylmethyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 2.98 min, $[M+1]^+$ m/z 398.2.

^{1}H NMR (700 MHz, DMSO) δ 8.93 (m, 1H), 8.90 (s, 1H), 8.66 (d, *J* = 9.3, 1H), 8.10 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.63 (t, *J* = 8.1, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 3.29 (m, 4H), 2.85 (q, *J* = 12.6 Hz, 2H), 1.99 (m, 1H), 1.87 (d, *J* = 13.3 Hz, 2H), 1.44 (m, 2H).

Yield: 99%.

Example 35

3-{2-[(Piperidin-4-ylmethyl)-amino]-imidazo[2,1-b][1,3,4]thiadiazol-5-yl}-benzonitrile

HPLC-MS (method 1): Rt= 2.65 min, $[M+1]^+$ m/z 339.2.

^{1}H NMR (300 MHz, MeOD) δ 8.38 (m, 2H), 8.16 (m, 1H), 7.57 (m, 2H), 3.45 (m, 4H), 3.03 (t, *J* = 12.8 Hz, 2H), 2.16 (m, 1H), 2.04 (m, 2H), 1.52 (m, 2H).

Yield: 47%.

Example 36

(2-Piperazin-1-yl-ethyl)-[5-(3-trifluoromethoxy-phenyl)-*im*idazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine, hydrochloride

HPLC-MS (method 1): Rt= 2.97 min, $[M+1]^+$ m/z 413.1.

Yield: 97%.

Example 37

N*1*-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-propane-1,3-diamine

HPLC-MS (method 3): Rt= 4.18 min, $[M+1]^+$ m/z 358.1.

^{1}H NMR (300 MHz, DMSO) δ 8.78 (m, 1H), 8.07 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 3H), 7.91 (s, 1H), 7.62 (t, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 3.46 (q, *J* = 6.4 Hz, 2H), 2.90 (m, 2H), 1.97 (m, 2H).

Yield: 81%.

General method D

To a solution of the appropriate BOC-protected amine derivative (1 equiv) (ex: 4-{[5-(3-dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester) in MeOH (32 mL/mmol), Amberlyst (3 equiv) was added. The mixture was stirred at rt overnight and filtered off. The resin was suspended in 7N NH_3 in MeOH (32 mL/mmol), and stirred at rt for 2 h. The mixture was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (Isolute Si- II, DCM:MeOH 100:0 to 97:3 followed by DCM:NH3 7N in MeOH, 99:1 to 20:80) to give the desired product

(ex: [5-(3-dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidin-4-ylmethyl-amine).

Example 38

[5-(3-Dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidin-4-ylmethyl-amine

HPLC-MS (method 3): Rt= 2.03 min, $[M+1]^+$ m/z 357.2.

^{1}H NMR (300 MHz, MeOD) δ 7.54 (m, 1H), 7.37 (s, 1H), 7.22 (m, 2H), 6.71 (d, *J* = 7.9 Hz, 1H), 3.32 (m, 3H), 3.09 (d, *J* = 12.5 Hz, 2H), 2.98 (s, 6H), 2.62 (td, *J* = 12.4, 2.3 Hz, 2H), 1.93 (m, 1H), 1.81 (d, *J* = 13.0 Hz, 2H), 1.25 (qd, *J* = 12.4, 4.0 Hz, 2H).

Yield: 52%.

Example 39

8-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2,8-diaza-spiro[4.5]decane

HPLC-MS (method 1): Rt= 3.43 min, $[M+1]^+$ m/z 424.1.

^{1}H NMR (300 MHz, MeOD) δ 7.98 (s, 1H), 7.85 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.52 (s, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 3.52 (m, 4H), 3.30 (m, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.80 (s, 1H), 1.73 (m, 6H).

Yield: 13%.

Example 40

(7-Aza-spiro[3.5]non-2-ylmethyl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 3.47 min, $[M+1]^+$ m/z 438.1.

^{1}H NMR (300 MHz, MeOD) δ 8.05 (s, 1H), 7.84 (t, *J* = 15.2 Hz, 1H), 7.49 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 3.46 (d, *J* = 7.2 Hz, 2H), 2.80 (m, 2H), 2.72 (m, 2H), 2.00 (m, 1H), 1.59 (m, 8H).

Yield: 67%.

Example 41

Piperidin-4-ylmethyl-[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 2.98 min, $[M+1]^+$ m/z 382.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.97 (dd, *J* = 4.2, 2.8 Hz, 1H), 7.50 (m, 2H), 7.43 (s, 1H), 5.97 (m, 1H), 3.32 (m, 2H), 3.16 (d, *J* = 12.2 Hz, 2H), 2.65 (td, *J* = 12.2, 2.4 Hz, 2H), 1.93 (m, 1H), 1.81 (d, *J* = 12.8 Hz, 2H), 1.28 (m, 2H).
Yield: 78%.

Example 42

(7-Aza-spiro[3.5]non-2-yl)-[5-(3-dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt = 1.97min, $[M+H]^+$ m/z 384.0.

^{1}H NMR (300 MHz, MeOD) δ 7.94 (s, 1H), 7.75 – 7.67 (m, 1H), 7.62 – 7.45 (m, 2H), 7.03 (dd, J = 8.1, 1.5 Hz, 1H), 5.23 (s, 5H), 4.52 (p, J = 7.9 Hz, 1H), 3.74 – 3.64 (m, 3H), 3.17 – 3.01 (m, 4H), 2.79 – 2.63 (m, 2H), 2.19 – 2.04 (m, 2H), 1.93 (dd, J = 10.9, 6.1 Hz, 4H).
Yield: 53.2%.

Example 43

N-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-cyclohexane-1,4-diamine

HPLC-MS (method 1): Rt= 4.07 min, $[M+1]^+$ m/z 398.2.

^{1}H NMR (300 MHz, MeOD) δ 8.47 (s, 1H), 8.04 (m, 1H), 7.83 (m, 1H), 7.49 (m, 2H), 7.15 (m, 1H), 4.01 (s, 1H), 3.26 (m, 1H), 2.20 (m, 2H), 1.82 (m, 4H).
Yield: 19%.

General method E

To a mixture of the appropriate amine (ex: (7-Aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine) (1 equiv) in MeCN (10 mL/mmol) was added Et_3N (3 equiv) and methanesulfonyl chloride (1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then at rt for 1 h. A saturated sodium bicarbonate solution was added and it was stirred for a while. Water was added, and the mixture was extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and concentrated.
In some cases the residue was triturated from Et_2O and MeCN to give the desired product (ex: (7-Methanesulfonyl-7-aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine). In other cases the residue

was purified by column chromatography (Isolute/Flash, SiII, 0% to 2% MeOH in DCM) and by preparative HPLC to yield the desired product.

Example 44

(7-Methanesulfonyl-7-aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 5.72 min, $[M+1]^+$ m/z 502.2.

^{1}H NMR (300 MHz, MeOD) δ 8.10 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 4.30 (p, *J* = 7.9 Hz, 1H), 3.28 (m, 2H), 3.13 (m, 2H), 2.82 (s, 3H), 2.48 (m, 2H), 1.90 (m, 2H), 1.84 (m, 2H), 1.71 (m, 2H).

Yield: 78%

Example 45

(1-Methanesulfonyl-piperidin-4-yl)-methyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 6.06 min, $[M+1]^+$ m/z 476.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.67 (m, 1H), 7.43 (s, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.07 (m, 1H), 4.00 (m, 3H), 3.01 (s, 3H), 2.81 (s, 3H), 2.78 (m, 2H), 1.95 (m, 4H).

Yield: 32%.

Example 46

(1-Methanesulfonyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 5.39 min, $[M+1]^+$ m/z 476.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.41 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 1H), 5.87 (t, *J* = 5.9 Hz, 1H), 3.85 (d, *J* = 11.9 Hz, 2H), 3.39 (t, *J* = 6.2 Hz, 2H), 2.76 (s, 3H), 2.67 (m, 2H), 1.97 (m, 1H), 1.91 (d, *J* = 11.4 Hz, 2H), 1.42 (dt, *J* = 11.9, 8.5 Hz, 2H).

Yield: 5%.

General method F

A mixture of the appropriate sulfinyl derivative such as Intermediate 39 described hereinbefore (ex:2-methanesulfinyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-

b][1,3,4]thiadiazole) (1 equiv), the appropriate amine (1.5 equiv) (ex: 2-(4-methyl-piperazin-1-yl)-ethylamine) and Et_3N (2 equiv) (0.092 mL, 0.662 mmol) in isopropanol (15 mL/mmol) was heated in a sealed tube at 110 °C for 40 h. On cooling, DCM was added and the mixture was washed with water. The organic layer was dried (sodium sulfate), filtered and concentrated. The residue was purified by column chromatography (Isolute/Flash, SiII, 0% to 20% MeOH in DCM) to give the desired product (ex: [2-(4-methyl-piperazin-1-yl)-ethyl]-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine).

Intermediate 41

2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-2,8-diaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester

HPLC-MS (method 1): Rt= 7.20 min, $[M+1]^+$ m/z 524.2.

^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.45 (s, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.09 (m, 1H), 3.62 (t, *J* = 7.1 Hz, 2H), 3.52 (m, 2H), 3.40 (m, 4H), 2.00 (dd, *J* = 8.3, 5.9 Hz, 2H), 1.62 (m, 4H), 1.47 (s, 9H).

Yield: 42%

Example 47

[2-(4-Methyl-piperazin-1-yl)-ethyl]-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 3.15 min, $[M+1]^+$ m/z 427.2.

^1H NMR (300 MHz, MeOD) δ 7.99 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.60 (m, 4H), 2.50 (m, 4H), 2.27 (s, 3H).

Yield: 48%

Example 48

4-{2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 2-methanesulfonyl-5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazole (116 mg, 0.319 mmol), 4-N-(2-aminoethyl)-1-N-boc-piperazine (110 mg, 0.479 mmol) and Et_3N (0.089 mL, 0.639 mmol) in ^iPrOH (5 mL) was heated in a sealed tube at 110°C for 16 hours. On cooling, DCM was added and the mixture was washed with H_2O. The organic layer was dried

(sodium sulfate), filtered and concentrated. The residue was purified by column chromatography (Isolute/Flash, Sill, 0% to 20% MeOH in DCM) to give the desired product (4-{2-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester) (20 mg, 12% yield).

HPLC-MS (method 1): Rt= 3.99 min, $[M+1]^+$ m/z 513.2.

^{1}H NMR (300 MHz, MeOD) δ 8.04 (s, 1H), 7.90 (m, 1H), 7.52 (s, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.19 (m, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.44 (m, 4H), 2.72 (t, *J* = 6.4 Hz, 2H), 2.54 (m, 4H), 1.46 (s, 9H).

Example 49

1-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidine-3-carboxylic acid

A mixture of 1-[5-(6-amino-5-trifluoromethyl-pyridin-3-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidine-3-carboxylic acid ethyl ester) (1 equiv) (60 mg, 0.136 mmol) in EtOH:water (14 ml/mmol, 1:1) was treated with potassium carbonate (14 equiv, 2N solution) and stirred at rt overnight. EtOH was evaporated and the water solution was acidified with acetic acid and a few drops of HCl. The solid was filtered, washed with cold water and dried to give the desired product (1-[5-(6-amino-5-trifluoromethyl-pyridin-3-yl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-piperidine-3-carboxylic acid) (Yield: 16%).

HPLC-MS (method 1): Rt= 5.44 min, $[M+1]^+$ m/z 413.2.

^{1}H NMR (700 MHz, MeOD) δ 7.98 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.54 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 4.03 (dd, *J* = 13.0, 4.2 Hz, 1H), 3.90 (m, 1H), 3.37 (m, 1H), 3.26 (m, 1H), 2.51 (m, 1H), 2.17 (m, 1H), 1.89 (m, 1H), 1.73 (m, 2H).

General procedure G

A mixture of the appropriate amine (ex: piperidin-4-ylmethyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine (1 equiv), appropriate alkylation reagent (e.g. 1-fluoro-2-iodoethane; 3 equiv) and Et_3N (3 equiv) in CH_3CN (17 ml/mmol) was heated at 100°C under microwave irradiation at 100°C for 5 h. The reaction mixture was evaporated and the residue was redissolved in EtOAc and washed with H_2O and brine. The organics were dried, filtered and evaporated. The residue was purified by HPLC to give the desired

product (ex: [1-(2-fluoro-ethyl)-piperidin-4-ylmethyl]-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine).

Example 50

[1-(2-Fluoro-ethyl)-piperidin-4-ylmethyl]-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 3.07 and 3.26 min, $[M+1]^+$ m/z 444.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.09 (m, 1H), 4.69 (m, 1H), 4.53 (m, 1H), 3.34 (t, *J* = 6.1 Hz, 2H), 3.08 (m, 2H), 2.75 (m, 2H), 2.15 (m, 2H), 1.82 (m, 3H), 1.49 (m, 2H).

Yield: 11%.

Example 51

1-(2-Methoxy-ethyl)-piperidin-4-ylmethyl]-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 3.40 min, $[M+H]^+$ m/z 456.0.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.47 - 7.36 (m, 2H), 7.08 (d, J = 8.2 Hz, 1H), 5.39 (s, 1H), 3.50 (t, J = 5.6 Hz, 2H), 3.37 - 3.27 (m, 5H), 3.01 (d, J = 11.5 Hz, 2H), 2.57 (t, J = 5.6 Hz, 2H), 2.02 (t, J = 11.8 Hz, 4H), 1.77 (d, J = 9.5 Hz, 3H), 1.55 - 1.33 (m, 2H).

Yield: 23%.

General procedure H

To a mixture of the appropriate amine derivative (1 equiv) (ex: (7-Aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine) in anhydrous DMF, Et_3N was added. After 5 min, DMAP and the appropriate alkylchloride were added (ex: 2-chloro-N,N-dimethyl-acetamide). The reaction mixture was stirred at rt for 3 h. Then, NH_4Cl (aq/ sat) was added together with HCl (aq./ 1.2M). The aq.layer was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was purified by column chromatography (Isolute/Flash, Sill, 0% to 20% MeOH in DCM) followed by semi-preparative HPLC to yield the desired product (ex: N,N-Dimethyl-2-{2-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]non-7-yl}-acetamide).

Example 52

N,N-Dimethyl-2-{2-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]non-7-yl}-acetamide

HPLC-MS (method 1): Rt = 3.37min, $[M+H]^+$ 509.0

^1H NMR (300 MHz, MeOD) δ 8.12 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.57 - 7.42 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 4.32 - 4.15 (m, 1H), 3.35 (d, J = 11.5 Hz, 6H), 3.20 (s, 3H), 3.10 (s, 4H), 2.95 (s, 4H), 2.47 (d, J = 26.8 Hz, 8H), 1.93 - 1.56 (m, 8H).

Yield: 38%.

Example 53

N,N-Dimethyl-2-(4-{[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidin-1-yl)-acetamide

HPLC-MS (method 4): Rt= 3.18 min, [M+H]+ m/z 467.0.

^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.05 – 7.91 (m, 1H), 7.57 – 7.42 (m, 2H), 5.72 (s, 1H), 3.39 (dd, *J* = 11.0, 4.9 Hz, 2H), 3.22 (s, 4H), 3.00 (d, *J* = 25.0 Hz, 3H), 2.52 (t, *J* = 10.8 Hz, 1H), 2.04 – 1.77 (m, 2H), 1.77 – 1.51 (m, 1H).

Yield: 7.7%.

General procedure I

A solution of the appropriate amine (ex: piperidin-4-ylmethyl-[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine) (1 equiv) and the appropriate aldehyde (ex: cyclopropanecarboxaldehyde) (5 equiv) in MeOH:THF (7.5 mL/mmol) and AcOH (cat) was stirred at rt overnight. Then $NaBH_3CN$ (1.2 equiv) was added and the reaction mixture was stirred at rt for 2 h. Sodium hydroxide (aq. 2N) was added and the mixture was evaporated. The aqueous layer was extracted with EtOAc and DCM. The combined organic layers were dried, filtered and evaporated. The residue was washed with *n*-pentane and Et_2O and filtered. The filtrate was evaporated and purified by HPLC to give the desired product (ex: (1-cyclopropylmethyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine).

Example 54

(1-Cyclopropylmethyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 3.46 min, $[M+1]^+$ m/z 436.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.40 (s, 1H), 7.96 (d, *J* = 6.2 Hz, 1H), 7.90 (s, 1H), 7.51 (m, 2H), 3.64 (d, *J* = 11.1 Hz, 2H), 3.44 (s, 2H), 2.80 (d, *J* = 6.8 Hz, 2H), 2.66 (m, 2H), 2.23 (m, 1H), 1.94 (m, 4H), 1.10 (m, 1H), 0.74 (d, *J* = 7.4 Hz, 2H), 0.35 (d, *J* = 4.6 Hz, 2H).

Yield: 38%.

Example 55

(7-Cyclopropylmethyl-7-aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

HPLC-MS (method 1): Rt= 4.31 min, $[M+1]^+$ m/z 478.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.39 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.90 (m, 1H), 4.23 (m, 1H), 2.93 (m, 2H), 2.67 (m, 2H), 2.46 (m, 4H), 1.94 (m, 6H), 1.03 (m, 1H), 0.67 (m, 2H), 0.27 (m, 2H).

Yield: 29%.

General method J

To a mixture of the appropriate amine derivative (1 equiv) (ex: (7-Aza-spiro[3.5]non-2-yl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine) in acetonitrile 7.5 mL/mmol), Et_3N (1.5 equiv) and acetic anhydride (1.2 equiv) were added. In some cases DMAP (0.1 equiv) was added. The reaction mixture was stirred at rt overnight. The mixture was filtered and rinsed with Et_2O to give the desired amide product (ex: 1-{2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]non-7-yl}-ethanone).

Example 56

1-(4-{[5-(3-Trifluoromethyl-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidin-1-yl)-ethanone

HPLC-MS (method 1): Rt= 4.90 min, $[M+1]^+$ m/z 424.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.96 (m, 1H), 7.50 (m, 2H), 7.42 (m, 1H), 7.20 (t, *J* = 5.4 Hz, 1H), 4.62 (d, *J* = 13.9 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.36 (m, 2H), 3.06 (m, 1H), 2.55 (m, 1H), 2.08 (s, 3H), 1.86 (m, 2H), 1.23 (m, 3H).
Yield: 71%.

Example 57

1-{2-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-7-aza-spiro[3.5]non-7-yl}-ethanone

HPLC-MS (method 2): Rt= 0.93min, $[M+H]^+$ m/z 466.0.

1H NMR (300 MHz, CDCl3) δ 8.14 (s, 1H), 7.95 (d, J = 10.0 Hz, 3H), 7.68 (d, J = 7.8 Hz, 3H), 7.41 (dd, J = 10.2, 5.8 Hz, 6H), 7.09 (d, J = 8.2 Hz, 3H), 5.75 (s, 3H), 4.36 - 4.12 (m, 3H), 3.63 - 3.25 (m, 14H), 2.56 - 2.41 (m, 6H), 2.08 (d, J = 7.7 Hz, 9H), 1.85 (dd, J = 10.3, 8.3 Hz, 6H), 1.75 - 1.50 (m, 12H).
Yield: 33%.

Example 58

4-{[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid ethylamide

To a suspension of piperidin-4-ylmethyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine (20 mg, 0.05 mmol) in acetonitrile (0.5 mL), ethyl isocyanate (0.005 mL, 0.06 mmol) and N,N-diisopropylethylamine (0.011 mL, 0.06 mmol) were added. The reaction mixture was stirred at rt for 90 min. MeOH was added and the mixture was evaporated. All attempts to separate the bis-urea by-product by column chromatography were not successful. Therefore the residue was dissolved in acetonitrile (0.5 mL) and treated with di-tert-butyl dicarbonate (0.028 mL, 0.12 mmol) and N,N-diisopropylethylamine (0.022 mL, 0.12 mmol) at rt for 6 h. The solvent was removed and the residue was purified by column chromatography (reverse phase) to give the Boc-protected desired product (5 mg, 14% yield) (1-ethylcarbamoyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-carbamic acid tert-butyl ester.

HPLC-MS (method 1): Rt= 3.78 min, $[M+1]^+$ m/z 569.2.

(1-Ethylcarbamoyl-piperidin-4-ylmethyl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-carbamic acid tert-butyl ester (5 mg, 0.009 mmol) was dissolved in a minimal amount of anhydrous 1,4-dioxane (0.1 mL) and

HCl (4M in 1,4-dioxane) (0.25 mL) was added dropwise. The reaction mixture was stirred at rt for 48 h and heated at 35 °C for 18 h. The solvent was removed and the residue was washed with Et_2O to give the desired product (4 mg, 99% yield) (4-{[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-methyl}-piperidine-1-carboxylic acid ethylamide).

HPLC-MS (method 1): Rt= 5.22 min, $[M+1]^+$ m/z 469.2.

^1H NMR (300 MHz, MeOD) δ 8.15 (s, 1H), 8.07 (s, 1H), 7.99 (d, *J* = 6.9 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 4.06 (d, *J* = 11.3 Hz, 2H), 3.68 (m, 2H), 3.42 (d, *J* = 5.0 Hz, 2H), 3.15 (m, 2H), 2.81 (m, 2H), 2.02 (m, 1H), 1.81 (d, *J* = 11.8 Hz, 2H), 1.10 (t, *J* = 6.6 Hz, 3H).

Intermediate 42

4-{[(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester

To a suspension of 2-Bromo-5-iodo-imidazo[2,1-b][1,3,4]thiadiazole (215 mg, 0.65 mmol) and 4-[(methylamino)methyl]piperidine-1-carboxyllic acid tert-butyl ester (223 mg, 0.97 mmol) in Acetonitrile (12 mL) was added Et_3N (0.27 mL, 1.95 mmol). The reaction mixture was heated at 105°C for 24 h. On cooling, the mixture was evaporated, EtOAc was added and the mixture was washed with H_2O and brine. The organic layer was dried, filtered and evaporated. The residue was purified by reverse phase chromatography to give Intermediate **42** (302 mg, 97%).

Intermediate 43

[4-(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester

A solution of 1-N-Boc-cis-1,4-cyclohexyldiamine (70 mg, 0.33 mmol), 2-bromo-5-iodo-imidazo[2,1-b][1,3,4]thiadiazole (72 mg, 0.22 mmol) and Et_3N (0.09 mL, 0.66 mmol) in acetonitrile (2.2 mL) was heated at 105°C for 72h. On cooling, the mixture was evaporated, EtOAc was added and the mixture was washed with H_2O and brine. The organic layer was dried, filtered and evaporated to give Intermediate **43** (130 mg, 71%) which was used as such in the next step.

HPLC-MS (method 4): Rt= 4.52 min, $[M+1]^+$ m/z 464.3.

Intermediate 44

4-({Methyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 4-{[(5-Iodo-imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid tert-butyl ester (296 mg, 0.62 mmol) in dioxane (9 mL) was added 3-(trifluoromethoxy)phenylboronic acid (166 mg, 0.81 mmol), cesium carbonate (606 mg, 1.86 mmol), H_2O (2.25 mL) and tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.007 mmol). The reaction mixture was heated at 110°C for 4h. On cooling, the mixture was evaporated, and the residue was purified by column chromatography (DCM:MeOH) to give Intermediate **44** (138mg, 49%).

HPLC-MS (method 4): Rt= 5.20 min, $[M+1]^+$ m/z 512.3.

Intermediate 45

4-({[5-(3-Dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-methyl-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.72 min, $[M+1]^+$ m/z 471.3.

Yield: 31%.

Intermediate 46

{4-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester

HPLC-MS (method 4): Rt= 4.95 min, $[M+1]^+$ m/z 498.2.

Yield: 28%.

Example 59

Methyl-piperidin-4-ylmethyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine

To a solution of 4-({Methyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester (138 mg, 0.27 mmol) in MeOH (10 mL) was added Amberlyst (310 mg). The reaction mixture was shaked gently at RT overnight. The mixture was filtered, and the Amberlyst was washed twice with MeOH. The resin was suspended in NH_3 7N in MeOH (30mL) and shaked at RT overnight. The mixture was filtered off and

the filtrate was evaporated. The residue was purified by column chromatography (DCM/MeOH to DCM/NH_3 7N in MeOH) to give methyl-piperidin-4-ylmethyl-[5-(3-trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-amine (60 mg, 50%).

HPLC-MS (method 1): Rt= 3.34 min, $[M+1]^+$ m/z 412.2.

^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.34 (m, 2H), 7.07 (d, *J* = 8.2 Hz, 1H), 3.31 (d, *J* = 7.3 Hz, 2H), 3.22 (s, 3H), 3.07 (m, 2H), 2.60 (td, *J* = 12.2, 2.3 Hz, 2H), 2.20 (m, 1H), 1.72 (d, *J* = 12.5 Hz, 2H), 1.40 – 1.16 (m, 2H).

Example 60

[5-(3-Dimethylamino-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-methyl-piperidin-4-ylmethyl-amine

HPLC-MS (method 1): Rt= 2.28 min, $[M+1]^+$ m/z 371.2.

^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.12 (m, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.56 – 6.48 (m, 1H), 3.30 – 3.24 (m, 2H), 3.21 (d, *J* = 7.1 Hz, 2H), 2.99 (d, *J* = 7.2 Hz, 3H), 2.84 (s, 6H), 2.71 – 2.55 (m, 2H), 2.05 – 1.86 (m, 1H), 1.70 (d, *J* = 12.6 Hz, 2H), 1.47 (dd, *J* = 23.1, 11.9 Hz, 2H).

Yield: 30%.

Example 61

N-[5-(3-Trifluoromethoxy-phenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-cyclohexane-1,4-diamine

HPLC-MS (method 1): Rt= 3.13 min, $[M+1]^+$ m/z 398.3.

^1H NMR (300 MHz, MeOD) δ 8.08 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 3.68 (m, 1H), 3.12 (m, 1H), 2.38 (m, 2H), 2.13 (m, 2H), 1.68 – 1.33 (m, 4H).

Yield: 10%.

Example 62

Analytical data and PIM-1, PIM-2, PIM-3 AND Flt3 activity

Biological activity in PIM-1, PIM-2 and/or PIM-3 for certain examples is represented in Table 1 by semi-quantative results: 1μM < IC50 < 30μM (X),

100nM < IC50 < 1μM (XX) and IC50 < 100 nM (XXX). Biological activity for certain examples is also shown by quantitative values.

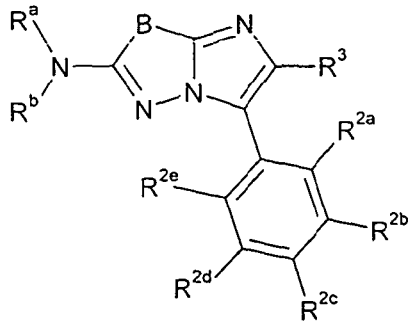
Example number	PIM1 IC50	PIM2 IC50	PIM3 IC50	FLT3 IC50
1	X			X
2	X			X
3	XX			X
4	X			
5	X	X		
6	X			
7	X			XX (105 nM)
8	XX	X	XX	XXX (92 nM)
9	X			
10	X			X
11	X			X
13	XXX (87 nM)	X	XX	XXX
14	XX	X		XXX
15	XX	X	XXX (23 nM)	XXX (14 nM)
16	XX	X		XXX (21 nM)
17	X			XX
18	X	X		XX
20	XX		X	XX
21	XX		X	XX
22	XX	X	XX	XXX
23	XXX (5 nM)	XX	XXX	XXX

24	XXX	X	XXX	XXX
25	XX	X	X	XX
26	X	X		X
27	XX	X		XX
28	XX	X	XX	XXX (31 nM)
29	XXX (16 nM)	XX	XXX	XXX
30	XX	X		XX
31	X	X		X
32	XX	X		XX
33	XX	X	XX	XX
34	XXX (12 nM)	XX	XXX (60 nM)	XXX (31 nM)
35	XX	X	XXX	XXX
36	XXX	X	XX	XXX (38 nM)
37	XX	X	XX	XXX
38	XXX (22 nM)	X	XXX	XXX
39	XX	X	XX	XX
40	XXX	X	XX	XXX
41	XXX	X	XXX	XXX
42	XXX (70 nM)		XX (119 nM)	XXX (26 nM)
43	XXX	XX	XX	XXX
44	XX	XX	X	X
45	XX	XX	XX	X
46	XX	X		XX
47	XX	X	X	XXX
48	X	X		

49	X			X
50	XX	X	XX	XX
51	XX	X		XX
52	XXX (24 nM)	XX	XX	XXX
53	XX	X	XX	XX
54	XXX	X	XX	XXX (37 nM)
55	XXX	XX	XX	XX
56	XXX	XX	XX	XX
57	XXX	XX	XX	XX
58	XX	X		X
59	XXX (20 nM)	XX	XXX	XXX
60	XXX	X	XXX	XX
61	XXX	XXX	XXX	XXX

Claims

1. A compound of formula I,



I

wherein:

B represents -S-, -S(O)- or -SO_2-;

R^{2a}, R^{2b}, R^{2c}, R^{2d} and R^{2e} independently represent hydrogen or a substituent selected from E^1;

R^a and R^b are defined as follows:

(I) 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 contains a further (second) ring as defined by Z^1, all of which cyclic groups, defined by the linkage of R^a and R^b (with the optional second ring defined by Z^1), are optionally substituted by one or more substituents selected from =O, =NOR^{7a} and E^2; or

(II) one of R^a and R^b represents T^1, and the other represents hydrogen or $C_{1\text{-}12}$ alkyl optionally substituted by one or more halo atoms;

T^1 represents:

(i) heterocycloalkyl, which optionally comprises a further ring as defined by Z^2, and which ring(s) (i.e. heterocycloalkyl and optional further ring) is/are

optionally substituted by one or more substituents selected from =O, =NOR^{7a} and Q^1;

(ii) acyclic C$_{1-12}$ alkyl substituted by:

(a) -N(R^{5a})-T-R^{5b} (in which T represents a direct bond, -C(O)-, -S(O)$_2$-, -C(O)N(R^{5c})- or -C(O)O-; and R^{5a}, R^{5b} and R^{5c} are independently hydrogen or C$_{1-6}$ alkyl optionally substituted by one or more fluoro atoms, or, R^{5b} and R^{5c} are linked together to form a 5- or 6-membered heterocycloalkyl group);

(b) one or more heterocycloalkyl group(s) (in which the heteroatoms are selected from sulfur and nitrogen and/or in which the heterocycloalkyl group is attached to the acyclic alkyl group *via* a single carbon atom), which heterocycloalkyl group may comprise a further ring as defined by Z^3; and/or

(c) one or more C$_{3-12}$ cycloalkyl group, which is substituted by Q^2 or comprises a further ring as defined by Z^{3a},

and which acyclic C$_{1-12}$ alkyl group, heterocycloalkyl group (and optional further ring, defined by Z^3) and cycloalkyl group (and requisite further ring system, defined by Z^{3a}) is/are (further) optionally substituted by one or more substituents selected from =NOR^{7b} and Q^2;

(iii) C$_{3-12}$ cycloalkyl, which comprises a further ring as defined by Z^4 (and which cycloalkyl group and further ring are optionally substituted by one or more substituents selected from =O, =NOR^{7c} and Q^3);

(iv) C$_{3-12}$ cycloalkyl, which is substituted by at least one W^1 substituent, and may be further optionally substituted by one or more substituents selected from =O, =NOR^{7d} and Q^4, provided that at least one of R^{2a} to R^{2e} represents a substituent selected from -CN, -OR^{5d}, -N(R^{5e})R^{5f}, -C(O)R^{5g} and C$_{1-6}$ alkyl (optionally substituted by one or more fluoro atoms) (and the others represent hydrogen or a substituent selected from E^1);

W^1 represents -N(R^{1a})-T^{1a}-R^{1b}, =NOR^{1c}, -C(O)N(H)R^{1d}, -C(O)N(R^{1e})-OR^{1f}, -O-C(O)-R^{1h} or -OR^{1i};

T^{1a} represents a direct bond, -C(O)-, -S(O)$_2$-, -C(O)N(R^{1g})- or -C(O)O-;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} independently represent hydrogen or C_{1-6} alkyl (optionally substituted by one or more substituents selected from halo, -CN, $-OR^{6a}$ and $-N(R^{6b})R^{6c}$) or aryl or heteroaryl (both of which are optionally substituted by one or more substituents selected from halo, -CN and C_{1-6} alkyl); or

any pair of R^{1a} and R^{1b} or R^{1a} and R^{1g} may be linked together to form a 4- to 8-membered ring optionally containing one or two further heteroatoms (in addition to the requisite N atom and any heteroatom contained within the definition of T^{1a}), and optionally containing one or two double bonds, which ring is optionally substituted by one or more substituents selected from =O, $=NOR^{7e}$ and Q^5;

R^{1h} and R^{1i} independently represent C_{1-6} alkyl optionally substituted by one or more substituents selected from halo, $-N(R^{2h})R^{3h}$ and $-OR^{4h}$;

R^{2h}, R^{3h}, R^{4h}, R^{6a}, R^{6b} and R^{6c} independently represent hydrogen or C_{1-6} alkyl;

R^{5d}, R^{5e}, R^{5f}, R^{5g}, R^{7a}, R^{7b}, R^{7c}, R^{7d} and R^{7e} independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

Z^1, Z^2, Z^3, Z^{3a} and Z^4 each independently represent a moiety that results in a further ring sytem (that is present in addition to the "first ring" i.e. in addition to the monocyclic cycloalkyl or heterocycloalkyl groups, to which that Z^1 to Z^4 group is attached) that is formed by that Z^1 to Z^4 group representing:

(a) 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 that is fused to the first ring;

(b) 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 ring (i.e. forming a bridged structure); or

(c) a second ring that is either a 3- to 12-membered saturated carbocyclic ring or 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);

R^3 *represents hydrogen or halo*;

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

halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-C(=Y)N(R^{10a})-OR^{11a}$, $-OC(=Y)-R^{10a}$, $-OC(=Y)-OR^{10a}$, $-OC(=Y)N(R^{10a})R^{11a}$, $-OS(O)_2OR^{10a}$, $-OP(=Y)(OR^{10a})(OR^{11a})$, $-OP(OR^{10a})(OR^{11a})$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, 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^3), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^4);

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^5), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^6); 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^7;

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

(i) Q^{20};

(ii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^{21}; or

any two E^1, E^2, E^3, E^4, E^5, E^6 or E^7 groups 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 unsaturations, and which ring is optionally substituted by one or more substituents selected from =O and J^1;

each Q^{20} and Q^{21} independently represent, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y)-R^{20}$, $-C(=Y)-OR^{20}$, $-C(=Y)N(R^{20})R^{21}$, $-OC(=Y)-R^{20}$, $-OC(=Y)-OR^{20}$, $-OC(=Y)N(R^{20})R^{21}$, $-OS(O)_2OR^{20}$, $-OP(=Y)(OR^{20})(OR^{21})$, $-OP(OR^{20})(OR^{21})$, $-N(R^{22})C(=Y)R^{21}$, $-N(R^{22})C(=Y)OR^{21}$, $-N(R^{22})C(=Y)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{20})R^{21}$, $-SC(=Y)R^{20}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$, 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^{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^{30};

(ii) C_{1-6} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^{31};

each Q^{30} and Q^{31} independently represents, on each occasion when used herein: halo, $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2N(R^{50})R^{51}$, $-N(R^{52})-C(O)-N(R^{50})R^{51}$, $-S(O)_2R^{50}$, $-SR^{50}$, $-S(O)R^{50}$ 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:
R^a and R^b are linked together as hereinbefore defined or one of R^a and R^b represents T^1, and the other represents hydrogen or C_{1-6} alkyl;
T^1 represents:

(i) heterocycloalkyl (as defined in Claim 1);
(ii) substituted acyclic C_{1-12} (e.g. C_{1-8}) alkyl (as defined in Claim 1):
(iii) C_{3-12} cycloalkyl, comprising a further ring (as defined Claim 1),
all of which groups defined by (i), (ii), (iii) above are, for the avoidance of doubt, optionally substituted as defined in Claim 1; and, more preferably,

T^1 represents:

(i) heterocycloalkyl (which preferably does not comprise a further ring) optionally substituted by one or more substituents selected from =O and Q^1;

(ii) acyclic C_{1-12} (e.g. C_{1-8}) alkyl substituted by:

(a) $-N(R^{5a})-R^{5b}$ (in which R^{5a} and R^{5b} are as defined in Claim 1);

(b) one heterocycloalkyl group (in which the heteroatoms are selected from nitrogen; and in which the heterocycloalkyl group is preferably not attached to the acyclic alkyl group *via* a single carbon atom), which heterocycloalkyl group may comprise a further ring as defined herein by Z^3 (but preferably does not comprise such a further ring); or

(c) one C_{3-12} cycloalkyl group, which comprises a further ring as defined by Z^{3a},

and which acyclic C_{1-12} alkyl group, heterocycloalkyl group (and optional further ring, defined by Z^3) and cycloalkyl group (and requisite further ring system, defined by Z^{3a}) is/are (further) optionally substituted by one or more substituents selected from Q^2;

(iii) C_{3-12} cycloalkyl, which comprises a further ring as defined by Z^4 (and which cycloalkyl group and further ring are optionally substituted by one or more substituents selected from =O and Q^3).

3. A compound as claimed in Claim 1, wherein:

one of R^a and R^b represents T^1, and the other represents hydrogen or C_{1-3} alkyl; and

T^1 represents C_{3-12} cycloalkyl, which is substituted by one W^1 substituent, in which W^1 preferably represents $-N(R^{1a})-T^{1a}-R^{1b}$ (in which T^{1a}, R^{1a} and R^{1b} are as defined in Claim 1), provided that at least one (e.g. one) of R^{2a} to R^{2e} (e.g. R^{2b}) represents a substituent selected from -CN, $-OR^{5d}$, $-N(R^{5e})R^{5f}$, $-C(O)R^{5g}$ and C_{1-6} alkyl (as defined in Claim 1); and, more preferably,

T^1 represents C_{3-12} cycloalkyl substituted by $-N(R^{1a})-T^{1a}-R^{1b}$ (in which T^{1a}, R^{1a}, R^{1b} and R^{1c} are as defined in Claim 1); and

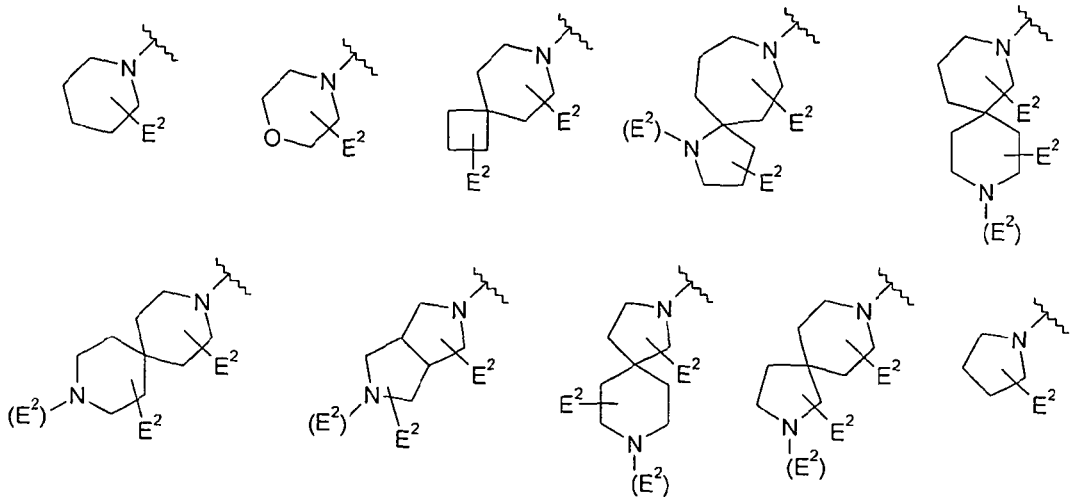
at least one (e.g. one) of R^{2a} to R^{2e} (e.g. R^{2b}) represents a substituent selected from -CN, $-OR^{5d}$, $-N(R^{5e})R^{5f}$, $-C(O)R^{5g}$ and optionally substituted C_{1-6} alkyl (all of which are as defined in Claim 1); preferred substituents in this regard include

-CN, $-OCH_3$, $-OCF_3$, -OH, $-N(CH_3)_2$, $-CF_3$ and $-C(O)CH_3$, and especially preferred is the $-OR^{5d}$ substituent, in which R^{5d} represents a C_{1-6} (e.g. C_{1-3}) perfluoroalkyl group, so forming e.g. a $-OCF_3$ substituent).

4. A compound as claimed in any one of the preceding claims, wherein:

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

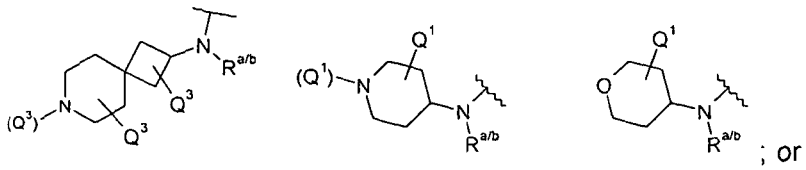
when R^a and R^b are linked together, they form one of the following:



;

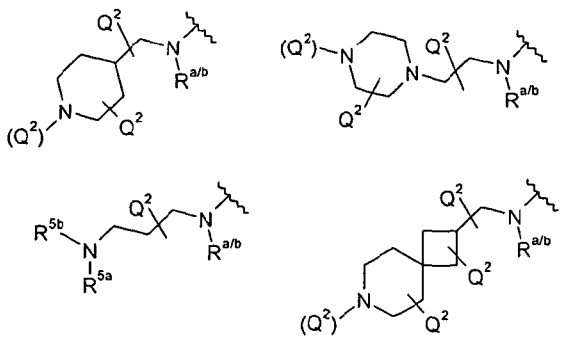
one of R^a and R^b represents hydrogen and the other represents T^1, in which T^1 may represent:

(i)



; or

(ii)



,

wherein in the relevant cases above, the squiggly line represents the point of attachment to the requisite imidazodiathiazole of the compound of formula I, $R^{a/b}$ (if present) represents R^a or R^b, and the 'floating' E^2, Q^1, Q^2 and Q^3 substituents each independently represent one or more optional substituents, and wherein certain cyclic groups may also be substituted with one or more (e.g. one) =O group (as indicated in Claim 1);

B represents -S-;

at least one of R^{2b}, R^{2c} and R^{2d} represent a substituent other than hydrogen, i.e. there is at least one *meta* or *para* substituent (preferably, *meta* substituent) present on the relevant phenyl ring;

E^1 represents Q^{20} or C_{1-3} alkyl (e.g. methyl) optionally substituted by one or more Q^{21} groups (so forming e.g. a $-CF_3$ group);

when E^1 represents Q^{20}, then Q^{20} preferably represents halo or, more preferably, -CN, $-OR^{20}$, $-N(R^{20})R^{21}$ or $-C(O)R^{20}$ (in which instances, R^{20} and R^{21} may represent hydrogen or C_{1-3} alkyl optionally substituted by one or more fluoro atoms);

Q^{21} represents halo (e.g. fluoro);

specific preferred E^1 groups include -CN, $-CF_3$, $-OCF_3$, -OH, $-OCH_3$, $-N(CH_3)_2$, and $-C(O)-CH_3$;

E^2 represents Q^{20} or C_{1-6} (e.g. C_{1-3}) alkyl (e.g. methyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^{21};

when E^2 represents Q^{20}, then Q^{20} represents $-C(=Y)-OR^{20}$ or $-N(R^{20})R^{21}$;

when E^2 represents C_{1-12} (e.g. C_{1-6}) alkyl substituted by Q^{21}, then Q^{21} represents $-N(R^{22})-C(=Y)-OR^{21}$ or $-N(R^{20})R^{21}$;

Q^1, Q^2, Q^3, Q^4 and Q^5 independently represent $-C(=Y)OR^{10a}$, $-C(=Y)R^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-S(O)_2R^{10a}$ or C_{1-6} alkyl (optionally substituted by one or more substituents selected from E^3);

each R^{10a} independently represents hydrogen or, preferably, C_{1-6} (e.g. C_{1-4}) alkyl (e.g. *tert*-butyl, methyl, ethyl);

R^{11a} represents hydrogen;

E^3 and E^4 independently represent Q^{20};

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

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

Q^{21} represents $-N(R^{22})-C(=Y)-OR^{21}$ or $-N(R^{20})R^{21}$;
Y and Y^a represent =O;
R^{20} represents hydrogen or C_{1-6} (e.g. C_{1-4}) alkyl;
R^{21} represents hydrogen or C_{1-6} (e.g. C_{1-4}) alkyl;
R^{22} represents hydrogen.

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 of PIM-1, PIM-2, PIM-3 and/or Flt3 is desired and/or required.

8. Use of a compound of formula I, as defined in any one of Claims 1 to 4, 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 of PIM-1, PIM-2, PIM-3 and/or Flt3 is desired and/or required.

9. A compound as claimed in Claim 7 or a use as claimed in Claim 8, wherein the disease is cancer, an immune disorder, a cardiovascular disease, a viral infection, inflammation, a metabolism/endocrine function disorder, a neurological disorder, an obstructive airways disease, an allergic disease, an inflammatory disease, immunosuppression, a disorder commonly connected with organ transplantation, an AIDS-related disease, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, a bone disorder, atherosclerosis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis, restenosis, stroke, diabetes, hepatomegaly, Alzheimer's disease, cystic

fibrosis, a hormone-related disease, an immunodeficiency disorder, a destructive bone disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukaemia, liver disease, a pathologic immune condition involving T cell activation, CNS disorders, and other associated diseases.

10. A method of treatment of a disease in which inhibition of of PIM-1, PIM-2, PIM-3 and/or Flt3 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:

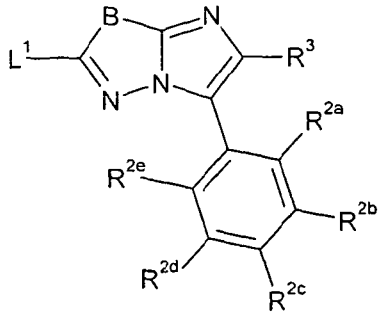
(A) a compound of formula I as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof; and

(B) another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease,

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

12. A 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,



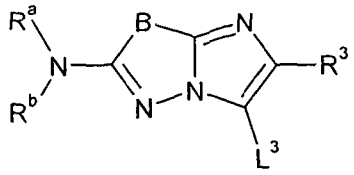
II

wherein L^1 represents a suitable leaving group, and B, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e} and R^3 are as defined in Claim 1, with a compound of formula III,

$$R^b(R^a)N\text{-}H \qquad \text{III}$$

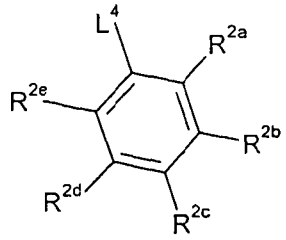
wherein R^a and R^b are as defined in Claim 1;

(ii) reaction of a compound of formula IV,



IV

wherein L^3 represents a suitable leaving group, and R^a, R^b, B and R^3 are as defined in Claim 1, with a compound of formula V,



V

wherein L^4 represents a suitable group;

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

$$R^x\text{-}L^5 \qquad \text{VI}$$

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

13. 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.

14. 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/GB2011/001189

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 C07D519/00 A61K31/438 A61K31/454 A61K31/5377
A61K31/433 A61K31/55 A61K31/496 A61P35/00 A61P35/02
A61P3/00 A61P5/00 A61P9/00 A61P11/00 A61P17/00

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/040552 A2 (CT NAC DE INVESTIGACIONES ONCO [ES]; PEVARELLO PAOLO [IT]; GARCIA COLL) 2 April 2009 (2009-04-02) cited in the application example 34; compounds 11,16,20,21,23,29,73,77,78,103 From Example 35: (2-Piperidin-1-yl-ethyl)-[5-(3-trifluoromethoxy-phenyl)-imidazo[2, 1 -b][1 ,3,4]thiadiazol-2-yl]-amine; 4-[2-(Tetrahydro-pyran-4-ylamino)-imidazo[2,1-b][1 ,3,4]thiadiazol-5-yl]-benzoic acid; [5-(3,4-Dimethoxy-phenyl)-imidazo[2,1-b][1 ,3,4]thiadiazol-2-yl]-(tetrahydro-pyran-4-yl)-amine the whole document	1,2,4-14

-/--

[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
29 September 2011	10/10/2011

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	Sarakinos, Georgios

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/001189

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/012345 A1 (MERCK PATENT GMBH [DE]; HOELZEMANN GUENTER [DE]; GREINER HARTMUT [DE];) 4 February 2010 (2010-02-04) cited in the application compounds 112, 115-118, 120-122, 126, 128, 132, 232-233 compounds 273-274,292,299-300,326-330,335,502,504,515 the whole document -----	1-3,5-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/001189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009040552 A2	02-04-2009	CN 101878219 A	03-11-2010
		EP 2193133 A2	09-06-2010
		JP 2010540508 A	24-12-2010
		US 2011190289 A1	04-08-2011
WO 2010012345 A1	04-02-2010	AR 072622 A1	08-09-2010
		AU 2009275544 A1	04-02-2010
		CA 2732186 A1	04-02-2010
		EP 2307425 A1	13-04-2011
		US 2011130396 A1	02-06-2011