

(43) International Publication Date
24 April 2014 (24.04.2014)(10) International Publication Number
WO 2014/060768 A1

(51) International Patent Classification:

C07D 403/14 (2006.01) *A61K 31/437* (2006.01)
C07D 471/04 (2006.01) *A61P 35/00* (2006.01)
C07D 519/00 (2006.01)

(21) International Application Number:

PCT/GB2013/052721

(22) International Filing Date:

18 October 2013 (18.10.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1218864.5 19 October 2012 (19.10.2012) GB
 61/716,089 19 October 2012 (19.10.2012) US

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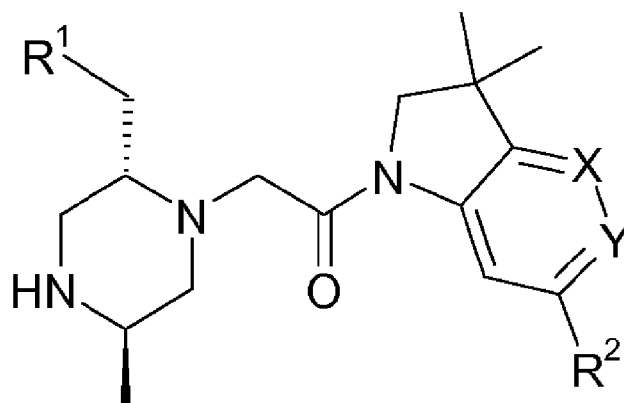
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(81) Designated States (unless otherwise indicated, for every
 kind of national protection available): AE, AG, AL, AM,
 AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
 BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
 DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
 HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
 SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
 TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
 ZW.

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

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(54) Title: BICYCLIC HETEROCYCLE COMPOUNDS AND THEIR USES IN THERAPY



(I)

(57) Abstract: The invention relates to new bicyclic heterocycle compounds of formula (I); wherein R1 is selected from specific pyrazolyl, imidazolyl, pridinyl and triazolyl groups. The invention also relates to pharmaceutical compositions comprising said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

**Declarations under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

BICYCLIC HETEROCYCLE COMPOUNDS AND THEIR USES IN THERAPY

FIELD OF THE INVENTION

The invention relates to new bicyclic heterocycle compounds, to pharmaceutical

- 5 compositions comprising said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

BACKGROUND OF THE INVENTION

IAP family

- 10 The family of inhibitor of apoptosis (IAP) proteins comprises 8 members, XIAP, cIAP1, cIAP2, NAIP, ILP2, ML-IAP, survivin and BRUCE (also known as apollon). Members of the IAP family have been shown to inhibit programmed cell death through their ability to directly inhibit members of the caspase family of apoptotic enzymes, although the precise role of all 8 members is yet to be fully defined. The common structural feature of all IAP family members
- 15 is a ~70 amino acid zinc-binding fold termed the baculovirus IAP repeat (BIR) domain, which is present in one to three copies.

- Many interactions between IAPs and other proteins are mediated via a surface groove on the BIR domain. BIR domains may be classified by their peptide-binding specificity. There are
- 20 three types of BIR domains; type III domains (capable of binding caspase (and caspase-like) peptides with a specificity for proline in the third (P3) position (e.g. XIAP BIR3), type II domains (like type III domains but lacking the proline requirement e.g. XIAP BIR2) and type I domains (which do not bind caspases or similar peptides, e.g. XIAP BIR1) (Eckelman et al. Cell Death and Differentiation 2008; 15: 920-928). BIRs are small (~70 amino acids) Zn-
- 25 coordinated domains and a variety of proteins use their N-terminal to interact with the BIR domains grooves. BIR antagonists prevent caspases binding to BIRs and hence result in increased caspase activity thereby inducing auto-ubiquitination and proteasomal degradation of IAPs.

- 30 IAPs are overexpressed in many cancers including renal, melanoma, colon, lung, breast, ovarian and prostate cancers (Tamm et al., Clin. Cancer Research 2000; 6(5): 1796-803), and have been implicated in tumour growth, pathogenesis and resistance to chemo- and radio-therapy (Tamm 2000).

XIAP

35 XIAP is a 57kDa protein with three BIR domains, the second and third of which bind caspases and a RING-type zinc finger (E3 ligase). XIAP binds several proteins in addition to

caspases, including ligation substrates such as TAK1 and cofactor TAB1, MURR1 involved in copper homeostasis (Burststein et al., EMBO 2004; 23: 244-254), endogenous inhibitors such as second mitochondria-derived activator of caspases (SMAC), and those of less clear function such as MAGE-D1, NRAGE (Jordan et al., J. Biol. Chem. 2001; 276: 39985-39989).

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The BIR3 domain binds and inhibits caspase-9, an apical caspase in the mitochondrial pathway of caspase activation. A groove on the surface of the BIR3 domain interacts with the N-terminus of the small subunit of caspase-9, locking caspase-9 in its inactive monomeric form with an incompetent catalytic site (Shiozaki et al., Mol. Cell 2003; 11: 519-527).

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In addition to caspase-binding, XIAP also inhibits apoptosis through other mechanisms. XIAP forms a complex with TAK1 kinase and its cofactor TAB1 that leads to activation of JNK and MAPK signal transduction pathways, in turn leading to activation of NF κ B (Sanna et al., Mol Cell Biol 2002; 22: 1754-1766). XIAP also activates NF κ B by promoting NF κ B translocation to the nucleus and degradation of I κ B (Hofer-Warbinek et al., J. Biol. Chem. 2000; 275: 22064-22068, Levkau et al., Circ. Res. 2001; 88: 282-290).

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Cells transfected with XIAP are able to block programmed cell death in response to a variety of apoptotic stimuli (Duckett et al., EMBO 1996; 15: 2685-2694, Duckett et al., MCB 1998; 18: 608-615, Bratton, Lewis, Butterworth, Duckett and Cohen, Cell Death and Differentiation 2002; 9: 881-892).

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XIAP is ubiquitously expressed in all normal tissues, but it is pathologically elevated in many acute and chronic leukaemias, prostate, lung, renal, and other types of tumours (Byrd et al., 2002; Ferreira et al., 2001; Hofmann et al., 2002; Krajewska et al., 2003; Schimmer et al., 2003; Tamm et al., 2000). In de novo acute myeloid leukaemia (AML), XIAP expression correlates with myelomonocytic French-American-British (FAB) subtypes M4/M5 ($P < 0.05$) and expression of monocytic markers in AML blasts. In addition, XIAP was found to be overexpressed in normal monocytes but undetectable in granulocytes. In AML, XIAP expression was significantly lower in patients with favourable rather than intermediate or poor cytogenetics ($n = 74$; $P < 0.05$) (Tamm et al., Hematol. J. 2004; 5(6): 489-95).

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Overexpression renders cells resistant to multi-agent therapy and is associated with poor clinical outcome in disease including AML, renal cancer, melanoma (Tamm et al., Clin. Cancer Research 2000; 6: 1796-1803) and lung cancer (Hofmann et al., J. Cancer Res. Clin. Oncology 2002; 128(10): 554-60).

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XIAP is translated by a cap-independent mechanism of translation initiation that is mediated by a unique internal ribosome entry site (IRES) sequence element located in its 5' untranslated region. This allows XIAP mRNA to be actively translated during conditions of cellular stress when the majority of cellular protein synthesis is inhibited. Translational upregulation of XIAP in response to stress increases resistance to radiation induced cell death (Holcik et al., Oncogene 2000; 19: 4174-4177).

XIAP inhibition has been investigated *in vitro* via several techniques including RNA silencing, gene knockout, peptidic ligand mimetics and small molecule antagonists, and has been shown to promote apoptosis as a monotherapy and to sensitise many tumour types to chemotherapy, including bladder (Kunze et al., 2008; 28(4B): 2259-63). XIAP knockout mice are born at the expected Mendelian frequency, with no obvious physical or histological defects, and normal life spans (Harlin et al., Mol. Cell Biol. 2001; 21(10): 3604-3608). This indicates that lacking XIAP activity is not toxic in normal tissues and suggests a therapeutic window over tumour cells. Further studies have shown XIAP is a critical discriminator between apoptosis in type 1 and type 2 cells including hepatocytes and therefore should be used with caution in patients with underlying liver conditions (Jost et al., Nature, 2009, 460, 1035-1041). It was noted that the cIAP1 and cIAP2 levels are upregulated in the XIAP knockout mouse and may protect from pathology via a compensatory mechanism, suggesting pan-inhibition may be required for functional knockout. Similarly, cIAP1 and cIAP2 knockout mice are also asymptomatic (Conze et al., Mol. Biol. Cell 2005; 25(8): 3348-56). While lack of any one of the IAPs produced no overt phenotype in mice, deletion of cIAP1 with cIAP2 or XIAP resulted in mid embryonic lethality (Moulin, EMBO J., 2012).

Endogenous IAP antagonists such as SMAC have been used to validate members of this family as targets for therapeutic agents. SMAC peptides chemosensitise tumour cells, and in combination with platins and Tumour Necrosis Factor α -related apoptosis inducing ligand (TRAIL) in xenografts, results in tumour growth delay (Fulda et al., Nat. Med. 2002; 808-815; Yang et al., Cancer Res. 2003; 63: 831-837).

A natural product, embellin, was identified as binding at the surface groove of the BIR3 domain of XIAP with similar affinity to the natural SMAC peptide. Embellin induces apoptosis in cell lines *in vitro* and results in tumour growth delay in xenografts (Nikolovska-Coleska et al., J. Med. Chem. 2004; 47(10): 2430-2440; Chitra et al., Chemotherapy 1994; 40: 109-113).

XIAP antisense oligonucleotides have been developed as therapeutic agents for solid tumour and haematological malignancies. *In vitro* these antisense oligonucleotides have been

shown to knockdown protein expression levels by ~70%, induce apoptosis and sensitise cells to chemotherapy and delay tumour growth *in vivo*. One of these agents, AEG351156, has been studied in clinical trials (Hu et al., Clin. Cancer Res. 2003; 9: 2826-2836; Cummings et al., Br. J. Cancer 2005; 92: 532-538).

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Small molecule antagonists of XIAP developed include peptidomimetics as well as synthetic agents. The peptidomimetics target the BIR3 domain, mimicking SMAC disruption of caspase-9 binding to XIAP, have shown induction of apoptosis in a variety of tumour cell lines as a single agent, as well as chemosensitisers and are being further investigated clinically (Oost et al., J. Med. Chem. 2004; 47: 4417-4426; Sun et al., Bioorg. Med. Chem. Lett. 2005; 15: 793-797).

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Synthetic small molecule antagonists of BIR3 and BIR2 domains also demonstrate anti-tumour activity in several different models, including induction of apoptosis by annexin-V staining and IC50s of <10µM against over one-third of the NCI60 cell line panel. XIAP antagonists also induced dose-dependent cell death of primary-cultured leukaemia cells in 5 out of 5 chronic lymphocytic leukaemia cell lines and 4 out of 5 acute myeloid leukaemia cell lines (Schimmer et al., Cancer Cell 2004; 5: 25-35; Berezovskaya et al., Cancer Res. 2005; 65(6): 2378-86).

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High levels of XIAP protein in tumour cell lines were inversely correlated with sensitivity to some anti-cancer drugs, particularly cytarabine and other nucleosides (Tamm et al., Clin. Cancer Research 2000; 6: 1796-1803). XIAP inhibition potentiates TRAIL-induced antitumor activity in two preclinical models of pancreatic cancer *in vivo* (Vogler 2008). Gene expression and transfection studies suggest that the increased expression of apoptosis suppressor XIAP plays an important role in anoikis resistance and in the survival of circulating human prostate carcinoma cells, thereby promoting metastasis. Small molecule antagonists were found to be anti-metastatic in these models (Berezovskaya et al., Cancer Res. 2005; 65(6): 2378-86).

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XIAP has also been found to be involved in other pathways associated with cancer and other diseases and these may also benefit from XIAP targeted agents. The E3 ligase activity of the RING finger domain of XIAP is able to bind both to TAB1 and to an upstream BMP receptor (type 1), suggesting that XIAP may signal in a TGF-β-mediated pathway (Yamaguchi et al., EMBO 1999; 179-187). Focal adhesion kinase (FAK) overexpression has been shown to result in upregulated XIAP expression (Sonoda et al., J. Biol. Chem. 2000; 275: 16309-16315). E3 ligases are attractive therapeutic targets and molecules which target

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this activity in other proteins such as MDM2 are being developed (Vassilev et al., Science 2004; 303: 844-848). Direct or indirect inhibition of the XIAP ligase activity may also be useful in the treatment of cancer and other diseases. Dysregulated apoptotic signalling, which would result from inhibition of IAP function in controlling programmed cell death, has also been implicated in many diseases, including disorders associated with cell accumulation (e.g. cancer, autoimmunity, inflammation and restenosis) or disorders where excessive apoptosis results in cell loss (e.g. stroke, heart failure, neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS, ischaemia (stroke, myocardial infarction) and osteoporosis).

XIAP is an important apoptotic regulator in experimental autoimmune encephalomyelitis and a potential pharmacological target for treating autoimmune diseases such as multiple sclerosis (MS) (Moore et al., 2004; 203(1): 79-93). Antisense-mediated knockdown of XIAP reverses paralysis in an animal model of MS suggesting that treatments targeting XIAP, and perhaps other IAPs, may have utility in the treatment of MS (Hebb et al., Curr. Drug Disc. Tech. 2008; 5(1): 75-7).

clAP1, clAP-2, XIAP and survivin are overexpressed in malignant pleural mesothelioma and are responsible for a large degree of the resistance of cultured mesothelioma cells to cisplatin. Levels of circulating TNF- α are significantly higher in mesothelioma patients prior to surgical tumor debulking compared with those after surgery. TNF- α increases mRNA and protein levels of IAP-1, IAP-2 and XIAP (Gordon et al., 2007). NF- κ B upregulation plays an important survival role in mesotheliomas in response to the inflammatory effects of exposure to asbestos fibres (Sartore-Bianchi et al., 2007). IAP antagonists have the potential to reverse the pro-survival effect of TNF- α .

The ability of cell lines to upregulate TNF- α expression sufficiently to act in an autocrine fashion and kill the cells, once clAP1 & 2 are depleted, is believed to be important for IAP activity (Nature Reviews Cancer (2010), 10(8), 561-74, Gryd-Hansen, M). *In vivo*, however, certain tumour types are surrounded by a pro-inflammatory cytokine network and hence the tumour cells which, on depletion of clAP1/2 are switched towards cell killing by apoptosis, may be triggered to apoptose by TNF- α (or other Death Receptor cytokine agonists) already being produced by surrounding cells in the tumour microenvironment, such as tumour-associated macrophages, or indeed by the tumour cells themselves. Certain tumour types such as breast, ovarian and melanoma display this "inflammatory phenotype" which could potentially be targeted by IAP antagonists.

clAP1 and clAP2

Cellular IAP (clAP) 1 and 2 are closely related members of the IAP family with three BIR domains, a RING domain and a caspase-recruitment (CARD) domain. A functional nuclear export signal exists within the CARD domain of clAP1 which appears to be important for cell differentiation (Plenchette et al., Blood 2004; 104: 2035-2043). The presence of this CARD domain is unique to clAP1 and clAP2 within the IAP family of proteins. These two genes reside in tandem on chromosome 11q22 and given their high degree of similarity are thought to have arisen via gene duplication.

clAP1, like XIAP and survivin, is widely expressed in tumour cell lines, and has been found to be expressed at high levels in colorectal cancers in particular, as well as lung, ovarian, renal, CNS and breast cancers (Tamm et al., Clin. Cancer Res. 2000; 6: 1796-1803). clAP2 expression is generally more restricted and is thought to be regulated through constitutive ubiquitination and degradation by clAP1 (Conze et al., Mol. Biol. Cell 2005; 25(8): 3348-56; Mahoney et al., PNAS 2008; 105: 11778-11783). Immunohistochemistry and western blot analysis identified clAP1 and clAP2 as potential oncogenes as both are overexpressed in multiple lung cancers with or without higher copy numbers (Dia et al., Human Mol. Genetics 2003; 12(7): 791-801). clAP1 expression level preferentially seems to play an important role in low-stage adenocarcinoma (Hofmann et al., J. Cancer Res. Clin. Oncology 2002; 128(10): 554-60).

Increased levels of clAP1 and clAP2 and reduced levels of endogenous inhibitors are associated with chemoresistance as has been seen for XIAP. clAP overexpression has been found to correlate *in vitro* to resistance to DNA alkylating agents such as carboplatin, cisplatin and topoisomerase inhibitor VP-16 (Tamm et al., Clin. Cancer Res. 2000; 6: 1796-1803). Levels of clAP1 and survivin were found to be high in thyroid cancer cells after cisplatin and doxorubicin treatment. Cells resistant to chemotherapy such as taxol showed reduced expression of SMAC and released minimal amounts of this protein from the mitochondria. Down-regulation of clAP1 and survivin has been found to increase the cytotoxicity of cisplatin and doxorubicin, whereas overexpression of SMAC improved the efficacy of taxol. However, silencing of clAP1 and survivin by RNA interference restored sensitivity to doxorubicin and cisplatin (Tirrò et al.; Cancer Res. 2006; 66(8): 4263-72).

SMAC mimetics such as LBW242 were originally thought to primarily target XIAP. However studies have shown that clAP1 was targeted for degradation by autoubiquitination in cells (Yang et al., J. Biol. Chem. 2004; 279(17): 16963-16970) and may have contributed to the apoptotic effects that resulted. SiRNA of clAP1 and Tumour Necrosis Factor (TNF)-alpha

induction (or stimulation) were found to combine synergistically and render cell lines more sensitive (Gaither et al. Cancer Res. 2007; 67 (24): 11493-11498).

clAP1 and clAP2 have been demonstrated to be critical regulators of the NF κ B signalling pathway which is involved in a diverse range of biological processes, particularly in innate and adaptive immunity as well as in proliferation and survival. NF κ B pathway deregulation is associated with inflammation and cancers including hepatitis and ulcerative colitis, gastritis, hepatocellular carcinoma colorectal cancer and gastric cancers, as well as angiogenesis and metastasis (Shen et al., Apoptosis 2009; 14: 348-363).

On ligand binding, the TNF Receptor (TNFR) recruits TNFR-associated Death Domain (TRADD) and receptor-interacting protein (RIP) 1. TRAF2 and clAP1/clAP2 are then recruited to form a large membrane complex. RIP1 is ubiquitinated and these polyubiquitin chains serve as a docking site for downstream kinases, resulting in NF κ B pathway signalling effects (Ea et al., Mol. Cell 2006; 22: 245-257; Wu et al., Nat. Cell Biol. 2006; 8: 398-406). The extended roles are complex and yet to be fully defined but clAP1 and clAP2 are identified as key components of TNF-alpha mediated NF κ B signalling regulation as well as constitutive (ligand-independent/classical) NF κ B signalling (Varfolomeev et al., Cell 2007; 131(4): 669-81). clAP1 and clAP2 have been shown to bind TRAF2, an adapter protein that functions in both the classical and alternative NF κ B pathways as well as MAPK pathway signalling pathway (Rothe et al., Cell 2005; 83: 1243-1252). clAP1 and clAP2 directly target RIP1 for ubiquitination *in vitro* (Betrand et al., Mol. Cell 2008; 30: 689-700).

TNF-alpha regulates many cellular functions, including apoptosis, inflammation, immune response, and cell growth and differentiation (Trace et al., Annu. Rev. Med. 1994; 45: 491-503) and therapeutic IAP antagonists may be of benefit in conditions where these functions are affected.

Production of TNF-alpha is seen in many malignant tumours, and is one of the key drivers of cancer-related inflammation that drives tumour development and/or progression. clAPs protect cancer cells from the lethal effects of TNF-alpha.

NAIP

NAIP was the first IAP to be discovered (Roy et al., Cell 1995; 80: 167-178). NAIP is unique among the IAPs in that it possesses a nucleotide-binding and oligomerisation domain, as well as leucine rich repeats which are similar to those contained in proteins normally involved

in innate immunity. There are indications that NAIP may also be over expressed in some cancers including breast and oesophageal cancer (Nemoto et al., Exp. Mol. Pathol. 2004; 76(3): 253-9) as well as MS (Choi et al., J. Korean Med. 2007; 22 Suppl: S17-23; Hebb et al., Mult. Sclerosis 2008; 14(5): 577-94).

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ML-IAP

Melanoma inhibitor of apoptosis protein (ML-IAP) contains a single BIR and RING finger motif. ML-IAP is a powerful inhibitor of apoptosis induced by death receptors and chemotherapeutic agents, probably functioning as a direct inhibitor of downstream effector caspases (Vucic et al., Curr. Biol. 2000; 10(21): 1359-66). ML-IAP is also known as Baculoviral IAP repeat-containing protein 7 (BIRC7), Kidney inhibitor of apoptosis protein (KIAP), RING finger protein 50 (RNF50) and Livin. The BIR domain of ML-IAP possesses an evolutionarily conserved fold that is necessary for anti-apoptotic activity. It has been found that the majority of melanoma cell lines express high levels of ML-IAP in contrast to primary melanocytes, which expressed undetectable levels. These melanoma cells were significantly more resistant to drug-induced apoptosis. Elevated expression of ML-IAP renders melanoma cells resistant to apoptotic stimuli and thereby potentially contributes to the pathogenesis of this malignancy.

ILP-2

ILP-2, also known as BIRC8, has a single BIR domain and a RING domain. ILP-2 is expressed only in testis in normal cells, and binds to caspase 9 (Richter et al, Mol. Cell. Biol. 2001; 21: 4292-301).

Survivin

Survivin, also known as BIRC5, inhibits both caspase 3 and caspase 7, but its primary function is mitotic progression regulation, rather than the regulation of apoptosis. Survivin promotes formation of microtubules in the mitotic spindle, counteracting apoptosis during cell cycle. Apoptosis inhibition by survivin is predictive of poor outcome in colorectal cancer (Kawasaki et al., Cancer Res. 1998; 58(22): 5071-5074) and stage III gastric cancer (Song et al., Japanese J. Clin. Oncol. 2009; 39(5): 290-296).

BRUCE

BRUCE (BIR repeat-containing ubiquitin-conjugating enzyme) is a peripheral membrane protein in the trans-Golgi network with a single BIR domain, most similar to that of survivin. BRUCE is inhibited via three mechanisms: (i) SMAC binding, (ii) HtrA2 protease and (iii) caspase-mediated cleavage. In addition, BRUCE acts as a E2/E3 ubiquitin ligase via

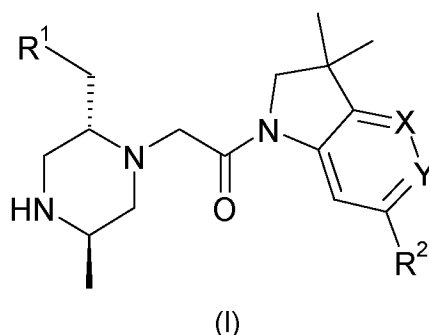
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ubiquitin-conjugating (UBC) domain.

SUMMARY OF THE INVENTION

The present invention provides compounds of formula (I). The present invention provides compounds which are useful in therapy, in particular in the treatment of cancer. The compounds of formula (I) may be antagonists of the IAP family of proteins (IAP), and especially XIAP, and/or cIAP (such as cIAP1 and/or cIAP2) and may be useful in the treatment of IAP-mediated conditions.

According to a first aspect of the invention, there is provided a compound of formula (I):



or tautomeric or stereochemically isomeric forms, N-oxides, pharmaceutically acceptable salts or the solvates thereof; wherein

X is CH and Y is CR³, or one of X or Y is CR³ and the other is nitrogen or X and Y are nitrogen;

R¹ is selected from

- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile,
- (ii) C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile,
- (iii) imidazolyl which is optionally substituted with one or two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile,
- (iv) pyridinyl which is substituted with two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile, and
- (v) triazolyl substituted with one substituent selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, =O and nitrile or two substituents independently

selected from halogen, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile;

R² is selected from: benzyl optionally substituted on the phenyl group by one or two substituents selected from fluorine and nitrile, and optionally substituted on the methylene by hydroxyl; and C₂₋₄ alkyl substituted by one or two substituents selected from fluorine and hydroxyl; and

R³ is selected from hydrogen and nitrile.

In a further aspect of the invention there is provided a compound of formula (I) for use in the prophylaxis or treatment of a disease or condition as described herein, pharmaceutical compositions comprising a compound of formula (I) and processes for the synthesis of compound of formula (I).

DEFINITIONS

Unless the context indicates otherwise, references to formula (I) in all sections of this document (including the uses, methods and other aspects of the invention) include references to all other sub-formula, sub-groups, preferences, embodiments and examples as defined herein.

By "IAP" we mean any of the IAP family members XIAP, cIAP (cIAP1 and/or cIAP2), NAIP, ILP2, ML-IAP, survivin and/or BRUCE, in particular XIAP, cIAP1, cIAP2, ML-IAP, more particularly XIAP, cIAP1 and/or cIAP2, most particularly XIAP and/or cIAP1. In particular we mean the BIR domains of IAP, in particular the BIR domains of XIAP, cIAP1, or cIAP2.

By "one or more IAP family members" we mean any of the IAP family members in particular XIAP, cIAP1 and/or cIAP2, more particularly XIAP and/or cIAP1.

"Potency" is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug evokes a larger response at low concentrations. Potency is proportional to affinity and efficacy. Affinity is the ability of the drug to bind to a receptor. Efficacy is the relationship between receptor occupancy and the ability to initiate a response at the molecular, cellular, tissue or system level.

The term "antagonist" refers to a type of receptor ligand or drug that blocks or dampens agonist-mediated biological responses. Antagonists have affinity but no agonistic efficacy for their cognate receptors, and binding will disrupt the interaction and inhibit the function of any ligand (e.g. endogenous ligands or substrates, an agonist or inverse agonist) at receptors.

The antagonism may arise directly or indirectly, and may be mediated by any mechanism and at any physiological level. An example of indirect antagonism, would be the indirect antagonism of cIAP as a consequence of ubiquitination of cIAP resulting in its degradation. As a result, antagonism of ligands may under different circumstances manifest itself in functionally different ways. Antagonists mediate their effects by binding to the active site or to allosteric sites on receptors, or they may interact at unique binding sites not normally involved in the biological regulation of the receptor's activity. Antagonist activity may be reversible or irreversible depending on the longevity of the antagonist–receptor complex, which, in turn, depends on the nature of antagonist receptor binding.

The term "treatment" as used herein in the context of treating a condition i.e. state, disorder or disease, pertains generally to treatment and therapy, whether for a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, diminishment or alleviation of at least one symptom associated or caused by the condition being treated and cure of the condition. For example, treatment can be diminishment of one or several symptoms of a disorder or complete eradication of a disorder.

The term "prophylaxis" (i.e. use of a compound as prophylactic measure) as used herein in the context of treating a condition i.e. state, disorder or disease, pertains generally to the prophylaxis or prevention, whether for a human or an animal (e.g. in veterinary applications), in which some desired preventative effect is achieved, for example, in preventing occurrence of a disease or guarding from a disease. Prophylaxis includes complete and total blocking of all symptoms of a disorder for an indefinite period of time, the mere slowing of the onset of one or several symptoms of the disease, or making the disease less likely to occur.

References to the prophylaxis or treatment of a disease state or condition such as cancer include within their scope alleviating or reducing the incidence of cancer.

As used herein, the term "mediated", as used e.g. in conjunction with IAP as described herein (and applied for example to various physiological processes, diseases, states, conditions, therapies, treatments or interventions) is intended to operate limitatively so that the various processes, diseases, states, conditions, treatments and interventions to which the term is applied are those in which the protein plays a biological role. In cases where the term is applied to a disease, state or condition, the biological role played by the protein may be direct or indirect and may be necessary and/or sufficient for the manifestation of the

symptoms of the disease, state or condition (or its aetiology or progression). Thus, the protein function (and in particular aberrant levels of function, e.g. over- or under-expression) need not necessarily be the proximal cause of the disease, state or condition: rather, it is contemplated that the mediated diseases, states or conditions include those having multifactorial aetiologies and complex progressions in which the protein in question is only partially involved. In cases where the term is applied to treatment, prophylaxis or intervention, the role played by the protein may be direct or indirect and may be necessary and/or sufficient for the operation of the treatment, prophylaxis or outcome of the intervention. Thus, a disease state or condition mediated by a protein includes the development of resistance to any particular cancer drug or treatment.

The term "optionally substituted" as used herein refers to a group which may be substituted or unsubstituted by a substituent as herein defined.

The prefix " C_{x-y} " (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-4} alkyl group contains from 1 to 4 carbon atoms, a C_{3-6} cycloalkyl group contains from 3 to 6 carbon atoms, a $haloC_{1-4}$ alkyl group contains from 1 to 4 carbon atoms, and so on.

The term "halo" or "halogen" as used herein refers to fluorine, chlorine, bromine or iodine.

The term " C_{1-4} alkyl" as used herein as a group or part of a group refers to a linear or branched saturated hydrocarbon group containing from 1 to 4 carbon atoms, respectively. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl and the like.

The term " C_{1-4} alkoxy" as used herein as a group or part of a group refers to an $-O-C_{1-4}$ alkyl group wherein C_{1-4} alkyl is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy and the like.

The term " $haloC_{1-4}$ alkyl" as used herein as a group or part of a group refers to a C_{1-4} alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. The term " $haloC_{1-4}$ alkyl" therefore includes monohalo C_{1-4} alkyl and also polyhalo C_{1-4} alkyl. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the $haloC_{1-4}$ alkyl may have one, two, three or more halogens. Examples of such groups include fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

Examples of N-linked pyrazolyl R¹ groups include 1H-pyrazol-1-yl.

Examples of C-linked pyrazolyl R¹ groups include 1H-pyrazol-3-yl, 1H-pyrazol-4-yl and 1H-pyrazol-5-yl.

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Examples of imidazolyl R¹ groups include 1H-imidazol-1-yl and 1H-imidazol-2-yl. Examples of N-linked imidazolyl R¹ groups include 1H-imidazol-1-yl.

Examples of pyridinyl R¹ groups include pyridin-1-yl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

10 Examples of N-linked pyridinyl R¹ groups include pyridin-1-yl.

Examples of triazolyl R¹ groups include 1H-1,2,3-triazol-1-yl and 1H-1,2,4-triazol-1-yl.

15 A combination of substituents is permissible only if such a combination results in a stable or chemically feasible compound (e.g. one that is not substantially altered when kept at 40°C or less for at least a week).

The various functional groups and substituents making up the compounds of the invention are typically chosen such that the molecular weight of the compound of the invention does
20 not exceed 1000 Daltons (Da). More usually, the molecular weight of the compound will be less than 750 Da, for example less than 700 Da, or less than 650 Da, or less than 600 Da, or less than 550 Da.

DETAILED DESCRIPTION OF THE INVENTION

25 In one embodiment, X is CH and Y is CR³; X is nitrogen and Y is CH; or X is CH and Y is nitrogen. In a further embodiment, X is CH and Y is C-CN; or X is nitrogen and Y is CH; or X is nitrogen and Y is C-CN; or X is CH and Y is nitrogen; or X and Y are nitrogen. In a further embodiment, X is CH and Y is CH; X is nitrogen and Y is CH; or X is CH and Y is nitrogen. In a yet further embodiment, X is nitrogen and Y is CH; or X is CH and Y is nitrogen. In a still
30 yet further embodiment, X is nitrogen and Y is CH. In one embodiment, X and Y are nitrogen. In another embodiment, X is CH and Y is nitrogen.

In one embodiment, X is nitrogen and Y is CR³, or X and Y are nitrogen, or X is CR³ and Y is nitrogen. In one embodiment, X is CH and Y is C-CN; or X is nitrogen and Y is CH; or X is
35 nitrogen and Y is C-CN; or X is CH and Y is nitrogen; or X and Y are nitrogen. In one embodiment, X is nitrogen and Y is CH, or X and Y are nitrogen, or X is CH and Y is nitrogen.

In one embodiment of the compounds of formula (Ia), X is CH and Y is CR³; X is nitrogen and Y is CR³; or X is CR³ and Y is nitrogen.

- 5 In one embodiment, X is nitrogen and Y is CR³ (such as CH). In one embodiment, Y is CR³, such as C-CN.

In one embodiment, X is CR³ (such as CH) and Y is nitrogen.

- 10 In one embodiment, X is nitrogen and Y is CR³, or X and Y are nitrogen, or X is CR³ and Y is nitrogen. In one embodiment, X and Y are nitrogen. In one embodiment, X is nitrogen and Y is CH, or X and Y are nitrogen, or X is CH and Y is nitrogen.

In one embodiment, R³ represents hydrogen. In one embodiment, R³ is nitrile.

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In one embodiment, R¹ is selected from:

- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;
- 20 (ii) C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyC₁₋₄ alkyl (such as hydroxymethyl) and haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), and further optionally substituted on the carbon atoms with one or two substituents
- 25 independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;
- (iii) imidazolyl which is optionally substituted with one or two substituents independently selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or
- 30 isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;
- (iv) pyridinyl which is substituted with one or two substituents independently selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl),
- 35 hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile; and

(v) triazolyl substituted with one substituent selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), =O and nitrile or two substituents independently selected from halogen (such as fluorine or chlorine), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile.

In a further embodiment, R¹ is selected from:

- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;
- (iii) imidazolyl which is optionally substituted with one or two substituents independently selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;
- (iv) pyridinyl which is substituted with one or two substituents independently selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile; and
- (v) triazolyl substituted with one substituent selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), =O and nitrile or two substituents independently selected from halogen (such as fluorine or chlorine), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile.

In one embodiment, when R¹ represents an N-linked pyrazolyl, said pyrazolyl is substituted on any of the carbon atoms with two substituents independently selected from C₁₋₄ alkyl. In a further embodiment, when R¹ represents an N-linked pyrazolyl, said pyrazolyl is substituted on any of the carbon atoms with two methyl substituents. In a further embodiment, when R¹ represents an N-linked pyrazolyl, said R¹ group is 4,5-dimethyl-1H-pyrazol-1-yl.

In one embodiment, R¹ is selected from:

(i) C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyC₁₋₄ alkyl (such as hydroxymethyl) and haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), and further optionally substituted on the carbon atoms with one or two substituents

independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;

(ii) C-linked imidazolyl which is optionally substituted with one or two substituents independently selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile;

(iii) C-linked pyridinyl which is substituted with one or two substituents independently selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile; and

(iv) C-linked triazolyl substituted with one substituent selected from halogen (such as fluorine or chlorine), C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), =O and nitrile or two substituents independently selected from halogen (such as fluorine or chlorine), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile.

In one embodiment, R¹ is a C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile.

In one embodiment, when R¹ represents a C-linked pyrazolyl which is substituted on a nitrogen atom with a substituent, said substituent is selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyC₁₋₄ alkyl (such as hydroxymethyl) and haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as

methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile.

In one embodiment, when R¹ represents a C-linked pyrazolyl, said pyrazolyl is optionally substituted on a nitrogen atom with a C₁₋₄ alkyl substituent and is further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl. In a further embodiment, when R¹ represents a C-linked pyrazolyl, said pyrazolyl is substituted on one nitrogen atom by a C₁₋₄ alkyl substituent and optionally substituted on one carbon atom by a C₁₋₄ alkyl substituent. In a further embodiment, when R¹ represents a C-linked pyrazolyl, said pyrazolyl is substituted on one nitrogen atom by a methyl substituent and substituted on one carbon atom by a methyl substituent. In a yet further embodiment, when R¹ represents a C-linked pyrazolyl, said R¹ group is 1,3-dimethyl-1H-pyrazol-5-yl. In an alternative embodiment, when R¹ represents a C-linked pyrazolyl, said pyrazolyl is substituted on one nitrogen atom by a methyl substituent and the carbon atoms are unsubstituted. In a yet further embodiment, when R¹ represents a C-linked pyrazolyl, said R¹ group is 1-methyl-1H-pyrazol-5-yl.

In one embodiment, when R¹ represents imidazolyl, said imidazolyl is N-linked imidazolyl.

In one embodiment, when R¹ represents imidazolyl, said imidazolyl is 1H-imidazol-1-yl optionally substituted with one or two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl, haloC₁₋₄ alkyl and nitrile. In one embodiment, when R¹ represents imidazolyl, said imidazolyl is unsubstituted. In an alternative embodiment, when R¹ represents imidazolyl, said imidazolyl is substituted with one substituent selected from halogen (such as chlorine), C₁₋₄ alkyl (such as methyl or ethyl), haloC₁₋₄ alkyl (such as trifluoromethyl) and nitrile. In a further embodiment, when R¹ represents imidazolyl, said imidazolyl is substituted with one substituent selected from chlorine, methyl, ethyl, trifluoromethyl and nitrile. In an alternative embodiment, when R¹ represents imidazolyl, said imidazolyl is substituted with two substituents independently selected from halogen (such as chlorine), C₁₋₄ alkyl (such as methyl), hydroxyC₁₋₄ alkyl (such as hydroxymethyl) and nitrile. In an alternative embodiment, when R¹ represents imidazolyl, said imidazolyl is substituted with two substituents independently selected from chlorine, methyl, hydroxymethyl and nitrile.

In one embodiment, when R¹ represents pyridinyl, said pyridinyl is N-linked pyridinyl (i.e. pyridin-1-yl). In one embodiment, when R¹ represents pyridinyl, said pyridinyl is substituted with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl) and =O.

In a further embodiment, when R¹ represents pyridinyl, said pyridinyl is substituted with two substituents independently selected from C₁₋₄ alkyl (such as methyl) and =O. In a further embodiment, when R¹ represents pyridinyl, said pyridinyl is substituted with two substituents selected from methyl and =O.

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In one embodiment, when R¹ represents triazolyl, said triazolyl is N-linked triazolyl (i.e. 1H-1,2,3-triazol-1-yl or 1H-1,2,4-triazol-1-yl). In one embodiment, when R¹ represents triazolyl, said triazolyl is substituted with one C₁₋₄ alkyl (such as methyl) substituent. In a further embodiment, when R¹ represents triazolyl, said triazolyl is substituted with one methyl

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In one embodiment, R¹ is selected from:

(i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;

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(iii) N-linked imidazolyl which is optionally substituted with one or two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile; and

(iv) N-linked pyridinyl which is substituted with two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile.

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In a further embodiment, R¹ is selected from:

(i) N-linked pyrazolyl which is substituted on two of the carbon atoms with a methyl substituent;

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(iii) N-linked imidazolyl which is optionally substituted with one or two substituents independently selected from chlorine, methyl, ethyl, hydroxymethyl, trifluoromethyl and nitrile; and

(iv) N-linked pyridinyl which is substituted with two substituents selected from methyl and =O.

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In a yet further embodiment, R¹ is selected from:

(i) N-linked pyrazolyl which is substituted on two of the carbon atoms with a methyl substituent;

(iii) N-linked imidazolyl which is substituted with one or two substituents independently selected from chlorine, methyl, ethyl, hydroxymethyl, trifluoromethyl and nitrile; and

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(iv) N-linked pyridinyl which is substituted with two substituents selected from methyl and =O.

In a further embodiment, R¹ is N-linked pyrazolyl which is substituted on two carbon atoms with a methyl substituent.

In one embodiment, R² is selected from: benzyl optionally substituted on the phenyl group by one or two substituents independently selected from fluorine and nitrile, and substituted on the methylene by hydroxyl; and C₂₋₄ alkyl substituted by one or two substituents selected from fluorine and hydroxyl.

In one embodiment, R² is selected from: benzyl optionally substituted on the phenyl group by one or two fluorine substituents, and optionally substituted on the methylene by hydroxyl; and C₂₋₄ alkyl substituted by one or two fluorine substituents.

In one embodiment, R² is benzyl optionally substituted on the phenyl group by one or two substituents selected from fluorine and nitrile, and optionally substituted on the methylene by hydroxyl. In another embodiment, R² is benzyl substituted on the phenyl group by one or two substituents selected from fluorine and nitrile, and optionally substituted on the methylene by hydroxyl.

In one embodiment, R² is benzyl optionally substituted on the phenyl group by one or two substituents selected from fluorine, and wherein the methylene is optionally substituted by a hydroxyl group (e.g. R² is selected from -C(H)(OH)-phenyl, -C(H)(OH)-2-fluorophenyl, -C(H)(OH)-3-fluorophenyl, -C(H)(OH)-4-fluorophenyl, -C(H)(OH)-2,3-difluorophenyl, -C(H)(OH)-2,4-difluorophenyl, -C(H)(OH)-2,5-difluorophenyl, -C(H)(OH)-2,6-difluorophenyl and -C(H)(OH)-3,4-difluorophenyl).

In one embodiment, R² is benzyl substituted on the phenyl group by one or two fluorine substituents, and optionally substituted on the methylene by hydroxyl.

In another embodiment, R² is benzyl substituted on the phenyl group by one or two fluorine substituents, and substituted on the methylene by hydroxyl.

In one embodiment, R² is benzyl substituted on the phenyl group by one or two substituents selected from fluorine, and wherein the methylene is optionally substituted by a hydroxyl group (e.g. -C(H)(OH)-2-fluorophenyl, -C(H)(OH)-3-fluorophenyl, -C(H)(OH)-4-fluorophenyl,

-C(H)(OH)-2,3-difluorophenyl, -C(H)(OH)-2,4-difluorophenyl, -C(H)(OH)-2,5-difluorophenyl, -C(H)(OH)-2,6-difluorophenyl or -C(H)(OH)-3,4-difluorophenyl).

In one embodiment, R² is benzyl optionally substituted on the phenyl group by one or two fluorines wherein the methylene is substituted by a hydroxyl group (e.g. -C(H)(OH)-4-fluorophenyl or -C(H)(OH)-2,4-difluorophenyl).

In one embodiment, R² is benzyl optionally substituted (e.g. substituted) on the phenyl group by one or two fluorines.

In a further embodiment, R² is benzyl optionally substituted on the phenyl group by one fluorine (such as 2-fluorobenzyl, 3-fluorobenzyl or 4-fluorobenzyl), two fluorines (such as 2,3-difluorobenzyl, 2,4-difluorobenzyl or 2,6-difluorobenzyl) or one fluorine and one nitrile (such as 2-cyano-4-fluorobenzyl).

In a further embodiment, R² is benzyl optionally substituted on the phenyl group by one fluorine (such as 4-fluorobenzyl), two fluorines (such as 2,4-difluorobenzyl) or one fluorine and one nitrile (such as 2-cyano-4-fluorobenzyl).

In one embodiment, R² is benzyl substituted on the methylene by an hydroxyl group and unsubstituted on the phenyl group.

In one embodiment, R² is -CH(OH)-phenyl where the phenyl group is optionally substituted with one or two substituents selected from fluorine.

In one embodiment, R² is benzyl optionally substituted on the phenyl group by one or two fluorines (such as 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2,3-difluorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 2,6-difluorobenzyl or 3,4-difluorobenzyl) or one fluorine and one nitrile (such as 2-cyano-4-fluorobenzyl), wherein the methylene is optionally substituted by a hydroxyl group (such as -C(H)(OH)-2-fluorophenyl, -C(H)(OH)-3-fluorophenyl, -C(H)(OH)-4-fluorophenyl, -C(H)(OH)-2,3-difluorophenyl, -C(H)(OH)-2,4-difluorophenyl or -C(H)(OH)-3,4-difluorophenyl) or R² is C₂₋₄ alkyl substituted by one or two fluorines (such as 1,1-difluoropropyl or 1,1-difluorobutyl).

In a yet further embodiment, R² is selected from unsubstituted benzyl and benzyl substituted on the phenyl group by one fluorine. In one embodiment R² is benzyl optionally substituted on the phenyl group by one or two fluorines (such as 4-fluorobenzyl or 2,4-difluorobenzyl). In

one embodiment R^2 is benzyl optionally substituted on the phenyl group by two fluorines (such as 2,4-difluorobenzyl). In a yet further embodiment, R^2 is benzyl optionally substituted on the phenyl group by one fluorine. In a still yet further embodiment, R^2 is 4-fluorobenzyl.

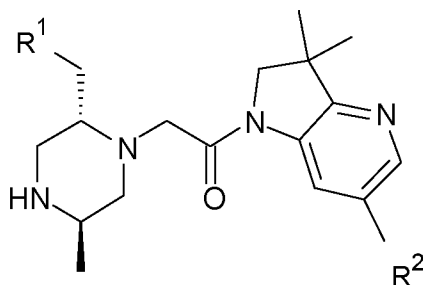
- 5 In one embodiment, R^2 is C_{2-4} alkyl substituted by one or two substituents selected from fluorine and hydroxyl.

In one embodiment, R^2 is C_{2-4} alkyl substituted by one hydroxyl (such as 1-hydroxybutyl).

- 10 In an alternative embodiment, R^2 is C_{2-4} alkyl substituted by one or two fluorines. In a further embodiment, R^2 is C_{2-4} alkyl substituted by two fluorines. In a yet further embodiment, R^2 is propyl or butyl substituted by two fluorines. In a still yet further embodiment, R^2 is selected from 1,1-difluoropropyl and 1,1-difluorobutyl. In one embodiment R^2 is difluorobutyl (such as 1,1-difluorobutyl). In one embodiment when X is CH and Y is nitrogen then R^2 is difluorobutyl
15 (such as 1,1-difluorobutyl).

Sub-Formulae

In one embodiment, the compound of formula (I) is a compound of formula (Ia):



- 20 (Ia)

or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein R^1 and R^2 are as herein defined or in any of the embodiments.

- 25 In one embodiment of the compound of formula (Ia), R^1 is selected from:

- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, $=O$ and nitrile;
- (ii) C-linked pyrazolyl which is substituted on a nitrogen atom with a substituent selected
30 from C_{1-4} alkyl (such as methyl) and further optionally substituted on the carbon atoms with one or two substituents independently selected from C_{1-4} alkyl (such as methyl);

(iii) N-linked imidazolyl which is optionally substituted with one or two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;

5 (iv) N-linked pyridinyl which is substituted with two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile; and

(v) N-linked triazolyl which is substituted with one methyl substituent.

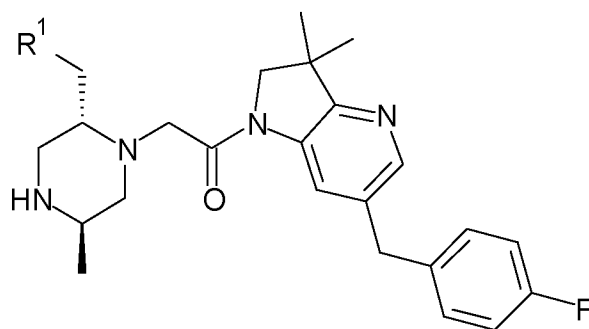
10 In one embodiment of the compound of formula (Ia), R¹ is C-linked pyrazolyl which is optionally substituted (e.g. substituted) on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl), hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl), hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile. In one embodiment of the compound of formula (Ia), R¹ is C-
15 linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents (e.g. one substituent) independently selected from C₁₋₄ alkyl (such as methyl).

20 In one embodiment of the compound of formula (Ia), R¹ represents a C-linked pyrazolyl substituted on the nitrogen with C₁₋₄ alkyl (such as methyl) and optionally on any of the carbon atoms with C₁₋₄ alkyl (such as methyl).

In one embodiment of the compound of formula (Ia), R² represents benzyl optionally substituted on the phenyl group by one or two fluorines. In a further embodiment, R² is
25 benzyl optionally substituted on the phenyl group by one fluorine (such as 4-fluorobenzyl) or two fluorines (such as 2,4-difluorobenzyl). In a yet further embodiment, R² is benzyl optionally substituted on the phenyl group by one fluorine. In a still yet further embodiment, R² is 4-fluorobenzyl.

30 In an alternative embodiment, R² is C₂₋₄ alkyl substituted by one or two fluorines. In a further embodiment, R² is C₂₋₄ alkyl substituted by two fluorines. In a yet further embodiment, R² is butyl substituted by two fluorines (such as 1,1-difluorobutyl).

In one embodiment, the compound of formula (I) is a compound of formula (Ib):



(Ib)

or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

5 wherein R¹ is as herein defined or in any of the embodiments.

In one embodiment of the compound of formula (Ib), R¹ is selected from:

- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;
- 10 (ii) C-linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl);
- (iii) N-linked imidazolyl which is optionally substituted with one or two substituents
- 15 independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;
- (iv) N-linked pyridinyl which is substituted with two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile; and
- 20 (v) N-linked triazolyl which is substituted with one methyl substituent.

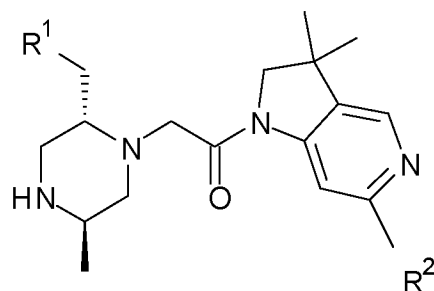
In one embodiment of the compound of formula (Ib), R¹ is C-linked pyrazolyl which is optionally substituted (e.g. substituted) on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl), hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally

25 substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl), hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile. In one embodiment of the compound of formula (Ib), R¹ is C-linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two

30 substituents (e.g. one substituent) independently selected from C₁₋₄ alkyl (such as methyl).

In one embodiment of the compound of formula (Ib), R^1 represent a C-linked pyrazolyl substituted on the nitrogen with C_{1-4} alkyl (such as methyl) and optionally on any of the carbon atoms with C_{1-4} alkyl (such as methyl).

- 5 In one embodiment, the compound of formula (I) is a compound of formula (Ic):



(Ic)

or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

- 10 wherein R^1 and R^2 are as herein defined or in any of the embodiments.

In one embodiment of the compound of formula (Ic), R^1 represents an N-linked pyrazolyl substituted on any of the carbon atoms with two substituents independently selected from C_{1-4} alkyl. In a further embodiment, R^1 represents an N-linked pyrazolyl substituted on two of the carbon atoms with a methyl substituent. In a further embodiment, R^1 represents 4,5-dimethyl-1H-pyrazol-1-yl.

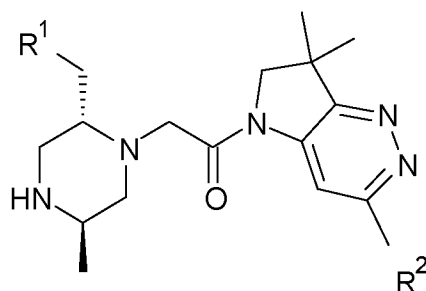
- In one embodiment of the compound of formula (Ic), R^1 is C-linked pyrazolyl which is optionally substituted (e.g. substituted) on a nitrogen atom with a substituent selected from C_{1-4} alkyl (such as methyl), hydroxy C_{1-4} alkyl and halo C_{1-4} alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C_{1-4} alkyl (such as methyl), hydroxyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl, methoxymethyl, =O and nitrile. In one embodiment of the compound of formula (Ia), R^1 is C-linked pyrazolyl which is substituted on a nitrogen atom with a C_{1-4} alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents (e.g. one substituent) independently selected from C_{1-4} alkyl (such as methyl).

- In one embodiment of the compound of formula (Ic), R^1 represent a C-linked pyrazolyl substituted on the nitrogen with C_{1-4} alkyl (such as methyl) and optionally on any of the carbon atoms with C_{1-4} alkyl (such as methyl).

In one embodiment of the compound of formula (Ic), R^2 represents benzyl optionally substituted on the phenyl group by one or two fluorines (such as 4-fluorobenzyl or 2,4-difluorobenzyl) or C_{2-4} alkyl substituted by two fluorines (such as butyl substituted by two fluorines, e.g. 1,1-difluorobutyl).

5

In one embodiment, the compound of formula (I) is a compound of formula (Id):



(Id)

or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof; wherein R^1 and R^2 are as herein defined or in any of the embodiments.

10

In one embodiment of the compound of formula (Id), R^1 is C-linked pyrazolyl which is optionally substituted (e.g. substituted) on a nitrogen atom with a substituent selected from C_{1-4} alkyl (such as methyl), hydroxy C_{1-4} alkyl and halo C_{1-4} alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C_{1-4} alkyl (such as methyl), hydroxyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl, methoxymethyl, =O and nitrile. In one embodiment of the compound of formula (Ia), R^1 is C-linked pyrazolyl which is substituted on a nitrogen atom with a C_{1-4} alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents (e.g. one substituent) independently selected from C_{1-4} alkyl (such as methyl).

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In one embodiment of the compound of formula (Id), R^1 represents a C-linked pyrazolyl substituted on the nitrogen with C_{1-4} alkyl (such as methyl) and optionally on any of the carbon atoms with C_{1-4} alkyl (such as methyl).

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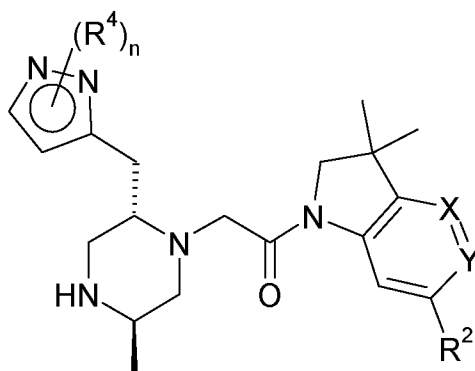
In one embodiment of the compound of formula (Id), R^1 represents an N-linked pyrazolyl substituted on two of the carbon atoms with a C_{1-4} alkyl substituent. In a further embodiment, R^1 represents an N-linked pyrazolyl substituted on two of the carbon atoms with a methyl substituent. In a further embodiment, R^1 represents 4,5-dimethyl-1H-pyrazol-1-yl.

30

In one embodiment of the compound of formula (Id), R^2 represents benzyl optionally substituted on the phenyl group by one or two fluorines. In a further embodiment, R^2 is benzyl optionally substituted on the phenyl group by one fluorine (such as 4-fluorobenzyl) or two fluorines (such as 2,4-difluorobenzyl). In a yet further embodiment, R^2 is benzyl optionally substituted on the phenyl group by one fluorine. In a still yet further embodiment, R^2 is 4-fluorobenzyl.

In an alternative embodiment, R^2 is C_{2-4} alkyl substituted by one or two fluorines. In a further embodiment, R^2 is C_{2-4} alkyl substituted by two fluorines. In a yet further embodiment, R^2 is butyl substituted by two fluorines (such as 1,1-difluorobutyl).

In one embodiment, the compound of formula (I) is a compound of formula (Ie):



(Ie)

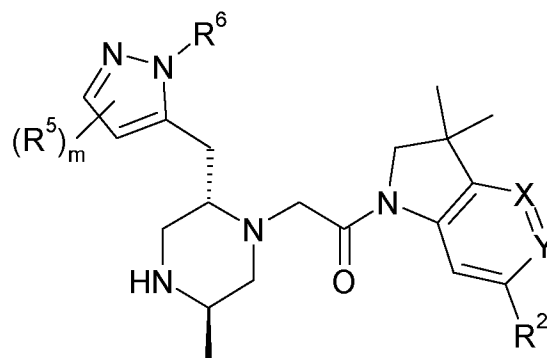
or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein X, Y and R^2 are as herein defined or in any of the embodiments, R^4 is independently selected from C_{1-4} alkyl, hydroxy C_{1-4} alkyl and halo C_{1-4} alkyl when on a nitrogen atom and selected from C_{1-4} alkyl, hydroxyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl, methoxymethyl, =O and nitrile when on a carbon atom; and n is 0, 1, 2 or 3.

In one embodiment, the compound of formula (I) is a compound of formula (Ie) wherein n is 1. In one embodiment, the compound of formula (I) is a compound of formula (Ie) wherein n is 2.

In one embodiment, the compound of formula (I) is a compound of formula (Ie) wherein n is 2 and R^4 is C_{1-4} alkyl (such as methyl). In one embodiment n is 1 and R^4 is C_{1-4} alkyl (such as methyl).

In one embodiment, the compound of formula (I) is a compound of formula (If):



(If)

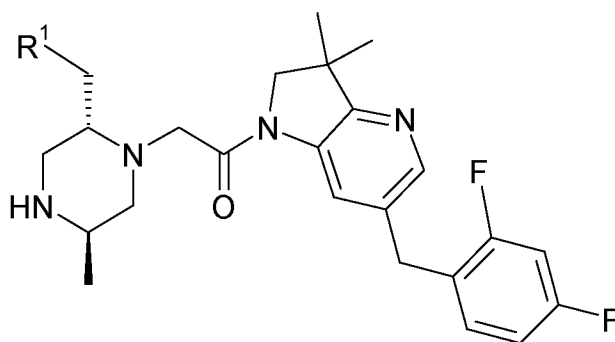
or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein X, Y and R² are as herein defined or in any of the embodiments, R⁶ is selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl; R⁵ is independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile; and m is selected from 0, 1 and 2. In one embodiment, R⁶ is C₁₋₄ alkyl (such as methyl).

In one embodiment, the compound of formula (I) is a compound of formula (If) wherein m is 1.

In one embodiment, the compound of formula (I) is a compound of formula (If) wherein m is 1 and R⁵ is C₁₋₄ alkyl (such as methyl).

In one embodiment, the compound of formula (I) is a compound of formula (Ig):



(Ig)

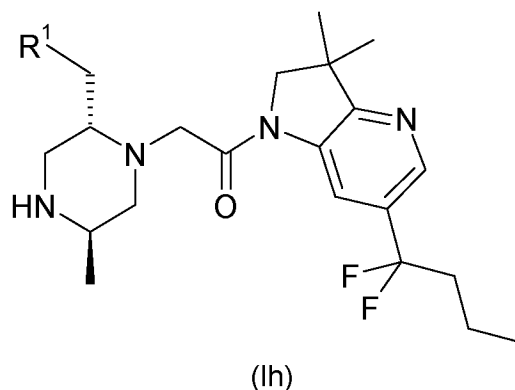
or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein R¹ is as herein defined or in any of the embodiments.

In one embodiment of the compound of formula (Ig), R¹ is selected from:

- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;
- (ii) C-linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl);
- (iii) N-linked imidazolyl which is optionally substituted with one or two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;
- (iv) N-linked pyridinyl which is substituted with two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile; and
- (v) N-linked triazolyl which is substituted with one methyl substituent.
- 15 In one embodiment of the compound of formula (Ig), R¹ is C-linked pyrazolyl which is optionally substituted (e.g. substituted) on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl), hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl), hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl,
- 20 methoxymethyl, =O and nitrile. In one embodiment of the compound of formula (Ig), R¹ is C-linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents (e.g. one substituent) independently selected from C₁₋₄ alkyl (such as methyl).
- 25 In one embodiment of the compound of formula (Ig), R¹ represent a C-linked pyrazolyl substituted on the nitrogen with C₁₋₄ alkyl (such as methyl) and optionally on any of the carbon atoms with C₁₋₄ alkyl (such as methyl).

In one embodiment, the compound of formula (I) is a compound of formula (Ih):



or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein R¹ is as herein defined or in any of the embodiments.

- 5 In one embodiment of the compound of formula (Ih), R¹ is selected from:
- (i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;
 - (ii) C-linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl) substituent and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl);
 - (iii) N-linked imidazolyl which is optionally substituted with one or two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;
 - 15 (iv) N-linked pyridinyl which is substituted with two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile; and
 - (v) N-linked triazolyl which is substituted with one methyl substituent.
- 20 In one embodiment of the compound of formula (Ih), R¹ is C-linked pyrazolyl which is optionally substituted (e.g. substituted) on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl), hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl), hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl,
- 25 methoxymethyl, =O and nitrile. In one embodiment of the compound of formula (Ih), R¹ is C-linked pyrazolyl which is substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl) and further optionally substituted on the carbon atoms with one or two substituents (e.g. one substituent) independently selected from C₁₋₄ alkyl (such as methyl).
- 30 In one embodiment of the compound of formula (Ih), R¹ represent a C-linked pyrazolyl substituted on the nitrogen with C₁₋₄ alkyl (such as methyl) and optionally on any of the carbon atoms with C₁₋₄ alkyl (such as methyl).

In one embodiment, the compound of formula (I) is a compound of formula (Ie) or (If)

- 35 wherein X is nitrogen and Y is CH.

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), (Ig) or (Ih) (such as formula (Ia), (Ib), (Ic) or (Id)), wherein R¹ represents a C-linked pyrazolyl which is substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyC₁₋₄ alkyl (such as hydroxymethyl) and haloC₁₋₄ alkyl (such as monofluoromethyl, trifluoromethyl), and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl), hydroxyl, hydroxyC₁₋₄ alkyl (such as hydroxymethyl), C₁₋₄ alkoxy (such as methoxy), haloC₁₋₄ alkyl (such as monofluoromethyl or trifluoromethyl), methoxymethyl, =O and nitrile.

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), (Ig) or (Ih) (such as formula (Ia), (Ib), (Ic) or (Id)), wherein R¹ represents a C-linked pyrazolyl which is substituted on a nitrogen atom with a C₁₋₄ alkyl (such as methyl, ethyl or isopropyl) substituent, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl (such as methyl, ethyl or isopropyl).

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), (Ig) or (Ih) (such as formula (Ia), (Ib), (Ic) or (Id)), wherein R¹ represents a C-linked pyrazolyl, said pyrazolyl is substituted on one nitrogen atom by a methyl substituent and substituted on one carbon atom by a methyl substituent (such as 1,3-dimethyl-1H-pyrazol-5-yl).

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), (Ig) or (Ih) (such as formula (Ia), (Ib), (Ic) or (Id)), wherein R¹ represents a C-linked pyrazolyl, said pyrazolyl is substituted on one nitrogen atom by a methyl substituent and the carbon atoms are unsubstituted (such as 1-methyl-1H-pyrazol-5-yl).

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ic), (Id), (Ie), (If) wherein R² is benzyl optionally substituted on the phenyl group by one or two fluorines (such as unsubstituted benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2,3-difluorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 2,6-difluorobenzyl or 3,4-difluorobenzyl) or one fluorine and one nitrile (such as 2-cyano-4-fluorobenzyl), wherein the methylene is optionally substituted by a hydroxyl group (e.g. -C(H)(OH)benzyl, -C(H)(OH)-2-fluorophenyl, -C(H)(OH)-3-fluorophenyl, -C(H)(OH)-4-fluorophenyl, -C(H)(OH)-2,3-difluorophenyl, -C(H)(OH)-2,4-difluorophenyl, -C(H)(OH)-2,5-difluorophenyl, -C(H)(OH)-2,6-difluorophenyl or -C(H)(OH)-3,4-difluorophenyl) or R² is C₂₋₄ alkyl substituted by one or two fluorines or hydroxyl, such as 1-hydroxybutyl, 1,1-difluoropropyl or 1,1-difluorobutyl, in particular 1,1-difluorobutyl.

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), (Ie) or (If) wherein R^2 is $-\text{CH}(\text{OH})$ -phenyl where the phenyl group is optionally substituted with one or two substituents selected from fluorine.

5

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ib), (Ic), (Id), (Ie) or (If) wherein R^2 is benzyl optionally substituted on the phenyl group by one or two fluorines (such as 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2,3-difluorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 2,6-difluorobenzyl or 3,4-difluorobenzyl) or one fluorine and one nitrile (such as 2-cyano-4-fluorobenzyl), wherein the methylene is optionally substituted by a hydroxyl group (such as $-\text{C}(\text{H})(\text{OH})$ -2-fluorophenyl, $-\text{C}(\text{H})(\text{OH})$ -3-fluorophenyl, $-\text{C}(\text{H})(\text{OH})$ -4-fluorophenyl, $-\text{C}(\text{H})(\text{OH})$ -2,3-difluorophenyl, $-\text{C}(\text{H})(\text{OH})$ -2,4-difluorophenyl or $-\text{C}(\text{H})(\text{OH})$ -3,4-difluorophenyl) or R^2 is C_{2-4} alkyl substituted by a hydroxyl group (such as 1-hydroxybutyl) or one or two fluorines (such as 1,1-difluoropropyl or 1,1-difluorobutyl).

10

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In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ic), (Id), (Ie) or (If), wherein R^2 is benzyl optionally substituted on the phenyl group by one or two fluorines (such as 4-fluorobenzyl or 2,4-difluorobenzyl) or one fluorine and one nitrile (such as 2-cyano-4-fluorobenzyl), wherein the methylene is optionally substituted by a hydroxyl group (e.g. $-\text{C}(\text{H})(\text{OH})$ -4-fluorophenyl or $-\text{C}(\text{H})(\text{OH})$ -2,4-difluorophenyl) or R^2 is C_{2-4} alkyl substituted by one or two fluorines or hydroxyl (such as 1-hydroxybutyl, 1,1-difluoropropyl or 1,1-difluorobutyl, in particular 1,1-difluorobutyl).

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In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ic), (Id), (Ie) or (If), wherein R^2 is benzyl optionally substituted on the phenyl group by one or two fluorines (such as 4-fluorobenzyl or 2,4-difluorobenzyl) or R^2 is C_{2-4} alkyl substituted by one or two fluorines, such as 1,1-difluoropropyl or 1,1-difluorobutyl e.g. 1,1-difluorobutyl.

30

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ic), (Id), (Ie) or (If), wherein R^2 is benzyl optionally substituted on the phenyl group by one or two fluorines (such as 4-fluorobenzyl or 2,4-difluorobenzyl).

35

In one embodiment, the compound of formula (I) is a compound of formula (Ia), (Ic), (Id), (Ie) or (If), wherein R^2 is C_{2-4} alkyl substituted by one or two fluorines, such as 1,1-difluoropropyl or 1,1-difluorobutyl e.g. 1,1-difluorobutyl.

In one embodiment, the invention provides a compound of formula (I) which comprises a compound of Examples 1-38 (in particular Examples 1-22, 30-31 and 38 or Examples 1-22) or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof. In one embodiment, the invention provides a compound of formula (I) which comprises a compound of Examples 23-37 or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof.

In one embodiment, the invention provides a compound of formula (I) which is a compound of Examples 1-38 (in particular Examples 1-22, 30-31 and 38 or Examples 1-22) or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof.

In one embodiment, the invention provides a compound of formula (I) which is the free base of a compound of Examples 1-38 (in particular Examples 1-22, 30-31 and 38 or Examples 1-22) or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof.

In one embodiment, the invention provides a compound of formula (I) which is the free base of a compound of Example 22 or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof.

In one embodiment, the invention provides a compound of formula (I) which is the free base of a compound of Example 30 or Example 31 or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example for one substituent may be combined with each general and specific preference, embodiment and example for one or more, preferably, all other substituents as defined herein and that all such embodiments are embraced by this application.

SALTS, SOLVATES, TAUTOMERS, ISOMERS, N-OXIDES, ESTERS, PRODRUGS AND ISOTOPES

A reference to a compound of the formula (I) and sub-groups thereof also includes ionic forms, salts, solvates, isomers (including geometric and stereochemical isomers), tautomers, *N*-oxides, esters, prodrugs, isotopes and protected forms thereof, for example, as discussed below; preferably, the salts or tautomers or isomers or *N*-oxides or solvates thereof; and

more preferably, the salts or tautomers or N-oxides or solvates thereof, even more preferably the salts or tautomers or solvates thereof.

Salts

- 5 Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulfonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.
- 10 The salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these
- 15 compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.
- Acid addition salts (mono- or di-salts) may be formed with a wide variety of acids, both
- 20 inorganic and organic. Examples of acid addition salts include mono- or di-salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulfonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-
- 25 hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrohalic acids (e.g. hydrobromic, hydrochloric, hydriodic), isethionic, lactic (e.g. (+)-L-lactic, ($\pm$)-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic, ($\pm$)-DL-mandelic, methanesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic, 1-hydroxy-2-naphthoic,
- 30 nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, pyruvic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, (+)-L-tartaric, thiocyanic, *p*-toluenesulfonic, undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.
- 35 One particular group of salts consists of salts formed from acetic, hydrochloric, hydriodic, phosphoric, nitric, sulfuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulfonic, toluenesulfonic, methanesulfonic (mesylate), ethanesulfonic,

naphthalenesulfonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids. One particular salt is the hydrochloride salt.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO⁻), then a salt may be formed with an organic or inorganic base, generating a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Li⁺, Na⁺ and K⁺, alkaline earth metal cations such as Ca²⁺ and Mg²⁺, and other cations such as Al³⁺ or Zn⁺. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH₄⁺) and substituted ammonium ions (e.g., NH₃R⁺, NH₂R₂⁺, NHR₃⁺, NR₄⁺). Examples of some suitable substituted ammonium ions are those derived from: methylamine, ethylamine, diethylamine, propylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is N(CH₃)₄⁺.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed.

The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salt forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

In one embodiment of the invention, there is provided a pharmaceutical composition comprising a solution (e.g. an aqueous solution) containing a compound of the formula (I) and sub-groups and examples thereof as described herein in the form of a salt in a concentration of greater than 10 mg/ml, typically greater than 15 mg/ml and preferably greater than 20 mg/ml.

N-Oxides

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

5

Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

- 10 N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

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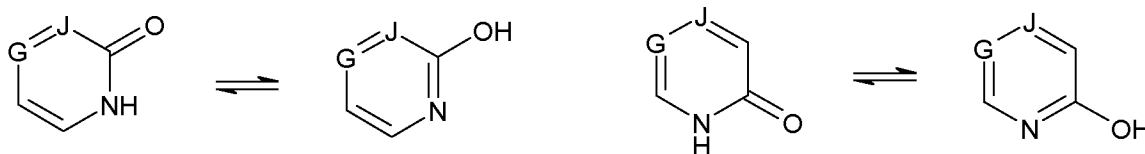
Geometric isomers and tautomers

Compounds of the formula (I) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

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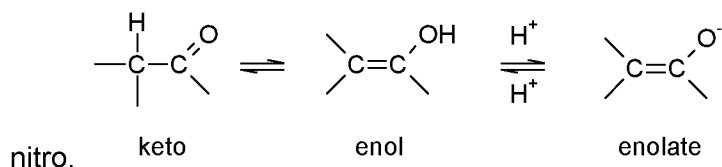
For example, in compounds of the formula (I), ring E can exist in two tautomeric forms as illustrated below. For simplicity, the general formula (I) illustrates one form A but the formula is to be taken as embracing both tautomeric forms.

25



Other examples of tautomeric forms include, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/enediamines, nitroso/oxime, thioketone/enethiol, and nitro/aci-

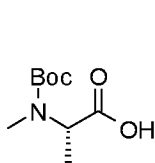
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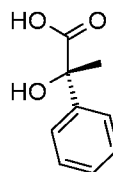
Stereoisomers

Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms.

- 5 Stereocentres are illustrated in the usual fashion, using 'hashed' or 'wedged' lines. e.g.



Boc-N-Methyl alanine



(S)-(+)-2-hydroxy-2-phenylpropionic acid

Where a compound is described as a mixture of two diastereoisomers / epimers, the configuration of the stereocentre is not specified and is represented by straight lines.

- 10 Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers, epimers and diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) or two or more optical isomers, unless the context requires otherwise.

- 15 The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers, or *d* and *l* isomers) or they may be characterised in terms of their absolute stereochemistry using the “R and S” nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, New York, 20 1992, pages 109-114, and see also Cahn, Ingold & Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 385-415.

- Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known 25 to the person skilled in the art.

- As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid, (-)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulfonic acid, 30 separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

Additionally enantiomeric separation can be achieved by covalently linking a enantiomerically pure chiral auxiliary onto the compound and then performing diastereoisomer separation using conventional methods such as chromatography. This is then followed by cleavage of the
5 aforementioned covalent linkage to generate the appropriate enantiomerically pure product.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to
10 use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99%
15 or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

Compounds encompassing double bonds can have an E (entgegen) or Z (zusammen) stereochemistry at said double bond. Substituents on bivalent cyclic or (partially) saturated
20 radicals may have either the *cis*- or *trans*-configuration. The terms *cis* and *trans* when used herein are in accordance with Chemical Abstracts nomenclature (J. Org. Chem. 1970, 35 (9), 2849-2867), and refer to the position of the substituents on a ring moiety.

Of special interest are those compounds of formula (I) which are stereochemically pure.
25 When a compound of formula (I) is for instance specified as R, this means that the compound is substantially free of the S isomer. If a compound of formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer. The terms *cis*, *trans*, R, S, E and Z are well known to a person skilled in the art.

30 Isotopic variations

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, i.e. compounds of formula (I), wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

35 Examples of isotopes suitable for inclusion in the compounds of the invention comprise isotopes of hydrogen, such as ^2H (D) and ^3H (T), carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine,

such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I , ^{125}I and ^{131}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S .

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The compounds of formula (I) can also have valuable diagnostic properties in that they can be used for detecting or identifying the formation of a complex between a labelled compound and other molecules, peptides, proteins, enzymes or receptors. The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances (for example, luminol, luminol derivatives, luciferin, aequorin and luciferase), etc. The radioactive isotopes tritium, *i.e.* ^3H (T), and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H (D), may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining target occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Esters

Esters such as carboxylic acid esters, acyloxy esters and phosphate esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group $-\text{C}(=\text{O})\text{OR}$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-12} heterocyclyl group, or a C_{5-12} aryl group, preferably a C_{1-6} alkyl group. Particular examples of ester groups include, but are not limited to $-\text{C}(=\text{O})\text{OCH}_3$, $-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$, and $-\text{C}(=\text{O})\text{OPh}$. Examples of acyloxy (reverse ester) groups are represented by $-\text{OC}(=\text{O})\text{R}$, wherein R is an acyloxy substituent, for example, a C_{1-6} alkyl group, a C_{3-12} heterocyclyl group, or a C_{5-12} aryl group, preferably a C_{1-6} alkyl group. Particular examples of acyloxy groups include, but are not limited to, $-\text{OC}(=\text{O})\text{CH}_3$

(acetoxo), $-\text{OC}(=\text{O})\text{CH}_2\text{CH}_3$, $-\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$, $-\text{OC}(=\text{O})\text{Ph}$, and $-\text{OC}(=\text{O})\text{CH}_2\text{Ph}$. Examples of phosphate esters are those derived from phosphoric acid.

In one embodiment of the invention, formula (I) includes within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. In another embodiment of the invention, formula (I) does not include within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group.

Solvates and Crystalline forms

Also encompassed by formula (I) are any polymorphic forms of the compounds, and solvates such as hydrates, alcoholates and the like.

The compounds of the invention may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid or ethanolamine and the like. The compounds of the invention may exert their biological effects whilst they are in solution.

Solvates are well known in pharmaceutical chemistry. They can be important to the processes for the preparation of a substance (e.g. in relation to their purification, the storage of the substance (e.g. its stability) and the ease of handling of the substance and are often formed as part of the isolation or purification stages of a chemical synthesis. A person skilled in the art can determine by means of standard and long used techniques whether a hydrate or other solvate has formed by the isolation conditions or purification conditions used to prepare a given compound. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray crystallography (e.g. single crystal X-ray crystallography or X-ray powder diffraction) and Solid State NMR (SS-NMR, also known as Magic Angle Spinning NMR or MAS-NMR). Such techniques are as much a part of the standard analytical toolkit of the skilled chemist as NMR, IR, HPLC and MS.

Alternatively the skilled person can deliberately form a solvate using crystallisation conditions that include an amount of the solvent required for the particular solvate. Thereafter the standard methods described above, can be used to establish whether solvates had formed.

- 5 Furthermore, the compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention.

Complexes

- 10 Formula (I) also includes within its scope complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds. Inclusion complexes, clathrates and metal complexes can be formed by means of methods well known to the skilled person.

Prodrugs

- Also encompassed by formula (I) are any pro-drugs of the compounds of the formula (I). By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).
- 20 For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound,
- 25 followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:

- C₁₋₇alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
- 30 C₁₋₇aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and acyloxy-C₁₋₇alkyl (e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carboxyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carboxyloxymethyl; 1-isopropoxy-carboxyloxyethyl; cyclohexyl-carboxyloxymethyl; 1-cyclohexyl-carboxyloxyethyl; cyclohexyloxy-carboxyloxymethyl; 1-
- 35 cyclohexyloxy-carboxyloxyethyl; (4-tetrahydropyranyloxy) carboxyloxymethyl; 1-(4-tetrahydropyranyloxy)carboxyloxyethyl; (4-tetrahydropyranyl)carboxyloxymethyl; and 1-(4-tetrahydropyranyl)carboxyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antigen-directed enzyme pro-drug therapy (ADEPT), gene-directed enzyme pro-drug therapy (GDEPT), and ligand-directed enzyme pro-drug therapy (LIDEPT), etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative. In one embodiment formula (I) does not include pro-drugs of the compounds of the formula (I) within its scope.

10 Advantages of Compounds of the Invention

The compounds of the formula (I) may have a number of advantages over prior art compounds.

Compounds of the invention may have particular advantage in one or more of the following aspects:

- (i) Superior selectivity versus the IKr (hERG) cardiac ion channel;
- (ii) Superior metabolic stability;
- (iii) Superior oral bioavailability; and
- (iv) Superior *in vivo* efficacy.

Superior selectivity versus the IKr (hERG) cardiac ion channel

In the late 1990s a number of drugs, approved by the US FDA, had to be withdrawn from sale in the US when it was discovered they were implicated in deaths caused by heart malfunction. It was subsequently found that a side effect of these drugs was the development of arrhythmias caused by the blocking of hERG channels in heart cells. The hERG channel is one of a family of potassium ion channels the first member of which was identified in the late 1980s in a mutant *Drosophila melanogaster* fruitfly (see Jan, L.Y. and Jan, Y.N. (1990). A Superfamily of Ion Channels. *Nature*, 345(6277):672). The biophysical properties of the hERG potassium ion channel are described in Sanguinetti, M.C., Jiang, C., Curran, M.E., and Keating, M.T. (1995). A Mechanistic Link Between an Inherited and an Acquired Cardiac Arrhythmia: HERG encodes the Ikr potassium channel. *Cell*, 81:299-307, and Trudeau, M.C., Warmke, J.W., Ganetzky, B., and Robertson, G.A. (1995). HERG, a Human Inward Rectifier in the Voltage-Gated Potassium Channel Family. *Science*, 269:92-95. Therefore, elimination of hERG blocking activity remains an important consideration in the development of any new drug.

It has been found that many compounds of the formula (I) have reduced hERG activity and/or a good separation between IAP activity and hERG activity (greater 'therapeutic window'). One method for measurement of hERG activity is the patch clamp electrophysiology method. Alternative methods for measurement of functional hERG activity include hERG binding assays, which can use commercially available membranes isolated from cells stably expressing the hERG channel or commercially available cell lines expressing the hERG channel.

Many compounds of the formula (I) have improved Cardiac Safety Index (CSI) [CSI = hERG IC₅₀ / C_{max}(unbound)] (Shultz et al, J. Med. Chem., 2011; Redfern et al, Cardiovasc. Res., 2003). This can be due to an increase in hERG IC₅₀ or a reduction in C_{max} required for efficacy (due to better IAP potency and/or PK).

The preferred compounds of formula (I) have reduced hERG ion channel blocking activity. Preferred compounds of the formula (I) have mean IC₅₀ values against hERG that are greater than 30 times, or greater than 40 times, or greater than 50 times the IC₅₀ values of the compounds in cellular proliferation assays. Preferred compounds of the formula (I) have mean IC₅₀ values against hERG that are greater than 5 µM, more particularly greater than 10 µM, and more preferably greater than 15 µM. Some compounds of the invention have mean IC₅₀ values against hERG that are greater than 30 µM or display % inhibition representative of such an IC₅₀ at concentrations of 1, 3, 10 or 30 µM. Some compounds of the invention have mean CSI of higher than minimum recommended value (30 fold).

Superior metabolic stability

The compounds of the formula (I) may have advantageous ADMET properties for example better metabolic stability (for example as determined with mouse liver microsomes), a better P450 profile and/or beneficial clearance (e.g. low clearance). These features could confer the advantage of having more drug available in the systemic circulation to reach the appropriate site of action to exert its therapeutic effect. Increased drug concentrations to exert pharmacological action in tumours potentially leads to improved efficacy which thereby allows reduced dosages to be administered. Thus, the compounds of formula (I) should exhibit reduced dosage requirements and should be more readily formulated and administered.

Many of the compounds of the formula (I) are advantageous in that they have different susceptibilities to P450 enzymes. For example, the preferred compounds of the formula (I) have IC₅₀ values of greater than 10 µM against each of the cytochrome P450 enzymes 1A2,

2C9, 2C19, 3A4 and 2D6 (in particular 3A4). In addition preferably the compounds are not P450 inhibitors nor substrates for P450 (i.e. not turned over by P450).

Superior oral bioavailability

- 5 Potentially the compounds of the invention have physiochemical properties suitable for oral exposure (oral exposure or AUC). In particular, compounds of the formula (I) may exhibit improved oral bioavailability. Oral bioavailability can be defined as the ratio (F) of the plasma exposure of a compound when dosed by the oral route to the plasma exposure of the compound when dosed by the intravenous (i.v.) route, expressed as a percentage.

10

Compounds having an oral bioavailability (F value) of greater than 30%, more preferably greater than 40%, are particularly advantageous in that they may be administered orally rather than, or as well as, by parenteral administration.

- 15 Superior *in vivo* efficacy

As a result of increased potency against XIAP and /or cIAP compounds of the invention may have increased *in vivo* efficacy in cancer cell lines and *in vivo* models.

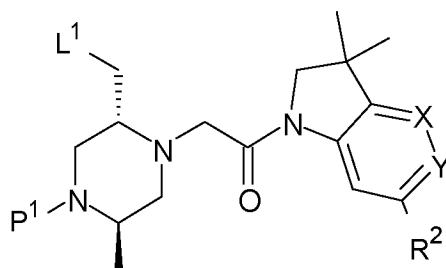
METHODS FOR THE PREPARATION OF COMPOUNDS OF FORMULA (I)

- 20 In this section, as in all other sections of this application unless the context indicates otherwise, references to formula (I) also include all other sub-groups and examples thereof as defined herein.

- Compounds of the formula (I) can be prepared in accordance with synthetic methods well
25 known to the skilled person.

According to a further aspect of the invention there is provided a process for preparing a compound of formula (I) as hereinbefore defined which comprises:

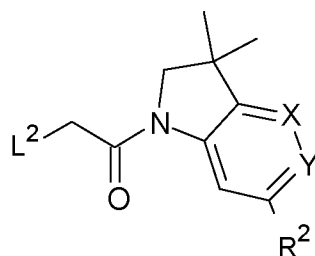
- 30 (a) (i) reacting a compound of formula (II):



(II)

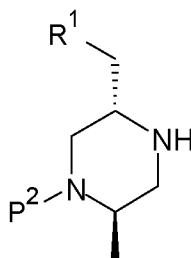
wherein R^2 , X and Y are as defined hereinbefore for compounds of formula (I), L^1 represents a suitable leaving group, such as a halogen atom (e.g. chlorine) and P^1 represents hydrogen or a suitable protecting group such as a tert-butyloxycarbonyl (tBoc) group, with a compound of formula R^1H or an optionally protected derivative thereof, followed by a deprotection reaction suitable to remove the P^1 protecting group and any other protecting groups as necessary; or

(ii) reacting a compound of formula (III):



(III)

wherein X, Y and R^2 are as defined hereinbefore for compounds of formula (I), and L^2 represents a suitable leaving group such as halogen (e.g. chlorine), with a compound of formula (IV):



(IV)

or an optionally protected derivative thereof; wherein R^1 is as defined hereinbefore for compounds of formula (I) and P^2 represents hydrogen or a suitable protecting group such as a tert-butyloxycarbonyl (tBoc) group, followed by a deprotection reaction suitable to remove the P^2 protecting group and any other protecting groups as necessary; and/or

(b) deprotection of a protected derivative of a compound of formula (I); and/or

(c) interconversion of a compound of formula (I) or protected derivative thereof to a further compound of formula (I) or protected derivative thereof; and

(d) optional formation of a pharmaceutically acceptable salt of a compound of formula (I).

Process (a)(i) typically comprises reacting a compound of formula (II) with a compound of formula R^1H optionally in the presence of a suitable additive such as potassium iodide and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile. Such a process may be carried out at ambient temperature or at elevated temperature, e.g. 70 °C.

Process (a)(ii) typically comprises reacting a compound of formula (III) with a compound of formula (IV), optionally in the presence of a suitable additive such as potassium iodide and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile.

Process (b) typically comprises any suitable deprotection reaction, the conditions of which will depend upon the nature of the protecting group. When the protecting group represents tBoc, such a deprotection reaction will typically comprise the use of a suitable acid in a suitable solvent. For example, the acid may suitably comprise trifluoroacetic acid or hydrogen chloride and the solvent may suitably comprise dichloromethane ethyl acetate, 1,4-dioxane, methanol or water. Optionally a mixture of solvents may be used, for example aqueous methanol or ethyl acetate / 1,4-dioxane.

Process (b) may be carried out in accordance with the procedures described herein as Preparation of Compounds of Formula (I), Methods 1 and 2.

It will be appreciated that, when the protecting group represents tBoc, deprotection using a suitable acid as described above may generate a compound of formula (I) as a pharmaceutically acceptable salt, which may be isolated directly. Alternatively, the compound of formula (I) may be isolated as the free base using methods well known in the art and thereafter optionally converted to a pharmaceutically acceptable salt according to process (d).

Process (c) typically comprises interconversion procedures known by one skilled in the art. For example, in compounds of formula (I), a first substituent may be converted by methods known by one skilled in the art into a second, alternative substituent. A wide range of well known functional group interconversions are known by a person skilled in the art for converting a precursor compound to a compound of formula I and are described in *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, 1992. For example possible metal catalysed functionalisations such as using organo-tin reagents (the Stille

reaction), Grignard reagents and reactions with nitrogen nucleophiles are described in 'Palladium Reagents and Catalysts' [Jiro Tsuji, Wiley, ISBN 0-470-85032-9] and Handbook of OrganoPalladium Chemistry for Organic Synthesis [Volume 1, Edited by Ei-ichi Negishi, Wiley, ISBN 0-471-31506-0].

5

Process (d) may be carried out by treatment of a compound of formula (I) in the free base form, dissolved in a suitable solvent, with a stoichiometric amount or an excess of a pharmaceutically acceptable organic or inorganic acid, then isolation of the resulting salt by methods well known in the art, e.g. evaporation of solvent or crystallisation.

10

If appropriate, the reactions previously described in processes (a), (b) and (c) are followed or preceded by one or more reactions known to the skilled of the art and are performed in an appropriate order to achieve the requisite substitutions on R¹ and R² defined above to afford other compounds of formula (I). Non-limiting examples of such reactions whose conditions

15 can be found in the literature include:

- protection of reactive functions,
- deprotection of reactive functions,
- halogenation,
- dehalogenation,

20

- dealkylation,
- alkylation and arylation of amine, aniline, alcohol and phenol,
- Mitsunobu reaction on hydroxyl groups,

- cycloaddition reactions on appropriate groups,
- reduction of nitro, esters, cyano, aldehydes,

25

- transition metal-catalyzed coupling reactions,
- acylation,

- sulfonylation/introduction of sulfonyl groups,
- saponification/hydrolysis of ester groups,
- amidification or transesterification of ester groups,

30

- esterification or amidification of carboxylic groups,
- halogen exchange,

- nucleophilic substitution with amine, thiol or alcohol,
- reductive amination,

- oxime formation on carbonyl and hydroxylamine groups,

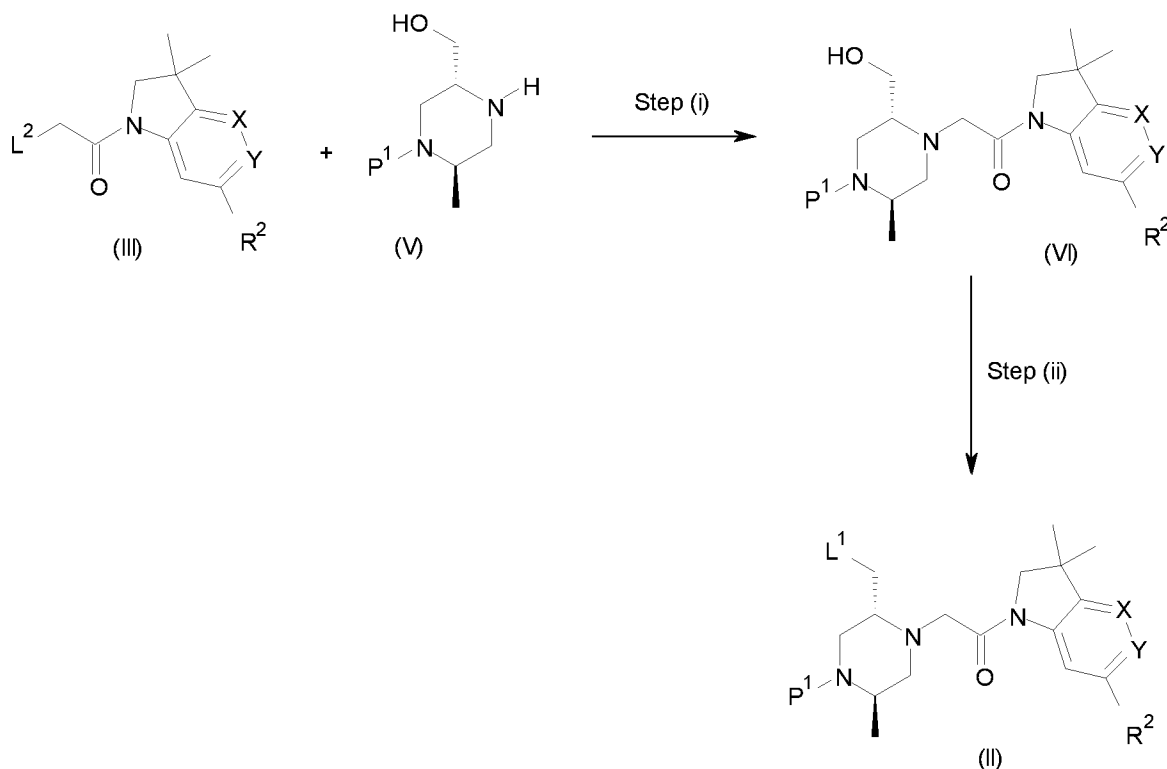
35

- S-oxidation,
- N-oxidation,
- salification.

Compounds of formula (II) may be prepared from compounds of formula (III) in accordance with the following Scheme 1:

5

Scheme 1



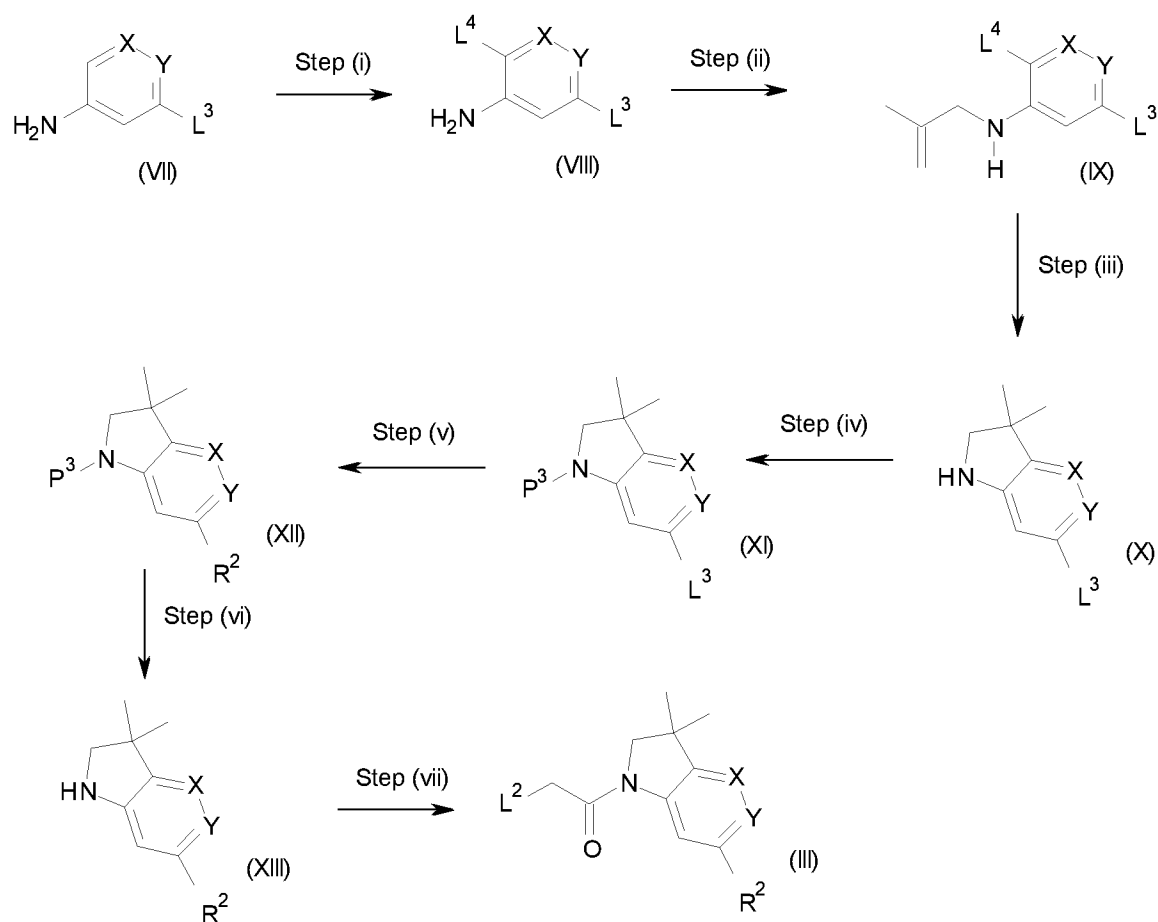
wherein X, Y, R², L¹, L² and P¹ are as defined hereinbefore.

10 Step (i) of Scheme 1 typically comprises reacting the compounds of formulae (III) and (V), optionally in the presence of a suitable additive such as potassium iodide and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile. An example of such a reaction is shown herein in Preparation 18.

15 When L¹ represents chlorine, step (ii) of Scheme 1 typically comprises reacting the compound of formula (VI) with a reagent capable of converting a hydroxyl group into a good leaving group, e.g. methylsulfonyl chloride in the presence of triethylamine. An example of such a reaction is shown herein in Preparation 19.

20 Compounds of formula (III) may be prepared in accordance with the following Scheme 2:

Scheme 2



wherein X, Y and R² are as defined hereinbefore for compounds of formula (III), L³ and L⁴ represent suitable leaving groups, such as a halogen atom, wherein L³ and L⁴ are chosen such that they have differential reactivity (for example L³ represents bromine and L⁴ represents iodine) and P³ represents a suitable protecting group, such as a tert-butyloxycarbonyl (tBoc) group.

When L³ represents bromine and L⁴ represents iodine, step (i) of Scheme 2 typically comprises reacting a compound of formula (VII) with an iodinating agent such as *N*-iodosuccinimide. An example of such a reaction is shown herein in Preparation 11.

Step (ii) of Scheme 2 typically comprises reacting the compound of formula (VIII) with 3-bromo-2-methylprop-1-ene in the presence of a base such as potassium tert-butoxide. An example of such a reaction is shown herein in Preparation 12.

Step (iii) of Scheme 2 typically comprises cyclisation of the compound of formula (IX) using a transition metal catalyst such as a palladium salt in the presence of base in a suitable solvent system. Suitable conditions for such a process may involve the use of tetrabutylammonium chloride, sodium formate, palladium acetate, triethylamine, water and dimethyl sulfoxide. An example of such a reaction is shown herein in Preparation 13.

When P^3 represents tBoc, step (iv) of Scheme 2 typically comprises reacting the compound of formula (X) with di-*tert*-butyldicarbonate in a suitable solvent such as THF in the presence of a base such as potassium *tert*-butoxide. An example of such a reaction is shown herein in Preparation 14.

Step (v) of Scheme 2 typically comprises reacting the compound of formula (XI) with a compound of formula R^2-M , wherein R^2 is as defined hereinbefore and M represents the residue of an organometallic species such that R^2-M represents a nucleophilic organometallic reagent such as an organozinc halide. An example of such a reaction is shown herein in Preparation 15. Alternatively, where L^3 represents a halogen such as bromine, the compound (XI) may be metallated using a suitable organometallic reagent such as butyllithium, ideally at low temperature in an inert solvent such as THF, and the resulting anion quenched with a suitable electrophile, for example a Weinreb amide such as N-methoxy-N-methylpropionamide, or an aldehyde such as 4-fluorobenzaldehyde, followed by subsequent functional group interconversion to give compounds of formula (XII).

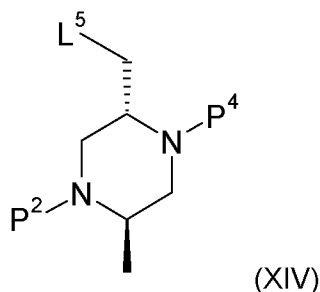
Step (vi) of Scheme 2 typically comprises a deprotection reaction of the compound of formula (XII). For example, when P^3 represent tBoc, step (vi) typically comprises treatment with hydrochloric acid. An example of such a reaction is shown herein in Preparation 16.

When L^2 represents a halogen such as chlorine, step (vii) of Scheme 2 typically comprises reacting the compound of formula (XIII) with a haloacetyl halide such as chloroacetyl chloride in the presence of acetonitrile. An example of such a reaction is shown herein in Preparation 17.

In the compounds (XII) and/or (XIII), functional group interconversions may optionally be carried out, for example to modify the group R^2 . Examples of such transformations are shown in Preparations 21 – 23.

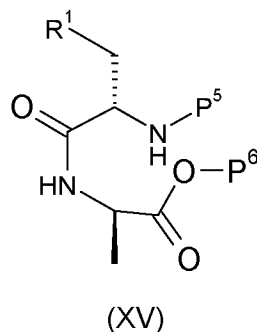
Compounds of formula (IV) or protected derivatives thereof as defined above may be prepared from compounds of formula (XIV)

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wherein P^2 is as defined hereinbefore, P^4 represents a protecting group, e.g. benzyl and L^5 represents a leaving group such as halogen (e.g. chloro); and a compound of formula R^1H or protected derivative thereof. Such a process may be carried out in a similar manner to that described for process (a)(i) above.

Compounds of formula (IV) or protected derivatives thereof may alternatively be prepared by cyclisation of a compound of formula (XV) for example where R^1 represents C-linked group, in particular a C-linked pyrazolyl

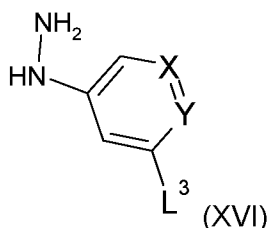


or an optionally protected derivative thereof; wherein R^1 is as defined hereinbefore and P^5 and P^6 independently represent hydrogen or a suitable protecting group, for example P^5 may represent tBoc or Cbz and P^6 may represent a C_{1-4} alkyl group; followed by reduction of the resulting diketopiperazine and protection to introduce the group P^2 . The cyclisation step in such a process may be effected using methods well known in the art for amide bond formation. In certain circumstances, cyclisation may proceed concomitantly on removal of protecting groups P^5 or P^6 . The reduction step may be carried out using a suitable reducing agent such as borane in a suitable solvent such as THF and re-protection to introduce the group P^5 may be effected using methods well known in the art.

Certain compounds of formula (XV) are known in the literature and/or may be prepared by coupling of two appropriately protected amino-acid derivatives using methods well known in the art for amide bond formation, for example using a procedure analogous to that described below in Preparation 28. A suitable sequence for the preparation of compounds (IV) and

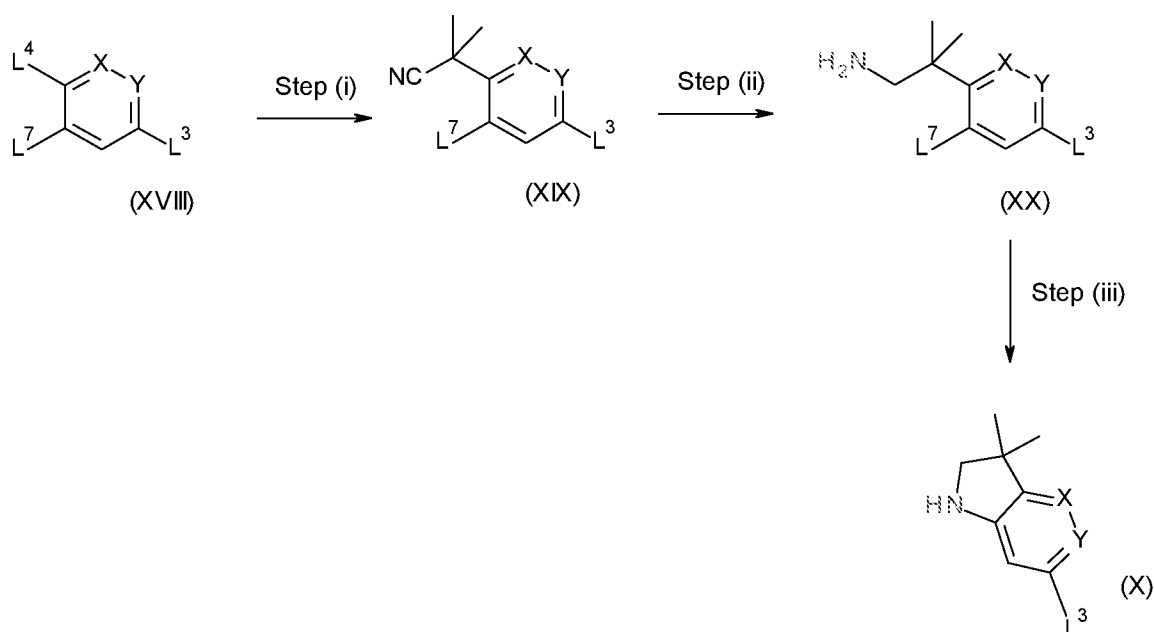
(XV) wherein R_1 represents C-linked pyrazolyl is shown below in Preparations 25 – 32 inclusive.

- 5 Compounds of formula (X) or (XIII) wherein X and Y both independently represent CH and CR^3 may be prepared by reaction of a compound of formula (XVI)



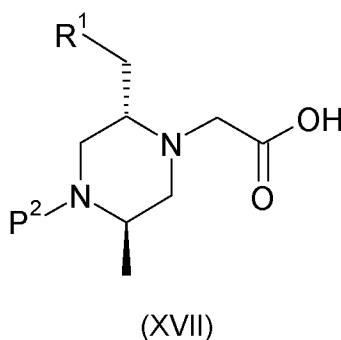
- wherein L^3 and R^3 are as defined above, with a compound of formula Me_2CHCHO , to form a hydrazone, then subsequent cyclisation to form the desired substituted indoline. Such a process is typically accomplished using acidic conditions, for example using acetic acid as solvent or using an appropriate acid in an inert solvent such as toluene. It will be appreciated that, for certain combinations of X and Y, this sequence will result in production of a mixture of regioisomers and that separation of these may be carried out by standard methods known by one skilled in the art e.g. column chromatography. Such a separation may be facilitated by N-acylation of the product from this process e.g. using chloroacetyl chloride or N-protection using, for example a tBoc protecting group after which the compound of formula (XIII) may optionally be re-generated by deprotection using standard conditions, e.g. for a tBoc protected compound, treatment with an appropriate acid such as HCl.
- 20 Alternatively, compounds of formula (X) as defined above wherein X is N and Y is CH may be prepared in accordance with the following Scheme 3:

Scheme 3



wherein L^3 and L^4 are as defined above and L^7 represents a suitable leaving group such as fluorine. Step (i) may be carried out by reaction with isobutyronitrile in the presence of a suitable base such as sodium bis(trimethylsilyl)amide in an appropriate solvent such as tetrahydrofuran. Step (ii) may be effected using a suitable reducing agent such as borane in a compatible solvent such as tetrahydrofuran. Cyclisation according to step (iii) may be carried out at elevated temperature in the presence of a suitable base such as potassium carbonate in an appropriate high boiling solvent such as 1-methyl-2-pyrrolidinone.

- Alternatively compounds of formula (I) can be synthesised by reacting a compound of formula (XVII):



or optionally protected derivative thereof; wherein R^1 and P^2 are as defined hereinbefore for compounds of formula (I), with a compound of formula (XIII) as defined hereinbefore, followed by a deprotection reaction suitable to remove the protecting group P^2 and any other protecting groups.

This reaction typically comprises reacting a compound of formula (XVII) with a compound of formula (XIII) in a suitable solvent and at a suitable temperature e.g. ambient temperature, in

the presence of a suitable base and a reagent capable of activating the carboxylic acid group present in the compound of formula (XVII). A suitable solvent should be inert toward the reagents used, for example dichloromethane. Examples of suitable bases are triethylamine and *N,N*-diisopropylethylamine (DIPEA). Examples of suitable activating reagents are
5 bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop), *O*-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU), 1,1'-carbonyldiimidazole, 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU). This process may optionally be carried out in the presence of a catalytic or stoichiometric amount of a
10 suitable co-activating reagent such as 1-hydroxybenzotriazole (HOBt) or 1-hydroxyazabenzotriazole (HOAt).

Compounds of formula (XVII) or optionally protected derivatives thereof may be prepared from compounds of formula (IV) or optionally protected derivatives thereof as defined above
15 by methods well known in the art, for example by reaction with an ester of a monohaloacetic acid such as benzyl bromoacetate in the presence of a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile; and subsequent ester hydrolysis (or optionally hydrogenolysis in the case of a benzyl ester).

It will be appreciated that certain compounds e.g. compounds of formulae (I), (II), (IV), (V), (VI), (XIV), (XV) and (XVII) can exist in different diastereomeric and/or enantiomeric forms and that processes for their preparation may make use of enantiomerically pure synthetic precursors. Alternatively racemic precursors may be used and the mixtures of diastereoisomers generated in these process may be separated by methods well known to
25 the person skilled in the art, for example using non-chiral or chiral preparative chromatography or resolution using diastereomeric derivatives: for example crystallisation of a salt formed with an enantiomerically pure acid such as L-tartaric acid; or enantiomer separation of a diastereomeric derivative formed by covalently linking a enantiomerically pure chiral auxiliary onto the compound, followed by separation using conventional methods such
30 as chiral chromatography. The aforementioned covalent linkage is then cleaved to generate the appropriate enantiomerically pure product.

The required intermediates, for example compounds of formula (V), (VII), (XVIII) and R^2 -M are either commercially available, known in the literature, prepared by methods analogous to
35 those in the literature or prepared by methods analogous to those described in the example experimental procedures below.

In a further embodiment the invention provides a novel intermediate. In one embodiment the invention provides a novel intermediate of formula (II) or (IV) or (V) or (VII) or (XVI) or (XVII).

Protecting Groups

5 In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

10

In particular the groups R^1 and R^2 may be synthesised in protected forms and the protecting groups removed to generate a compound of formula (I).

15

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a tetrahydropyranyl (THP) ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃).

20

An aldehyde or ketone group may be protected, for example, as an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is treated with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

25

An amine group may be protected, for example, as an amide (-NRCO-R) or a carbamate (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyl carbamate (-NHCO-OCH₂C₆H₅, -NH-Cbz or NH-Z); as a t-butyl carbamate (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propyl carbamate (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethyl carbamate (-NH-Fmoc), as a 6-nitroveratryl carbamate (-NH-Nvoc), as a 2-trimethylsilylethyl carbamate (-NH-Teoc), as a 2,2,2-trichloroethyl carbamate (-NH-Troc), as an allyl carbamate (-NH-Alloc), or as a 2-(phenylsulfonyl)ethyl carbamate (-NH-Psec).

30

For example, in compounds of formula II contains an amino group, the amino group can be protected by means of a protecting group as hereinbefore defined, one preferred group being the *tert*-butyloxycarbonyl (Boc) group while the additional functionalisation is introduced.

35

Where no subsequent modification of the amino group is required, the protecting group can be carried through the reaction sequence to give an N-protected form of a compound of the

formula (I) which can then be de-protected by standard methods (e.g. treatment with acid in the case of the Boc group) to give the compound of formula (I).

Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulfonyl (tosyl) and methanesulfonyl (mesyl) groups, benzyl groups such as a *para*-methoxybenzyl (PMB) group and tetrahydropyranyl (THP) groups.

A carboxylic acid group may be protected as an ester for example, as: a C₁₋₇ alkyl ester (e.g., a methyl ester; a *t*-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester; *para*-methoxybenzyl ester. A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

Isolation and purification of the compounds of the invention

The compounds of the invention can be isolated and purified according to standard techniques well known to the person skilled in the art and examples of such methods include chromatographic techniques such as column chromatography (e.g. flash chromatography) and HPLC. One technique of particular usefulness in purifying the compounds is preparative liquid chromatography using mass spectrometry as a means of detecting the purified compounds emerging from the chromatography column.

Preparative LC-MS is a standard and effective method used for the purification of small organic molecules such as the compounds described herein. The methods for the liquid chromatography (LC) and mass spectrometry (MS) can be varied to provide better separation of the crude materials and improved detection of the samples by MS. Optimisation of the preparative gradient LC method will involve varying columns, volatile eluents and modifiers, and gradients. Methods are well known in the art for optimising preparative LC-MS methods and then using them to purify compounds. Such methods are described in Rosentreter U, Huber U.; Optimal fraction collecting in preparative LC/MS; *J Comb Chem.*; 2004; 6(2), 159-64 and Leister W, Strauss K, Wisnoski D, Zhao Z, Lindsley C., Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries; *J Comb Chem.*; 2003; 5(3); 322-9. An example of such a system for purifying compounds via preparative LC-MS is described below in the Examples section of this application (under the heading "Mass Directed Purification LC-MS System").

Methods of recrystallisation of compounds of formula (I) and salt thereof can be carried out by methods well known to the skilled person – see for example (P. Heinrich Stahl (Editor),

Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Chapter 8, Publisher Wiley-VCH). Products obtained from an organic reaction are seldom pure when isolated directly from the reaction mixture. If the compound (or a salt thereof) is solid, it may be purified and/or crystallized by recrystallisation from a suitable solvent. A good recrystallisation solvent should dissolve a moderate quantity of the substance to be purified at elevated temperatures but only a small quantity of the substance at lower temperature. It should dissolve impurities readily at low temperatures or not at all. Finally, the solvent should be readily removed from the purified product. This usually means that it has a relatively low boiling point and a person skilled in the art will know recrystallising solvents for a particular substance, or if that information is not available, test several solvents. To get a good yield of purified material, the minimum amount of hot solvent to dissolve all the impure material is used. In practice, 3-5% more solvent than necessary is used so the solution is not saturated. If the impure compound contains an impurity which is insoluble in the solvent it may then be removed by filtration and then allowing the solution to crystallize. In addition, if the impure compound contains traces of coloured material that are not native to the compound, it may be removed by adding a small amount of decolorizing agent e.g. activating charcoal to the hot solution, filtering it and then allowing it to crystallize. Usually crystallization spontaneously occurs upon cooling the solution. If it is not, crystallization may be induced by cooling the solution below room temperature or by adding a single crystal of pure material (a seed crystal). Recrystallisation can also be carried out and/or the yield optimized by the use of an anti-solvent or co-solvent. In this case, the compound is dissolved in a suitable solvent at elevated temperature, filtered and then an additional solvent in which the required compound has low solubility is added to aid crystallization. The crystals are then typically isolated using vacuum filtration, washed and then dried, for example, in an oven or via desiccation.

Other examples of methods for purification include sublimation, which includes an heating step under vacuum for example using a cold finger, and crystallization from melt (Crystallization Technology Handbook 2nd Edition, edited by A. Mersmann, 2001).

BIOLOGICAL EFFECTS

The compounds of the invention, subgroups and examples thereof, are antagonists of inhibitor of apoptosis protein (IAP), and which may be useful in preventing or treating disease states or conditions described herein. In addition the compounds of the invention, and subgroups thereof, will be useful in preventing or treating diseases or condition mediated by IAP. References to the preventing or prophylaxis or treatment of a disease state or condition such as cancer include within their scope alleviating or reducing the incidence of cancer.

Thus, for example, it is envisaged that the compounds of the invention will be useful in alleviating or reducing the incidence of cancer.

- 5 The compounds of the present invention may be useful for the treatment of the adult population. The compounds of the present invention may be useful for the treatment of the pediatric population.

10 More particularly, the compounds of the formula (I) and sub-groups thereof are antagonists of IAP. For example, compounds of the invention have affinity against XIAP, cIAP1 and/or cIAP2, and in particular an IAP selected from XIAP and cIAP1.

Preferred compounds are compounds that have affinity for one or more IAP selected from XIAP, cIAP1 and cIAP2. Preferred compounds of the invention are those having IC₅₀ values
15 of less than 0.1 μ M.

The antagonist compounds of formula (I) are capable of binding to IAP and exhibiting potency for IAP. In one embodiment the antagonist compounds of formula (I) exhibit selectivity for one or more IAP over other IAP family members, and may be capable of
20 binding to and/or exhibiting affinity for XIAP and/or cIAP in preference to binding to and/or exhibiting affinity for other of the IAP family members.

In addition many of the compounds of the invention exhibit selectivity for the XIAP compared to cIAP or vice versa, selectivity for the cIAP compared to XIAP (in particular cIAP1), and
25 such compounds represent one embodiment of the invention. In particular compounds of the invention may have at least 10 times greater affinity against one or more IAP family member in particular XIAP, cIAP1 and/or cIAP2 than other IAP family members. This can be determined using the methods described herein. In a further embodiment compounds of the invention may have equivalent affinity for XIAP, cIAP1 and/or cIAP2, in particular equivalent
30 affinity (i.e. less than 10-fold difference in affinity) for XIAP and cIAP1.

Activity against XIAP and cIAP1 may be particularly advantageous. Antagonising XIAP and cIAP1 with equipotency should enable triggering of apoptosis via activation of caspase-8 and the switch away from pro-survival NF-kappaB signalling towards apoptosis; and potent
35 antagonism of XIAP will ensure that apoptosis is achieved before any inherent resistance mechanism is upregulated to block the process. On depletion of cIAP1 via autoubiquitination and proteasomal degradation there is a temporary upregulation of NF-kappaB signalling that

is responsible for expression of TNF-alpha in sensitive cell lines - this is also responsible for upregulation of anti-apoptotic factors such as cIAP2 and c-FLIP. Hence the need for potent XIAP antagonism to potentiate effector caspase activation and cell death, rather than allowing cIAP2-mediated resistance to build up. It is generally believed that toxicities that arise on dosing these compounds *in vivo* will arise from the temporary induction of NFkappaB signalling and resultant upregulation of pro-inflammatory cytokines, which is mediated solely by cIAP1/2 antagonism. Therefore dual potency should enable a therapeutic window to be achieved before dose-limiting toxicities are encountered.

IAP function in controlling programmed cell death has also been implicated in many diseases, including disorders associated with cell accumulation (e.g. cancer, autoimmune disorders, inflammation and restenosis), disorders where excessive apoptosis results in cell loss (e.g. stroke, heart failure, neurodegeneration such as Alzheimers' disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS, ischemia (stroke, myocardial infarction) and osteoporosis or treating autoimmune diseases such as multiple sclerosis (MS).

Therefore, it is also envisaged that the compounds of the invention may be useful in treating other conditions such as inflammation, hepatitis, ulcerative colitis, gastritis, autoimmunity, inflammation, restenosis, stroke, heart failure, neurodegenerative conditions such as Alzheimers' disease, Parkinson's disease, Huntington's disease, myotonic dystrophy, and amyotrophic lateral sclerosis, AIDS, ischemia such as traumatic brain injury, spinal cord injury, cerebral ischemia, cerebral ischemia/reperfusion (I/R) injury, acute and chronic CNS injury ischemia, stroke or myocardial infarction, degenerative diseases of the musculoskeletal system such as osteoporosis, autoimmune diseases such as multiple sclerosis (MS) and Type I diabetes, and eye diseases such as retinal degeneration which result from loss of control of programmed cell death.

As a consequence of their affinity for IAP, the compounds will be useful in providing a means of controlling programmed cell death. It is therefore anticipated that the compounds may prove useful in treating or preventing proliferative disorders such as cancers. In addition, the compounds of the invention may be useful in the treatment of diseases in which there is a disorder associated with cell accumulation or where excessive apoptosis results in cell loss.

Examples of cancers (and their benign counterparts) which may be treated (or inhibited) include, but are not limited to tumours of epithelial origin (adenomas and carcinomas of various types including adenocarcinomas, squamous carcinomas, transitional cell

carcinomas and other carcinomas) such as carcinomas of the bladder and urinary tract, breast, gastrointestinal tract (including the esophagus, stomach (gastric), small intestine, colon, rectum and anus), liver (hepatocellular carcinoma), gall bladder and biliary system, exocrine pancreas, kidney, lung (for example adenocarcinomas, small cell lung carcinomas, non-small cell lung carcinomas, bronchioalveolar carcinomas and mesotheliomas), head and neck (for example cancers of the tongue, buccal cavity, larynx, pharynx, nasopharynx, tonsil, salivary glands, nasal cavity and paranasal sinuses), ovary, fallopian tubes, peritoneum, vagina, vulva, penis, cervix, myometrium, endometrium, thyroid (for example thyroid follicular carcinoma), adrenal, prostate, skin and adnexae (for example melanoma, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, dysplastic naevus); haematological malignancies (i.e. leukemias, lymphomas) and premalignant haematological disorders and disorders of borderline malignancy including haematological malignancies and related conditions of lymphoid lineage (for example acute lymphocytic leukemia [ALL], chronic lymphocytic leukemia [CLL], B-cell lymphomas such as diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, T-cell lymphomas and leukaemias, natural killer [NK] cell lymphomas, Hodgkin's lymphomas, hairy cell leukaemia, monoclonal gammopathy of uncertain significance, plasmacytoma, multiple myeloma, and post-transplant lymphoproliferative disorders), and haematological malignancies and related conditions of myeloid lineage (for example acute myelogenous leukemia [AML], chronic myelogenous leukemia [CML], chronic myelomonocytic leukemia [CMML], hypereosinophilic syndrome, myeloproliferative disorders such as polycythaemia vera, essential thrombocythaemia and primary myelofibrosis, myeloproliferative syndrome, myelodysplastic syndrome, and promyelocytic leukemia); tumours of mesenchymal origin, for example sarcomas of soft tissue, bone or cartilage such as osteosarcomas, fibrosarcomas, chondrosarcomas, rhabdomyosarcomas, leiomyosarcomas, liposarcomas, angiosarcomas, Kaposi's sarcoma, Ewing's sarcoma, synovial sarcomas, epithelioid sarcomas, gastrointestinal stromal tumours, benign and malignant histiocytomas, and dermatofibrosarcoma protuberans; tumours of the central or peripheral nervous system (for example astrocytomas, gliomas and glioblastomas, meningiomas, ependymomas, pineal tumours and schwannomas); endocrine tumours (for example pituitary tumours, adrenal tumours, islet cell tumours, parathyroid tumours, carcinoid tumours and medullary carcinoma of the thyroid); ocular and adnexal tumours (for example retinoblastoma); germ cell and trophoblastic tumours (for example teratomas, seminomas, dysgerminomas, hydatidiform moles and choriocarcinomas); and paediatric and embryonal tumours (for example medulloblastoma, neuroblastoma, Wilms tumour, and primitive neuroectodermal tumours); or syndromes, congenital or otherwise, which leave the patient susceptible to malignancy (for example Xeroderma Pigmentosum).

Growth of cells is a closely controlled function. Cancer, a condition of abnormal cell growth, results when cells replicate in an uncontrolled manner (increasing in number), uncontrollably grow (getting larger) and/or experience reduced cell death by apoptosis (programmed cell death), necrosis, or anoikis. In one embodiment abnormal cell growth is selected from uncontrolled cell proliferation, excessive cell growth or reduced programmed cell death. In particular, the condition or disease of abnormal cell growth is a cancer. Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth (i.e. uncontrolled and/or rapid cell growth), the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

In one embodiment the haematological malignancies is leukaemia. In another embodiment the haematological malignancies is lymphoma.

Many diseases are characterized by persistent and unregulated angiogenesis. Chronic proliferative diseases are often accompanied by profound angiogenesis, which can contribute to or maintain an inflammatory and/or proliferative state, or which leads to tissue destruction through the invasive proliferation of blood vessels. Tumour growth and metastasis have been found to be angiogenesis-dependent. Compounds of the invention may therefore be useful in preventing and disrupting initiation of tumour angiogenesis. In particular, the compounds of the invention may be useful in the treatment of metastasis and metastatic cancers.

Metastasis or metastatic disease is the spread of a disease from one organ or part to another non-adjacent organ or part. The cancers which can be treated by the compounds of the invention include primary tumours (i.e. cancer cells at the originating site), local invasion (cancer cells which penetrate and infiltrate surrounding normal tissues in the local area), and metastatic (or secondary) tumours i.e. tumours that have formed from malignant cells which have circulated through the bloodstream (haematogenous spread) or via lymphatics or across body cavities (trans-coelomic) to other sites and tissues in the body.

Particular cancers include hepatocellular carcinoma, melanoma, oesophageal, renal, colon, colorectal, lung e.g. mesothelioma or lung adenocarcinoma, breast, bladder, gastrointestinal, ovarian and prostate cancers.

Particular cancers include renal, melanoma, colon, lung, breast, ovarian and prostate cancers. In one embodiment the cancer is selected from melanoma, colon, breast and

ovarian. In one embodiment the cancer is melanoma. In one embodiment the cancer is inflammatory breast cancer.

A further aspect of the invention includes a compound of the invention for use in the prophylaxis or treatment of cancer in a patient selected from a sub-population possessing cancers with a high inflammatory component. Such cancers are also known as "inflammatory phenotype" and include tumours with elevated cytokine signalling (e.g. TNF). In one embodiment the cancer is an inflammatory tumour, for example, melanoma, colon, breast and ovarian, in particular, melanoma.

In one embodiment the disease to be treated is leukaemia, such as acute and chronic leukaemias, acute myeloid leukaemia (AML), and chronic lymphocytic leukaemia (CLL). In one embodiment the leukaemia is refractory DLBCL.

In one embodiment the cancer is mesothelioma including malignant peritoneal mesothelioma or malignant pleural mesothelioma.

Certain cancers are resistant to treatment with particular drugs. This can be due to the type of the tumour (most common epithelial malignancies are inherently chemoresistant) or resistance can arise spontaneously as the disease progresses or as a result of treatment. In this regard, references to mesothelioma includes mesothelioma with resistance towards topoisomerase poisons, alkylating agents, antitubulines, antifolates, platinum compounds and radiation therapy, in particular cisplatin-resistant mesothelioma. Similarly references to multiple myeloma includes bortezomib-sensitive multiple myeloma or refractory multiple myeloma and references to chronic myelogenous leukemia includes imatinib-sensitive chronic myelogenous leukemia and refractory chronic myelogenous leukemia.

The cancers may be cancers which are sensitive to antagonism of any one or more IAP selected from XIAP, cIAP1, cIAP2, NAIP, ILP2, ML-IAP, survivin and BRUCE, more preferably XIAP, cIAP1, cIAP2, ML-IAP, most preferably XIAP.

It is further envisaged that the compounds of the invention, and in particular those compounds having IAP affinity will be particularly useful in the treatment or prevention of cancers of a type associated with or characterised by the presence of elevated levels of IAP or amplification of 11q22 for example the cancers referred to in this context in the introductory section of this application.

Elevated levels of IAP due to overexpression of IAP is found in many cancers and is associated with a poor prognosis. In addition, cancers with the 11q22 amplification may also be sensitive to an IAP antagonist. The elevated levels of IAP and amplification of 11q22 can be identified by the techniques outlined herein. Whether a particular cancer is one which is sensitive to IAP function, may be determined by a method as set out in the section headed "Methods of Diagnosis".

A further aspect provides the use of a compound for the manufacture of a medicament for the treatment of a disease or condition as described herein, in particular cancer.

The compounds may also be useful in the treatment of tumour growth, pathogenesis, resistance to chemo- and radio-therapy by sensitising cells to chemotherapy and as an anti-metastatic agent.

Therapeutic anticancer interventions of all types necessarily increase the stresses imposed on the target tumour cells. In mitigating the deleterious effects of such stresses, IAPs are directly implicated in resisting the effects of cancer drugs and treatment regimens. Thus, antagonists of IAP represent a class of chemotherapeutics with the potential for: (i) sensitizing malignant cells to anticancer drugs and/or treatments; (ii) alleviating or reducing the incidence of resistance to anticancer drugs and/or treatments; (iii) reversing resistance to anticancer drugs and/or treatments; (iv) potentiating the activity of anticancer drugs and/or treatments; (v) delaying or preventing the onset of resistance to anticancer drugs and/or treatments.

As a consequence of their affinity for IAP, the compounds will be useful in providing a means of controlling programmed cell death. Therefore, it is also envisaged that the compounds of the invention may be useful in treating other conditions such as inflammatory disorders such as hepatitis, ulcerative colitis, and gastritis; neurodegenerative conditions such as Alzheimers' disease, Parkinson's disease, Huntington's disease, myotonic dystrophy, and amyotrophic lateral sclerosis; AIDS, ischemia such as restenosis, traumatic brain injury, spinal cord injury, cerebral ischemia, cerebral ischemia/reperfusion (I/R) injury, acute and chronic CNS injury ischemia, stroke or myocardial infarction; degenerative diseases of the musculoskeletal system such as osteoporosis; autoimmune diseases such as multiple sclerosis (MS) and Type I diabetes, and eye diseases such as retinal degeneration.

The affinity of the compounds of the invention as antagonists of IAP can be measured using the biological and biophysical assays set forth in the examples herein and the level of affinity

exhibited by a given compound can be defined in terms of the IC_{50} value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than $1\mu M$, more preferably less than $0.1\mu M$.

- 5 In one embodiment the invention provides a compound for use in the treatment of a disease or condition which is mediated by IAP (e.g. XIAP and/or cIAP e.g. cIAP1). In a further embodiment the invention provides a compound for use in the treatment of a disease or condition which overexpresses IAP (e.g. XIAP and/or cIAP e.g. cIAP1).
- 10 In one embodiment the invention provides a compound for use in the treatment of a disease or condition which is mediated by IAP, wherein the compound is an antagonist of IAP having an IC_{50} of less than $50\mu M$ in at least one assay (e.g. a displacement binding) against an IAP. In particular the IAP is XIAP, cIAP1 and/or cIAP2. In a further embodiment the disease or condition which is mediated by IAP is a cancer which is characterised by overexpression of at
- 15 least one IAP and/or amplification of 11q22.

In one embodiment the invention provides a compound for use in the treatment of a disease or condition which is mediated by IAP, wherein the compound has an IC_{50} of less than $10\mu M$ against at least one IAP in an assay (e.g. displacement binding) against IAP.

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A further aspect provides the use of a compound for the manufacture of a medicament for the treatment of a disease or condition which is mediated by IAP, wherein the compound is an antagonist of IAP having an IC_{50} of less than $50\mu M$ against at least one IAP in an assay (e.g. a displacement binding).

25

METHODS OF DIAGNOSIS

- Prior to administration of a compound of the formula (I), a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having affinity for IAP. The term
- 30 'patient' includes human and veterinary subjects.

- For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which
- 35 leads to up-regulation of the levels of IAP or to sensitisation of a pathway to normal IAP function or to upregulation of a biochemical pathway downstream of IAP activation.

Examples of such abnormalities that result in activation or sensitisation of the IAP, loss of, or inhibition of apoptotic pathways, up-regulation of the receptors or ligands, cytogenetic aberrations or presence of mutant variants of the receptors or ligands. Tumours with up-regulation of IAP, in particular over-expression of IAP, may be particularly sensitive to IAP antagonists. For example, overexpression of XIAP and cIAP has been identified in a range of cancers as discussed in the Background section.

Amplification of chromosome 11q22 has been detected in cell lines and primary tumours from squamous cell carcinomas of the esophagus (Imoto et al., 2001) and cervix (Imoto et al., 2002) as well as in primary lung cancers/cell lines (Dai et al., 2003).

Immunohistochemistry and western blot analysis have identified cIAP1 and cIAP2 as potential oncogenes in this region as both are overexpressed in cancers in which this rare amplification arises.

The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies), cytogenetic aberration and increased expression by a transcriptional effect. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of IAP. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify presence of mutations of IAP or 11q22 amplification. The term marker also includes markers which are characteristic of up regulation of IAP, including protein levels, protein state and mRNA levels of the aforementioned proteins.

The diagnostic tests and screens are typically conducted on a biological sample (i.e. body tissue or body fluids) selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), cerebrospinal fluid, plasma, serum, saliva, stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, buccal smears, skin biopsy or urine.

Methods of identification and analysis of cytogenetic aberration, genetic amplification, mutations and up-regulation of proteins are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or *in situ* hybridization such as fluorescence *in situ* hybridization (FISH).

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of PCR

amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. *et al.*, eds. (2004) *Current Protocols in Molecular Biology*, John Wiley & Sons Inc., or Innis, M.A. *et al.*, eds. (1990) *PCR Protocols: a guide to methods and applications*, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook *et al.*, (2001), 3rd Ed, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference.

An example of an *in situ* hybridisation technique for assessing mRNA expression would be fluorescence *in situ* hybridisation (FISH) (see Angerer (1987) *Meth. Enzymol.*, 152: 649).

Generally, *in situ* hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labelled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F.M. *et al.*, eds. (2004) *Current Protocols in Molecular Biology*, John Wiley & Sons Inc and *Fluorescence In Situ Hybridization: Technical Overview* by John M. S. Bartlett in *Molecular Diagnosis of Cancer, Methods and Protocols*, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: *Methods in Molecular Medicine*.

Methods for gene expression profiling are described by (DePrimo *et al.* (2003), *BMC Cancer*, 3:3). Briefly, the protocol is as follows: double-stranded cDNA is synthesized from total RNA using a (dT)24 oligomer for priming first-strand cDNA synthesis, followed by second strand cDNA synthesis with random hexamer primers. The double-stranded cDNA is used as a template for *in vitro* transcription of cRNA using biotinylated ribonucleotides. cRNA is chemically fragmented according to protocols described by Affymetrix (Santa Clara, CA, USA), and then hybridized overnight on Human Genome Arrays.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtitre plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques for detection of upregulation of IAP, detection of IAP variants or mutants, or detection of 11q22 amplification could be applicable in the present case.

Abnormal levels of proteins such as IAP can be measured using standard protein assays, for example, those assays described herein. Elevated levels or overexpression could also be detected in a tissue sample, for example, a tumour tissue by measuring the protein levels with an assay such as that from Chemicon International. The protein of interest would be immunoprecipitated from the sample lysate and its levels measured.

Alternative methods for the measurement of the over expression or elevation of IAPs including the isoforms thereof, include the measurement of microvessel density. This can for example be measured using methods described by Orre and Rogers (Int J Cancer (1999), 84(2), 101-8). Assay methods also include the use of markers.

Therefore all of these techniques could also be used to identify tumours particularly suitable for treatment with the compounds of the invention.

Therefore in a further aspect of the invention includes use of a compound according to the invention for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having affinity for IAP (i.e. an IAP antagonist).

Another aspect of the invention includes a compound of the invention for use in the prophylaxis or treatment of cancer in a patient selected from a sub-population possessing overexpression of one or more of the IAP family members (e.g. cIAP and/or XIAP).

Another aspect of the invention includes a compound of the invention for use in the prophylaxis or treatment of cancer in a patient selected as possessing a cytogenetic aberration that results in overexpression of IAPs, for example, a patient selected as possessing the 11q22 amplification.

MRI determination of vessel normalization (e.g. using MRI gradient echo, spin echo, and contrast enhancement to measure blood volume, relative vessel size, and vascular permeability) in combination with circulating biomarkers may also be used to identify for treatment with a compound of the invention.

Thus a further aspect of the invention is a method for the diagnosis and treatment of a disease state or condition mediated by a IAP, which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having affinity for IAP; and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of formula (I) and sub-groups or examples thereof as defined herein.

PHARMACEUTICAL FORMULATIONS

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising (e.g. admixing) at least one compound of formula (I) (and sub-groups thereof as defined herein), together with one or more pharmaceutically acceptable excipients and optionally other therapeutic or prophylactic agents, as described herein.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents, fillers or bulking agents, granulating agents, coating agents, release-controlling agents, binding agents, disintegrants, lubricating agents, preservatives, antioxidants, buffering agents, suspending agents, thickening agents, flavouring agents, sweeteners, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions. Examples of excipients for various types of pharmaceutical compositions are set out in more detail below.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a

reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump or syringe driver.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, co-solvents, surface active agents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, *inter alia*, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended recipient. Pharmaceutical formulations for parenteral administration may also take the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents (R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230).

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules, vials and prefilled syringes, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

The pharmaceutical formulation can be prepared by lyophilising a compound of formula (I), or sub-groups thereof. Lyophilisation refers to the procedure of freeze-drying a composition. Freeze-drying and lyophilisation are therefore used herein as synonyms.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Pharmaceutical compositions of the present invention for parenteral injection can also
5 comprise pharmaceutically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use.

Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles
10 include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as sunflower oil, safflower oil, corn oil or olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of thickening or coating materials such as lecithin, by the maintenance of the required particle size in the case of
15 dispersions, and by the use of surfactants.

The compositions of the present invention may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal
20 agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include agents to adjust tonicity such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

25 In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion. For intravenous administration, the solution can be dosed as is, or can be injected into an infusion bag (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

30 In another preferred embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or
35 uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated. Coatings may act either as a protective film (e.g. a polymer, wax or varnish) or as a mechanism for controlling drug release or for aesthetic or identification purposes. The coating (e.g. a Eudragit TM type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum, duodenum, jejunum or colon.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to release the compound in a controlled manner in the gastrointestinal tract. Alternatively the drug can be presented in a polymer coating e.g. a polymethacrylate polymer coating, which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. In another alternative, the coating can be designed to disintegrate under microbial

action in the gut. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations (for example formulations based on ion exchange resins) may be prepared in accordance with methods well known to those skilled in the art.

The compound of formula (I) may be formulated with a carrier and administered in the form of nanoparticles, the increased surface area of the nanoparticles assisting their absorption. In addition, nanoparticles offer the possibility of direct penetration into the cell. Nanoparticle drug delivery systems are described in "Nanoparticle Technology for Drug Delivery", edited by Ram B Gupta and Uday B. Kompella, Informa Healthcare, ISBN 9781574448573, published 13th March 2006. Nanoparticles for drug delivery are also described in J. Control. Release, 2003, 91 (1-2), 167-172, and in Sinha *et al.*, Mol. Cancer Ther. August 1, (2006) 5, 1909.

The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient or combination of excipients. Preferably, the compositions comprise from approximately 20% (w/w) to approximately 90%,% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically acceptable excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, tablets or capsules.

The pharmaceutically acceptable excipient(s) can be selected according to the desired physical form of the formulation and can, for example, be selected from diluents (e.g solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), disintegrants, buffering agents, lubricants, flow aids, release controlling (e.g. release retarding or delaying polymers or waxes) agents, binders, granulating agents, pigments, plasticizers, antioxidants, preservatives, flavouring agents, taste masking agents, tonicity adjusting agents and coating agents.

The skilled person will have the expertise to select the appropriate amounts of ingredients for use in the formulations. For example tablets and capsules typically contain 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents

(depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragee cores or capsules. It is also possible for them to be incorporated into a polymer or waxy matrix that allow the active ingredients to diffuse or be released in measured amounts.

The compounds of the invention can also be formulated as solid dispersions. Solid dispersions are homogeneous extremely fine disperse phases of two or more solids. Solid solutions (molecularly disperse systems), one type of solid dispersion, are well known for use in pharmaceutical technology (see (Chiou and Riegelman, J. Pharm. Sci., 60, 1281-1300 (1971)) and are useful in increasing dissolution rates and increasing the bioavailability of poorly water-soluble drugs.

This invention also provides solid dosage forms comprising the solid solution described above. Solid dosage forms include tablets, capsules, chewable tablets and dispersible or effervescent tablets. Known excipients can be blended with the solid solution to provide the desired dosage form. For example, a capsule can contain the solid solution blended with (a) a disintegrant and a lubricant, or (b) a disintegrant, a lubricant and a surfactant. In addition a capsule can contain a bulking agent, such as lactose or microcrystalline cellulose. A tablet can contain the solid solution blended with at least one disintegrant, a lubricant, a surfactant, a bulking agent and a glidant. A chewable tablet can contain the solid solution blended with a bulking agent, a lubricant, and if desired an additional sweetening agent (such as an artificial sweetener), and suitable flavours. Solid solutions may also be formed by spraying solutions of drug and a suitable polymer onto the surface of inert carriers such as sugar beads ('non-pareils'). These beads can subsequently be filled into capsules or compressed into tablets.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

Compositions for topical use and nasal delivery include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound. Solutions of the active compound may also be used for rectal administration.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administered in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the formula (I) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

METHODS OF TREATMENT

- 5 The compounds of the formula (I) and sub-groups as defined herein may be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by IAP. Thus, according to a further aspect of the invention there is provided a method of treating a disease state or condition mediated by IAP, such as an XIAP and/or cIAP which comprises administering to a subject in need thereof a compound of formula (I) as described herein.
- 10 According to a further aspect of the invention there is provided a method of treating a disease state or condition which overexpresses IAP, such as an XIAP and/or cIAP which comprises administering to a subject in need thereof a compound of formula (I) as described herein. Examples of such disease states and conditions are set out above, and in particular include cancer.
- 15 The compounds are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.
- The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for
- 20 example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.
- 25 The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a continuous manner or in a manner that provides intermittent dosing (e.g. a pulsatile manner).
- 30 A typical daily dose of the compound of formula (I) can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 5 nanograms to 25 milligrams per kilogram of bodyweight, and more usually 10 nanograms to 15 milligrams per kilogram (e.g. 10 nanograms to 10 milligrams, and more typically 1 microgram per kilogram to 20 milligrams per kilogram, for example 1 microgram to 10 milligrams per kilogram) per kilogram
- 35 of bodyweight although higher or lower doses may be administered where required. The compound of the formula (I) can be administered on a daily basis or on a repeat basis every 2, or 3, or 4, or 5, or 6, or 7, or 10 or 14, or 21, or 28 days for example.

The compounds of the invention may be administered orally in a range of doses, for example 1 to 1500 mg, 2 to 800 mg, or 5 to 500 mg, e.g. 2 to 200 mg or 10 to 1000 mg, particular examples of doses including 10, 20, 50 and 80 mg. The compound may be administered once or more than once each day. The compound can be administered continuously (i.e. taken every day without a break for the duration of the treatment regimen). Alternatively, the compound can be administered intermittently (i.e. taken continuously for a given period such as a week, then discontinued for a period such as a week and then taken continuously for another period such as a week and so on throughout the duration of the treatment regimen).

Examples of treatment regimens involving intermittent administration include regimens wherein administration is in cycles of one week on, one week off; or two weeks on, one week off; or three weeks on, one week off; or two weeks on, two weeks off; or four weeks on two weeks off; or one week on three weeks off - for one or more cycles, e.g. 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more cycles.

In one particular dosing schedule, a patient will be given an infusion of a compound of the formula (I) for periods of one hour daily for up to ten days in particular up to five days for one week, and the treatment repeated at a desired interval such as two to four weeks, in particular every three weeks.

More particularly, a patient may be given an infusion of a compound of the formula (I) for periods of one hour daily for 5 days and the treatment repeated every three weeks.

In another particular dosing schedule, a patient is given an infusion over 30 minutes to 1 hour followed by maintenance infusions of variable duration, for example 1 to 5 hours, e.g. 3 hours.

In a further particular dosing schedule, a patient is given a continuous infusion for a period of 12 hours to 5 days, in particular a continuous infusion of 24 hours to 72 hours.

Ultimately, however, the quantity of compound administered and the type of composition used will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

It has been discovered that IAP antagonists can be used as a single agent or in combination with other anticancer agents. For example, it may be beneficial to combine an antagonist that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development.

Combination experiments can be performed, for example, as described in Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regulat* 1984;22: 27–55.

- 5 The compounds as defined herein can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds (or therapies) for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or
- 10 more other medicinal agents, more particularly, with other anti-cancer agents or adjuvants (supporting agents in the therapy) in cancer therapy. Examples of other therapeutic agents or treatments that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include but are not limited to:
- Topoisomerase I inhibitors;
 - 15 • Antimetabolites;
 - Tubulin targeting agents;
 - DNA binder and topoisomerase II inhibitors;
 - Alkylating Agents;
 - Monoclonal Antibodies;
 - 20 • Anti-Hormones;
 - Signal Transduction Inhibitors;
 - Proteasome Inhibitors;
 - DNA methyl transferases;
 - Cytokines and retinoids;
 - 25 • Chromatin targeted therapies;
 - Radiotherapy; and
 - Other therapeutic or prophylactic agents.

Particular examples of anti-cancer agents or adjuvants (or salts thereof), include but are not

30 limited to any of the agents selected from groups (i)-(xlvi), and optionally group (xlvii), below:

- (i) Platinum compounds, for example cisplatin (optionally combined with amifostine), carboplatin or oxaliplatin;
- (ii) Taxane compounds, for example paclitaxel, paclitaxel protein bound particles (AbraxaneTM), docetaxel, cabazitaxel or larotaxel;
- 35 (iii) Topoisomerase I inhibitors, for example camptothecin compounds, for example camptothecin, irinotecan(CPT11), SN-38, or topotecan;

- (iv) Topoisomerase II inhibitors, for example anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, or teniposide;
- (v) Vinca alkaloids, for example vinblastine, vincristine, liposomal vincristine (Onco-TCS), vinorelbine, vindesine, vinflunine or vinvesir;
- 5 (vi) Nucleoside derivatives, for example 5-fluorouracil (5-FU, optionally in combination with leucovorin), gemcitabine, capecitabine, tegafur, UFT, S1, cladribine, cytarabine (Ara-C, cytosine arabinoside), fludarabine, clofarabine, or nelarabine;
- (vii) Antimetabolites, for example clofarabine, aminopterin, or methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine, thiopurine, 6-mercaptopurine, or
10 hydroxyurea (hydroxycarbamide);
- (viii) Alkylating agents, such as nitrogen mustards or nitrosourea, for example cyclophosphamide, chlorambucil, carmustine (BCNU), bendamustine, thiotepa, melphalan, treosulfan, lomustine (CCNU), altretamine, busulfan, dacarbazine, estramustine, fotemustine, ifosfamide (optionally in combination with mesna),
15 pipobroman, procarbazine, streptozocin, temozolomide, uracil, mechlorethamine, methylcyclohexylchloroethylnitrosourea, or nimustine (ACNU);
- (ix) Anthracyclines, anthracenediones and related drugs, for example daunorubicin, doxorubicin (optionally in combination with dexrazoxane), liposomal formulations of doxorubicin (eg. Caelyx™, Myocet™, Doxil™), idarubicin, mitoxantrone, epirubicin,
20 amsacrine, or valrubicin;
- (x) Epothilones, for example ixabepilone, patupilone, BMS-310705, KOS-862 and ZK-EPO, epothilone A, epothilone B, desoxyepothilone B (also known as epothilone D or KOS-862), aza-epothilone B (also known as BMS-247550), aulimalide, isolaulimalide, or luetherobin;
- 25 (xi) DNA methyl transferase inhibitors, for example temozolomide, azacytidine or decitabine;
- (xii) Antifolates, for example methotrexate, pemetrexed disodium, or raltitrexed;
- (xiii) Cytotoxic antibiotics, for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, or mithramycin;
- (xiv) Tubulin-binding agents, for example combrestatin, colchicines or nocodazole;
- 30 (xv) Signal Transduction inhibitors such as Kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, VEGFR (vascular endothelial growth factor receptor) inhibitors, PDGFR (platelet-derived growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), Raf inhibitors, mTOR inhibitors for example imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, dovotinib, axitinib, nilotinib, vandetanib, vatalinib,
35 pazopanib, sorafenib, sunitinib, temsirolimus, everolimus (RAD 001), or vemurafenib (PLX4032/RG7204);

- (xvi) Aurora kinase inhibitors for example AT9283, barasertib (AZD1152), TAK-901, MK0457 (VX680), cenisertib (R-763), danusertib (PHA-739358), alisertib (MLN-8237), or MP-470;
- (xvii) CDK inhibitors for example AT7519, roscovitine, seliciclib, alvocidib (flavopiridol),
 5 dinaciclib (SCH-727965), 7-hydroxy-staurosporine (UCN-01), JNJ-7706621, BMS-387032 (a.k.a. SNS-032), PHA533533, PD332991, ZK-304709, or AZD-5438;
- (xviii) PKA/B inhibitors and PKB (akt) pathway inhibitors for example AT13148, AZ-5363, Semaphore, SF1126 and MTOR inhibitors such as rapamycin analogues, AP23841 and AP23573, calmodulin inhibitors (forkhead translocation inhibitors), API-2/TCN
 10 (tricitiribine), RX-0201, enzastaurin HCl (LY317615), NL-71-101, SR-13668, PX-316, or KRX-0401 (perifosine/ NSC 639966);
- (xix) Hsp90 inhibitors for example AT13387, herbimycin, geldanamycin (GA), 17-allylamino-17-desmethoxygeldanamycin (17-AAG) e.g. NSC-330507, Kos-953 and CNF-1010, 17-dimethylaminoethylamino-17-demethoxygeldanamycin hydrochloride (17-DMAG) e.g.
 15 NSC-707545 and Kos-1022, NVP-AUY922 (VER-52296), NVP-BEP800, CNF-2024 (BIIB-021 an oral purine), ganetespib (STA-9090), SNX-5422 (SC-102112) or IPI-504;
- (xx) Monoclonal Antibodies (unconjugated or conjugated to radioisotopes, toxins or other agents), antibody derivatives and related agents, such as anti-CD, anti-VEGFR, anti-HER2 or anti-EGFR antibodies, for example rituximab (CD20), ofatumumab (CD20),
 20 ibritumomab tiuxetan (CD20), GA101 (CD20), tositumomab (CD20), epratuzumab (CD22), lintuzumab (CD33), gemtuzumab ozogamicin (CD33), alemtuzumab (CD52), galiximab (CD80), trastuzumab (HER2 antibody), pertuzumab (HER2), trastuzumab-DM1 (HER2), ertumaxomab (HER2 and CD3), cetuximab (EGFR), panitumumab (EGFR), necitumumab (EGFR), nimotuzumab (EGFR), bevacizumab (VEGF),
 25 ipilimumab (CTLA4), catumaxumab (EpCAM and CD3), abagovomab (CA125), farletuzumab (folate receptor), elotuzumab (CS1), denosumab (RANK ligand), figitumumab (IGF1R), CP751,871 (IGF1R), mapatumumab (TRAIL receptor), metMAB (met), mitumomab (GD3 ganglioside), naptumomab estafenatox (5T4), or siltuximab (IL6);
- (xxi) Estrogen receptor antagonists or selective estrogen receptor modulators (SERMs) or inhibitors of estrogen synthesis, for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, or raloxifene;
- (xxii) Aromatase inhibitors and related drugs, such as exemestane, anastrozole, letrozole, testolactone aminoglutethimide, mitotane or vorozole;
- (xxiii) Antiandrogens (i.e. androgen receptor antagonists) and related agents for example
 35 bicalutamide, nilutamide, flutamide, cyproterone, or ketoconazole;

- (xxiv) Hormones and analogues thereof such as medroxyprogesterone, diethylstilbestrol (a.k.a. diethylstilboestrol) or octreotide;
- (xxv) Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), fluoxymestrone or gossypol,
- 5 (xxvi) Steroidal cytochrome P450 17 α -hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone;
- (xxvii) Gonadotropin releasing hormone agonists or antagonists (GnRAs) for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate, triptorelin, buserelin, or deslorelin;
- 10 (xxviii) Glucocorticoids, for example prednisone, prednisolone, dexamethasone;
- (xxix) Differentiating agents, such as retinoids, rexinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane, alitretinoin, bexarotene, or tretinoin;
- (xxx) Farnesyltransferase inhibitors for example tipifarnib;
- 15 (xxxi) Chromatin targeted therapies such as histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamide acid (SAHA), depsipeptide (FR 901228), dacinostat (NVP-LAQ824), R306465/ JNJ-16241199, JNJ-26481585, trichostatin A, vorinostat, chlamydocin, A-173, JNJ-MGCD-0103, PXD-101, or apicidin;
- (xxxii) Proteasome Inhibitors for example bortezomib, carfilzomib, CEP-18770, MLN-9708,
- 20 or ONX-0912;
- (xxxiii) Photodynamic drugs for example porfimer sodium or temoporfin;
- (xxxiv) Marine organism-derived anticancer agents such as trabectedin;
- (xxxv) Radiolabelled drugs for radioimmunotherapy for example with a beta particle-emitting isotope (e.g. , Iodine -131, Yttrium -90) or an alpha particle-emitting isotope (e.g.,
- 25 Bismuth-213 or Actinium-225) for example ibritumomab or Iodine tositumomab;
- (xxxvi) Telomerase inhibitors for example telomestatin;
- (xxxvii) Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat;
- (xxxviii) Recombinant interferons (such as interferon- γ and interferon α) and
- 30 interleukins (e.g. interleukin 2), for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, or peginterferon alfa 2b;
- (xxxix) Selective immunoresponse modulators for example thalidomide, or lenalidomide;
- (xl) Therapeutic Vaccines such as sipuleucel-T (Provenge) or OncoVex;
- (xli) Cytokine-activating agents include Picibanil, Romurtide, Sizofiran, Virulizin, or
- 35 Thymosin;
- (xlii) Arsenic trioxide;
- (xliii) Inhibitors of G-protein coupled receptors (GPCR) for example atrasentan ;

(xlv) Enzymes such as L-asparaginase, pegaspargase, rasburicase, or pegademase;

(xlv) DNA repair inhibitors such as PARP inhibitors for example, olaparib, velaparib, iniparib, INO-1001, AG-014699, or ONO-2231;

(xlv) Agonists of Death receptor (e.g. TNF-related apoptosis inducing ligand (TRAIL)

5 receptor), such as mapatumumab (formerly HGS-ETR1), conatumumab (formerly AMG 655), PRO95780, lexatumumab, dulanermin, CS-1008, apomab or recombinant TRAIL ligands such as recombinant Human TRAIL/Apo2 Ligand;

(xlvii) Prophylactic agents (adjuncts); i.e. agents that reduce or alleviate some of the side effects associated with chemotherapy agents, for example

- 10 – anti-emetic agents,
- agents that prevent or decrease the duration of chemotherapy-associated neutropenia and prevent complications that arise from reduced levels of platelets, red blood cells or white blood cells, for example interleukin-11 (e.g. oprelvekin), erythropoietin (EPO) and analogues thereof (e.g. darbepoetin alfa), colony-
- 15 stimulating factor analogs such as granulocyte macrophage-colony stimulating factor (GM-CSF) (e.g. sargramostim), and granulocyte-colony stimulating factor (G-CSF) and analogues thereof (e.g. filgrastim, pegfilgrastim),
- agents that inhibit bone resorption such as denosumab or bisphosphonates e.g. zoledronate, zoledronic acid, pamidronate and ibandronate,
- 20 – agents that suppress inflammatory responses such as dexamethasone, prednisone, and prednisolone,
- agents used to reduce blood levels of growth hormone and IGF-I (and other hormones) in patients with acromegaly or other rare hormone-producing tumours, such as synthetic forms of the hormone somatostatin e.g. octreotide acetate,
- 25 – antidote to drugs that decrease levels of folic acid such as leucovorin, or folinic acid,
- agents for pain e.g. opiates such as morphine, diamorphine and fentanyl,
- non-steroidal anti-inflammatory drugs (NSAID) such as COX-2 inhibitors for example celecoxib, etoricoxib and lumiracoxib,
- agents for mucositis e.g. palifermin,
- 30 – agents for the treatment of side-effects including anorexia, cachexia, oedema or thromboembolic episodes, such as megestrol acetate.

Each of the compounds present in the combinations of the invention may be given in individually varying dose schedules and via different routes. As such, the posology of each of

35 the two or more agents may differ: each may be administered at the same time or at different times. A person skilled in the art would know through his or her common general knowledge the dosing regimes and combination therapies to use. For example, the

compound of the invention may be using in combination with one or more other agents which are administered according to their existing combination regimen. Examples of standard combination regimens are provided below.

5 The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2 , particularly for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

10 The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2 , particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment.

15 The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250 mg/m^2 , particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

20 The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2 , for vincristine in a dosage of about 1 to 2 mg/m^2 , and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

25 The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to 1500 mg/m^2 , particularly for 5-FU in a dosage of 200 to 500 mg/m^2 , for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 2500 mg/m^2 per course of treatment.

30 The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2 , particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150
35 mg/m^2 per course of treatment.

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2 , particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2 , for daunorubicin in a dosage of about 25 to 45 mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m^2) of body surface area, or as known in the art, if different. Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m^2) of body surface area, particularly 2 to 4 mg/m^2 per course of treatment.

Where the compound of the formula (I) is administered in combination therapy with one, two, three, four or more other therapeutic agents (preferably one or two, more preferably one), the compounds can be administered simultaneously or sequentially. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s). These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend

on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

The compounds of the present invention also have therapeutic applications in sensitising tumour cells for radiotherapy and chemotherapy. Hence the compounds of the present invention can be used as "radiosensitizer" and/or "chemosensitizer" or can be given in combination with another "radiosensitizer" and/or "chemosensitizer". In one embodiment the compound of the invention is for use as chemosensitiser.

The term "radiosensitizer" is defined as a molecule administered to patients in therapeutically effective amounts to increase the sensitivity of the cells to ionizing radiation and/or to promote the treatment of diseases which are treatable with ionizing radiation.

The term "chemosensitizer" is defined as a molecule administered to patients in therapeutically effective amounts to increase the sensitivity of cells to chemotherapy and/or promote the treatment of diseases which are treatable with chemotherapeutics.

Many cancer treatment protocols currently employ radiosensitizers in conjunction with radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, tin etioporphyrin, pheoborbid-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of radiosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour with or without additional radiation; or other therapeutically effective compounds for treating cancer or other diseases.

Chemosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of chemosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour or other therapeutically effective compounds for treating cancer or other disease. Calcium antagonists, for example verapamil, are found useful in combination with antineoplastic agents to establish chemosensitivity in tumor cells resistant to accepted chemotherapeutic agents and to potentiate the efficacy of such compounds in drug-sensitive malignancies.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) and one, two, three, four or more other therapeutic agents can be, for example, formulated together in a dosage form containing two, three, four or more therapeutic agents i.e. in a unitary pharmaceutical composition containing all components. In an alternative

embodiment, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

5 In one embodiment is provided a combination of a compound of formula (I) with one or more (e.g. 1 or 2) other therapeutic agents (e.g. anticancer agents as described above).

10 In another embodiment is provided a compound of formula (I) in combination with one or more (e.g. 1 or 2) other therapeutic agents (e.g. anticancer agents) for use in therapy, such as in the prophylaxis or treatment of cancer.

10 In one embodiment the pharmaceutical composition comprises a compound of formula (I) together with a pharmaceutically acceptable carrier and optionally one or more therapeutic agent(s).

15 In another embodiment the invention relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting the growth of tumour cells.

20 In a further embodiment the invention relates to a product containing a compound of formula (I) and one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

EXAMPLES

25 The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples. Compounds are named using an automated naming package such as AutoNom (MDL) or are as named by the chemical supplier.

30 The following synthetic procedures are provided for illustration of the methods used; for a given preparation or step the precursor used may not necessarily derive from the individual batch synthesised according to the step in the description given. In the examples, the following abbreviations are used.

AcOH	acetic acid
Boc	<i>tert</i> -butyloxycarbonyl
Boc-Abu-OH	(S)-2-(Boc-amino)butyric acid
BuLi	butyllithium

CDI	1,1-carbonyldiimidazole
DAST	Diethylaminosulfur trifluoride
DCM	dichloromethane
DIPEA	<i>N</i> -ethyl- <i>N</i> -(1-methylethyl)-2-propylamine
DMC	dimethyl carbonate
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
Et ₂ O	diethyl ether
HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HBTU	O-benzotriazole- <i>N,N,N',N'</i> -tetramethyl-uronium-hexafluorophosphate
HCl	hydrochloric acid
HOAc	acetic acid
HOAt	1-hydroxyazabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
IPA	isopropyl alcohol
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium bis(trimethylsilyl)amide
MeCN	acetonitrile
MeOH	methanol
mins.	minutes
MS	mass spectrometry
NaBH(OAc) ₃	sodium triacetoxyborohydride
NaOtBu	potassium <i>tert</i> -butoxide
NMP	<i>N</i> -methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
Pd ₂ (dba) ₃	<i>tris</i> (dibenzylideneacetone)dipalladium (0)
Pd(OAc) ₂	palladium (2) acetate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium (0)
petrol	petroleum ether fraction with boiling point range 40 – 60 °C

PyBrop	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
RT	room temperature
SiO ₂	silica
TBABr	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBTU	<i>N,N,N',N'</i> -tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	<i>N,N,N,N</i> -tetramethylethylenediamine

NMR Data: Unless indicated, ¹H NMR spectra were recorded at 25°C on a Bruker Avance I spectrometer operating at 400 MHz. The data were processed and analysed using Topspin 2.1 software. For NMR data, where the number of protons assigned is less than the
5 theoretical number of protons in the molecule, it is assumed that the apparently missing signal(s) is/are obscured by solvent and/or water peaks. In addition, where spectra were obtained in protic NMR solvents, exchange of NH and/or OH protons with solvent occurs and hence such signals are normally not observed.

10 **IR Data:** IR Spectra were recorded using Bruker Alpha P IR spectrometer.

Analytical and Preparative LC-MS systems

Analytical LC-MS system and method description

In the following examples, compounds were characterised by mass spectroscopy using the
15 systems and operating conditions set out below. Where atoms with different isotopes are present and a single mass quoted, the mass quoted for the compound is the monoisotopic mass (i.e. ³⁵Cl; ⁷⁹Br etc.).

Waters Platform LC-MS system:

20 HPLC System: Waters 2795
Mass Spec Detector: Micromass Platform LC
PDA Detector: Waters 2996 PDA

- Platform MS conditions:

25 Capillary voltage: 3.6 kV (3.40 kV on ES negative)
Cone voltage: 30 V

Source Temperature: 120 °C
 Scan Range: 125-800 amu
 Ionisation Mode: ElectroSpray Positive or
 ElectroSpray Negative or
 ElectroSpray Positive & Negative

Waters Fractionlynx LC-MS system:

HPLC System: 2767 autosampler – 2525 binary gradient pump
 Mass Spec Detector: Waters ZQ
 PDA Detector: Waters 2996 PDA

• Fractionlynx MS conditions:

Capillary voltage: 3.5 kV (3.25 kV on ES negative)
 Cone voltage: 40 V (25 V on ES negative)
 Source Temperature: 120 °C
 Scan Range: 125-800 amu
 Ionisation Mode: ElectroSpray Positive or
 ElectroSpray Negative or
 ElectroSpray Positive & Negative

Agilent 1200SL-6140 LC-MS system - RAPID:

HPLC System: Agilent 1200 series SL
 Mass Spec Detector: Agilent 6140 single quadrupole
 Second Detector: Agilent 1200 MWD SL

• Agilent MS conditions:

Capillary voltage: 4000V on ES pos (3500V on ES Neg)
 Fragmentor/Gain: 100
 Gain: 1
 Drying gas flow: 7.0 L/min
 Gas Temperature: 345 °C
 Nebuliser Pressure: 35 psig
 Scan Range: 125-800 amu
 Ionisation Mode: ElectroSpray Positive-Negative switching

Preparative LC-MS system and method description

Preparative LC-MS is a standard and effective method used for the purification of small organic molecules such as the compounds described herein. The methods for the liquid chromatography (LC) and mass spectrometry (MS) can be varied to provide better separation of the crude materials and improved detection of the samples by MS.

Optimisation of the preparative gradient LC method will involve varying columns, volatile eluents and modifiers, and gradients. Methods are well known in the art for optimising preparative LC-MS methods and then using them to purify compounds. Such methods are described in Rosentreter U, Huber U.; Optimal fraction collecting in preparative LC/MS; *J Comb Chem.*; 2004; 6(2), 159-64 and Leister W, Strauss K, Wisnoski D, Zhao Z, Lindsley C., Development of a custom high-throughput preparative liquid chromatography/mass spectrometer platform for the preparative purification and analytical analysis of compound libraries; *J Comb Chem.*; 2003; 5(3); 322-9.

Several systems for purifying compounds via preparative LC-MS are described below although a person skilled in the art will appreciate that alternative systems and methods to those described could be used. From the information provided herein, or employing alternative chromatographic systems, a person skilled in the art could purify the compounds described herein by preparative LC-MS.

Waters Fractionlynx system:

- Hardware:

- 2767 Dual Loop Autosampler/Fraction Collector

- 2525 preparative pump

- CFO (column fluidic organiser) for column selection

- RMA (Waters reagent manager) as make up pump

- Waters ZQ Mass Spectrometer

- Waters 2996 Photo Diode Array detector

- Waters ZQ Mass Spectrometer

- Waters MS running conditions:

- Capillary voltage: 3.5 kV (3.2 kV on ES Negative)

- Cone voltage: 25 V

- Source Temperature: 120 °C

- Scan Range: 125-800 amu

- Ionisation Mode: ElectroSpray Positive or

- ElectroSpray Negative

Agilent 1100 LC-MS preparative system:

• Hardware:

Autosampler: 1100 series "prepALS"

Pump: 1100 series "PrepPump" for preparative flow gradient and 1100 series

"QuatPump" for pumping modifier in prep flow

UV detector: 1100 series "MWD" Multi Wavelength Detector

MS detector: 1100 series "LC-MSD VL"

Fraction Collector: 2 x "Prep-FC"

Make Up pump: "Waters RMA"

Agilent Active Splitter

• Agilent MS running conditions:

Capillary voltage: 4000 V (3500 V on ES Negative)

Fragmentor/Gain: 150/1

Drying gas flow: 12.0 L/min

Gas Temperature: 350 °C

Nebuliser Pressure: 50 psig

Scan Range: 125-800 amu

Ionisation Mode: ElectroSpray Positive or
ElectroSpray Negative

• Columns:

A range of commercially available columns – both achiral and chiral - may be used such that, in conjunction with the changes in mobile phase, organic modifier and pH, they enabled the greatest cover in terms of a broad range of selectivity. All columns were used in accordance with the manufacturers recommended operating conditions.

Typically 5 micron particle sized columns were used where available. For example, columns from Waters (including but not limited to XBridge™ Prep OBD™ C18 and Phenyl, Atlantis® Prep T3 OBD™ and Sunfire™ Prep OBD C18 5 µm 19 x 100 mm), Phenomenex (including but not limited to Synergy MAX-RP and LUX™ Cellulose-2), Astec (Chirobiotic™ columns including but not limited to V, V2 and T2) and Diacel® (including but not limited to Chiralpak® AD-H) were available for screening.

• Eluents:

Mobile phase eluent was chosen in conjunction with column manufacturers recommended stationary phase limitations in order to optimise a columns separation performance.

• Methods:

Achiral Preparative Chromatography

The compound examples described have undergone HPLC purification, where indicated, using methods developed following recommendations as described in Snyder L. R., Dolan J. W., High-Performance Gradient Elution The Practical Application of the Linear-Solvent-Strength Model, Wiley, Hoboken, 2007.

Chiral Preparative Chromatography

Preparative separations using Chiral Stationary Phases (CSPs) are the natural technique to apply to the resolution of enantiomeric mixtures. Equally, it can be applied to the separation of diastereomers and achiral molecules. Methods are well known in the art for optimising preparative chiral separations on CSPs and then using them to purify compounds. Such methods are described in Beesley T. E., Scott R.P.W.; Chiral Chromatography; Wiley, Chichester, 1998.

Preparation 1: (*R*)-2-((*S*)-2-Benzoyloxycarbonylamino-3-hydroxy-propionyl-amino)-propionic acid methyl ester

Diisopropylethylamine (375 mL) was added dropwise to a cooled mixture of (*R*)-2-amino-propionic acid methyl ester hydrochloride (100 g, 0.716 mol), EDC (165 g, 0.86 mol), carbobenzyloxy-L-serine (171.4 g, 0.716 mol) and DCM (3.6 L). The resulting mixture was stirred under nitrogen at ambient temperature for 16 h. After removing solvent *in vacuo* at 40 °C, the residue was diluted with saturated sodium carbonate (1 L), water (1 L) and extracted with EtOAc (2 L, 2 x 1 L). The combined organic phases were washed with 2 M hydrochloric acid (1 L), saturated brine solution (1 L), dried over magnesium sulfate and concentrated *in vacuo* at 40 °C, to give the title compound (172 g) as a colourless solid. ¹H NMR (Me-d₃-OD): 7.44-7.28 (6H, m), 5.13 (2H, s), 4.46 (1H, d), 4.43 (1H, d), 4.25 (1H, t), 3.82-3.68 (5H, m), 1.39 (3H, d).

Preparation 2: (3*S*,6*R*)-3-Hydroxymethyl-6-methyl-piperazine-2,5-dione

To (*R*)-2-((*S*)-2-benzyloxycarbonylamino-3-hydroxy-propionylamino)-propionic acid methyl ester (172 g, 0.53 mol) was added 10% Pd / C (8.6 g), MeOH (530 mL) and cyclohexene (344 mL) under nitrogen. The mixture was heated to reflux for 17 h. MeOH (500 mL) was added and the reflux continued for 1 h. The hot reaction mixture was filtered through a pad of celite, cake washing with hot MeOH (2 x 500 mL). The combined filtrates were concentrated. The resulting solid was slurried in 2-butanone (400 mL) and petrol (400 mL) was added gradually over 10 min. After stirring for 30 min, the solids were filtered, cake washed with 2:1 petrol / 2-butanone (300 mL). The filter cake was dried *in vacuo* at 40 °C, to give the title compound (68.3 g) as an off white solid. ¹H NMR (DMSO-d₆): 8.08 (1H, s), 7.90

(1H, s), 5.11 (1H, t), 3.92 (1H, q), 3.80-3.71 (1H, m), 3.71-3.60 (1H, m), 3.58-3.47 (1H, m), 1.24 (3H, d).

Preparation 3: ((2R,5R)-5-Methyl-piperazin-2-yl)-methanol hydrochloride

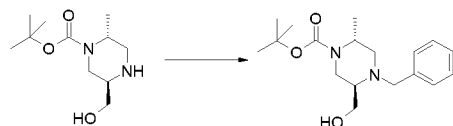
- 5 To (3S,6R)-3-hydroxymethyl-6-methyl-piperazine-2,5-dione (34 g, 0.215 mol) was added a solution of borane in THF (1 M, 1.6 L, 1.6 mol) and the mixture was heated to 70 °C for 18 h. The solution was cooled in ice, then MeOH (425 mL) was gradually added, followed by 5 M hydrochloric acid (113 mL). The mixture was heated to 70 °C for 2 h and then cooled to ambient temperature. The resulting solid was filtered, cake washed with THF (200 mL) and
10 dried *in vacuo* at 40 °C, to give the title compound (39.3 g) as a colourless solid. ¹H NMR (DMSO-d₆): 9.79 (3H, s), 5.59 (1H, s), 3.76-3.40 (5H, m), 3.19-2.94 (2H, m), 1.28 (3H, d).

Preparation 4: (2R,5R)-5-Hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

- 15 To ((2R,5R)-5-methyl-piperazin-2-yl)-methanol hydrochloride (20 g, 119 mmol) in MeOH (96 mL) at 0 °C (ice bath) was added triethylamine (48.7 mL, 357 mmol). *tert*-Butyl dicarbonate (61 g, 280 mmol) in MeOH (145 mL) was added over 30 min. The reaction temperature was maintained at <10 °C for 1 h, warmed to ambient temperature over 1 h and then heated to 50 °C for 18 h. The reaction was concentrated and the residue dissolved in ethanol (397 mL). A
20 solution of NaOH (23.8 g, 595 mmol) in water (397 mL) was added and the reaction heated to 100 °C for 18 h, then cooled to ambient temperature. Mixture was neutralised with 1M HCl (~300 mL) to pH 9 (using a pH meter), then extracted with chloroform (3 x 700 mL), dried over sodium sulfate, filtered and concentrated. The residue was redissolved in MeOH and concentrated, then dried *in vacuo* at 40 °C, to give the title compound (21 g, 75%) as a
25 colourless solid. ¹H NMR (Me-d₃-OD): 4.20-4.07 (1H, m), 3.79 (1H, dd), 3.71-3.58 (2H, m), 3.54 (1H, dd), 3.24 (1H, dd), 3.18-3.01 (1H, m), 3.01-2.89 (1H, m), 2.55 (1H, dd), 1.48 (9H, s), 1.25 (3H, s).

Preparation 5: (2R,5R)-4-Benzyl-5-hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

30



- A mixture of (2R,5R)-5-hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (3.48 g, 15.1 mmol), benzaldehyde (1.76 g, 16.6 mmol), sodium triacetoxyborohydride (3.84 g, 18.1 mmol) and 1,2-dichloroethane (30 mL) was stirred at 20 °C for 18 h, then partitioned
35 between saturated aqueous NaHCO₃ (150 mL) and DCM (3 x 50 mL). Combined organic

extracts were dried (Na_2SO_4) then evaporated *in vacuo* to give an oil. Chromatography (SiO_2 , 0 – 30% EtOAc in petrol) gave the title compound (4.588 g, 74%) as a colourless solid. MS: $[\text{M}+\text{H}]^+ = 321$.

5 **Preparation 6: (2R,5R)-4-Benzyl-5-chloromethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester**

Methanesulfonyl chloride (570 μL , 7.35 mmol) was added to a solution of (2R,5R)-4-benzyl-5-hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (1.9 g, 6.12 mmol) containing TEA (2.6 mL, 18.4 mmol) in DCM (30 mL) at 0 °C. The solution was stirred at
10 room temperature for 18 h. The reaction was partitioned between aqueous NH_4Cl and DCM. The organic phase was collected, dried over MgSO_4 , filtered and concentrated *in vacuo*. Chromatography (30% EtOAc in petrol) gave the title compound (1.6 g) as a white solid. MS: $[\text{M}+\text{H}]^+ = 339$.

15 **Preparation 7: 2-Chloro-5-iodo-pyridin-4-ylamine**

N-Iodosuccinimide (24.75 g, 110.0 mmol) was added to a solution of 2-chloro-pyridin-4-ylamine (12.85 g, 100.0 mmol) in acetonitrile (400 mL) and the mixture stirred and held at reflux overnight. Upon cooling to room temperature the solvent was removed *in vacuo* and residue partitioned between EtOAc (250 mL), saturated sodium thiosulfate (100 mL) and
20 water (250 mL). The organic layer was separated, washed with water (2×250 mL), separated and the solvent removed *in vacuo* to afford an orange oil that was subjected to column chromatography on silica. Gradient elution with 30-50% EtOAc in petrol afforded a pale orange solid that was rinsed with 25% EtOAc in petrol (80 mL). Solids were collected by filtration and sucked dry to afford the title compound (7.32 g) as an off-white solid. The
25 mother liquors were concentrated to dryness *in vacuo* and the residues subjected to column chromatography on silica. Elution with 30-50% EtOAc in petrol afforded further pure material (1.90 g). Combined yield : (9.22 g, 36%) ^1H NMR ($\text{DMSO}-d_6$) 8.20 (1H, s), 6.64 (1H, s), 6.50 (2H, br s). MS: $[\text{M}+\text{H}]^+ = 255$.

30 **Preparation 8: (2-Chloro-5-iodo-pyridin-4-yl)-(2-methyl-allyl)-amine**

Potassium *tert*-butoxide (4.56 g, 40.73 mmol) was added to a stirred solution of 2-chloro-5-iodo-pyridin-4-ylamine (8.62 g, 33.94 mmol) in anhydrous THF (140 mL) and the mixture was stirred at room temperature for 0.25 h. 3-Bromo-2-methyl-prop-1-ene (5.51g, 40.73 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was
35 removed *in vacuo* and the residues partitioned between DCM (100 mL) and water (100 mL). The organic layer was separated, the solvent removed *in vacuo* and the residues subjected to column chromatography on silica. Gradient elution with 5-20% EtOAc in petrol afforded

the title compound (7.93 g, 76%) as a pale yellow oil. ¹H NMR (DMSO-d₆) 8.24 (1H, s), 6.50 (1H, br t), 6.39 (1H, s), 4.84 (1H, d), 4.73 (1H, d), 3.83 (2H, d), 1.70 (3H, s). MS: [M+H]⁺ 309.

Preparation 9: 6-Chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine

5 Palladium (II) acetate (300 mg, 1.34 mmol), sodium formate (2.40 g, 30.53 mmol), tetra-n-butyl-ammonium chloride (8.48 g, 30.53 mmol) and triethylamine (10.6 mL, 76.32 mmol) were added to a solution of (2-chloro-5-iodo-pyridin-4-yl)-(2-methyl-allyl)-amine (7.85 g, 25.44 mmol) in toluene (200 mL) and water (10 mL) and the mixture was stirred and held at 100°C under a nitrogen atmosphere overnight. The mixture was filtered whilst hot and the solids
10 rinsed with toluene (50 mL), water (50 mL) and EtOAc (50 mL). The organic solvent was removed *in vacuo*, the aqueous residues were diluted with water (100 mL) and extracted with EtOAc (2 × 200 mL). The organic layer was separated, the solvent was removed *in vacuo* and the residues subjected to column chromatography on silica. Elution with 30-100% EtOAc in petrol afforded the title compound (4.12 g, 89%) as a colourless solid. ¹H NMR (DMSO-d₆)
15 7.72 (1H, s), 6.75 (1H, br s), 6.33 (1H, s), 3.32 (2H, d), 1.25 (6H, s). MS: [M+H]⁺ 183.

Preparation 10: 6-Chloro-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester

To a solution of 6-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine (1.3 g, 7.4 mmol)
20 in THF (20 mL) were added *tert*-butyl dicarbonate (4.1 g, 18.6 mmol) and dimethyl-pyridin-4-yl-amine (2.22 g, 18.6 mmol) and the solution was stirred for 2 h. Water (60 mL) was added and the product was extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄), filtered and evaporated. Chromatography (SiO₂, eluted with petrol – EtOAc 0-40%) gave the title compound (1.04 g). ¹H NMR (Me-d₃-OD): 8.04 (1H, s), 7.60 (1H, s), 3.81 (2H, s), 1.59 (9H, s), 1.40 (6H, s). MS: [M+H]⁺ = 283.
25

Alternative procedure: Potassium *tert*-butoxide (600 mg, 5.36 mmol) was added to a stirred solution of 6-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine (800 mg, 4.38 mmol) in anhydrous THF (15 mL) and the mixture was stirred at room temperature for 10 minutes. A
30 solution of di-*tert*-butyl dicarbonate (1.07 g, 4.89 mmol) in anhydrous THF (15 mL) was added and the mixture was stirred at room temperature overnight. The organic solvent was removed *in vacuo*, the aqueous residues were diluted with water (100 mL) and extracted with EtOAc (2 x 200 mL). The organic layers were combined and the solvent was removed *in vacuo* to afford the title compound (1.19g, 96%), NMR data consistent with those previously
35 obtained.

Preparation 11: 5-Bromo-2-iodo-pyridin-3-ylamine



3-Amino-5-bromopyridine (13.8 g, 79.8 mmol) was dissolved in acetic acid (440 mL) and placed under a nitrogen atmosphere. *N*-Iodosuccinimide (16.15 g, 71.8 mmol) was charged to the reaction which was stirred at room temperature overnight. The reaction was concentrated and the residue partitioned between EtOAc (200 mL) and saturated aqueous sodium hydrogen carbonate (200 mL). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (200 mL). The aqueous phase was extracted with EtOAc (3 x 200 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated. Chromatography (silica; 1.4 Kg packed in 70% DCM:30% heptane, eluting with 70-100% DCM in heptane) gave the title compound (11.5 g). ^1H NMR (270 MHz, CDCl_3): 7.83 (1H, m), 7.04 (1H, m), 4.33 (2H, br s).

Preparation 12: (5-Bromo-2-iodo-pyridin-3-yl)-(2-methyl-allyl)-amine



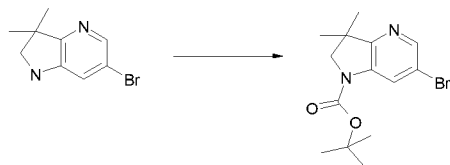
The title compound was prepared following similar methods to those described in Preparation 8, except using 5-bromo-2-iodopyridinyl-3-amine, potassium tert-butoxide (1.1 eq) and 3-bromo-2-methylprop-1-ene (1.1 eq), ^1H NMR (270 MHz, CDCl_3): 7.76 (1H, d), 6.72 (1H, d), 4.92 (2H, m), 4.61 (1H, s), 3.70 (2H, d), 1.69 (3H, s).

Preparation 13: 6-Bromo-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine



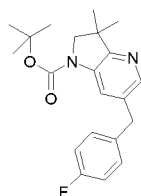
A mixture of (5-bromo-2-iodo-pyridin-3-yl)-(2-methyl-allyl)-amine (10.2 g, 28.9 mmol), tetrabutylammonium chloride (9.64 g, 34.7 mmol), sodium formate (2.36 g, 34.7 mmol), palladium acetate (0.97 g, 4.3 mmol), triethylamine (8.76 g, 86.7 mmol), water (12.1 mL) and dimethyl sulfoxide (255 mL) was stirred at 100 °C under nitrogen for 1 h. The mixture was cooled by the addition of ice (100 g) then was diluted with water (200 mL) with stirring. The mixture was partitioned between water (1 L) and a mixture of toluene (600 mL) and EtOAc (50 mL). The organic phase was washed with water (4 x 250 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a brown oil. Chromatography (SiO_2 , gradient elution with 0 – 100% diethyl ether in 40 – 60 petroleum ether) gave the title compound (2.84 g) as a yellow solid. MS: $[\text{M}+\text{H}]^+ = 227, 229$.

Preparation 14: 6-Bromo-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridine-1-carboxylic acid *tert*-butyl ester



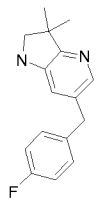
6-Bromo-2,3-dihydro-3,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.45 g, 10.8 mmol) was dissolved in THF (44 mL) and placed under a nitrogen atmosphere. Potassium *tert*-butoxide (1.2 g, 10.8 mmol) was added to the reaction which was stirred at room temperature for 10 minutes. Di-*tert*-butyldicarbonate (2.73 mL, 11.9 mmol) was charged to the reaction which was stirred for 1 h. An additional charge of di-*tert*-butyldicarbonate (0.25 mL, 1.0 mmol) was added to the reaction. After a further 45 minutes the reaction was concentrated. The residue was partitioned between water (50 mL) and DCM (50 mL). The layers were separated and the aqueous was extracted with DCM (2 x 50 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated. Chromatography (silica; 250 g packed in heptane, eluting with 5% EtOAc:heptane) gave the title compound (2.3 g), MS: $[M+H]^+ = 327$.

Preparation 15: 6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-*b*]pyridine-1-carboxylic acid *tert*-butyl ester



To a nitrogen-degassed mixture of 6-bromo-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-*b*]pyridine-1-carboxylic acid *tert*-butyl ester (3.27 g, 10.0 mmol), lithium bromide (2.58 g, 30.0 mmol), (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium (II) dichloride (0.136 g, 0.2 mmol), 1-methyl-2-pyrrolidinone (30 mL) and THF (30 mL) was added a solution of 4-fluorobenzylzinc chloride in THF (0.5 M, 40 mL, 20 mmol) and resulting mixture was stirred at 20 °C for 3 h. The mixture was poured into water (150 mL) and 5% aqueous citric acid (30 mL) and the resulting mixture extracted with Et₂O (3x70 mL). The organic phase was washed with water (100 mL), brine (3x100 mL), dried (MgSO₄) and evaporated *in vacuo* to give an oil. Chromatography (SiO₂, eluted with petrol – EtOAc 0-30%) gave the title compound (3.5 g, 99%) as an oil. MS: $[M+H]^+ = 357$.

Preparation 16: 6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine



A solution of 6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridine-1-carboxylic acid *tert*-butyl ester (9.0 g, 25 mmol) in methanol (62.5 mL) was treated with 5 M hydrochloric acid (62.5 mL) and the mixture stirred at 20 °C for 18 h then heated at 50 °C for 2 h. Solvent was evaporated and the residue was partitioned between water (200 mL) and EtOAc (3x). The aqueous phase was slowly poured into saturated aqueous NaHCO₃ and the resulting solid collected by filtration to afford the title compound (3.45 g). ¹H NMR (CDCl₃): 7.81 (1H, s), 7.16 (2H, dd), 6.99 (2H, t), 6.58 (1H, d), 3.84 (2H, s), 3.38 (2H, s), 1.36 (6H, s). MS: [M+H]⁺ = 257. Further title compound (1.5 g) was obtained by aqueous acid extraction of the combined organic extracts and subsequent basification of the combined aqueous extracts.

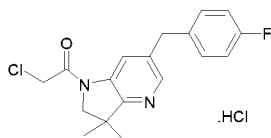
The following compounds were prepared following methods analogous to those described in Preparations 15 and 16:

6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine; MS: [M+H]⁺ = 257.

6-(2,4-Difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine; MS: [M+H]⁺ = 275.

6-(2,4-Difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine; MS: [M+H]⁺ = 275.

Preparation 17: 2-Chloro-1-[6-(4-fluorobenzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-ethanone hydrochloride



To a stirred suspension of 6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine (6.68 g, 26 mmol) in acetonitrile (20 mL) at 20 °C was added, steadily over 0.2 h, a solution of chloroacetyl chloride (3.83 g, 2.7 mL, 33.9 mmol) in acetonitrile (10 mL), maintaining the reaction mixture at or below 20 °C using an external ice-methanol bath. A clear solution resulted then, as the internal temperature reached 0 °C, a solid began to crystallize from the reaction mixture. Stirring at 20 °C was continued for 1 h then toluene (20 mL) and 40 – 60 petroleum ether (20 mL) were added slowly and stirring continued for 0.2 h. The resulting colourless solid was collected by filtration to give the title compound (8.0 g, 83%). ¹H NMR (Me-d₃-OD): 8.81 (1H, s), 8.31 (1H, s), 7.39-7.29 (2H, m), 7.16-7.04 (2H, m), 4.45 (2H, s), 4.19 (4H, s), 1.58 (6H, s). MS: [M+H]⁺ = 333.

The following compounds were prepared following a similar procedure to that described in Preparation 17:

17A: 2-Chloro-1-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl]-ethanone hydrochloride; MS: $[M+H]^+ = 333$.

17B: 2-Chloro-1-[6-(2,4-difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl]-ethanone hydrochloride; MS: $[M+H]^+ = 351$.

17C: 2-Chloro-1-[6-(2,4-difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-ethanone hydrochloride; MS: $[M+H]^+ = 351$.

17D: 2-Chloro-1-[6-(1,1-difluoro-butyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl]-ethanone; MS: $[M+H]^+ = 317$.

Preparation 18: (2R,5R)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-5-hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

Finely ground potassium iodide (7.5 g, 45.26 mmol) was added to a mixture of (2R,5R)-5-hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (5.7 g, 24.89 mmol), 2-chloro-1-[6-(4-fluorobenzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-ethanone hydrochloride (8.35 g, 22.63 mmol) potassium carbonate (12.5 g, 90.51 mmol) and acetonitrile (100 mL) under nitrogen. The mixture was stirred at 20 °C overnight. The mixture was partitioned between water (300 mL) and EtOAc (300 mL) and the organic phase was dried and evaporated *in vacuo* to give the title compound (12.14 g). MS: $[M+H]^+ = 527$.

Preparation 19: (2R,5R)-5-Chloromethyl-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

Methylsulfonyl chloride (0.76 mL, 10 mmol) was added to a solution of (2R,5R)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-5-hydroxymethyl-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (4.33 g, 8.23 mmol) and triethylamine (3.6 mL, 24.7 mmol) in DCM (50 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred under a nitrogen atmosphere overnight. The mixture was partitioned between aqueous ammonium chloride (100 mL) and DCM (100 mL) and the organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography (SiO_2 , eluted with petrol – EtOAc 0-70% gradient), gave the title compound (3.44 g, 77%). MS: $[M+H]^+ = 545$.

Preparation 20: (2R,5S)-5-(2-Cyano-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of (2R,5R)-5-chloromethyl-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester (0.10 g, 0.18 mmol), 2-cyanoimidazole (0.025 g, 0.27 mmol), potassium carbonate (0.10 g, 0.72 mmol) and potassium iodide (0.09 g, 0.54 mmol) in acetonitrile (5 mL) was heated at 90 °C for 18 h, cooled, then partitioned between water (30 mL) and DCM (3 x 20 mL). The combined organic extracts were dried and evaporated to give an oil. Chromatography (SiO₂, 0 – 100% EtOAc in petrol gradient) gave the title compound (0.102 g) as an oil. MS: [M+H]⁺ = 602.

Compounds listed below were prepared by following an analogous method to that described in Preparation 20:

- (2R,5R)-5-(3,5-Dimethyl-pyrazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: [M+H]⁺ = 605.
- (2R,5S)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(2-methyl-imidazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: [M+H]⁺ = 591.
- 2-[(2R,5R)-2-(4,5-Dimethyl-imidazol-1-ylmethyl)-5-methyl-piperazin-1-yl]-1-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-ethanone; MS: [M+H]⁺ = 605.
- 2-[(2R,5R)-2-(2-Ethyl-imidazol-1-ylmethyl)-5-methyl-piperazin-1-yl]-1-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-ethanone; MS: [M+H]⁺ = 605.
- (2R,5S)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(2-trifluoromethyl-imidazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: [M+H]⁺ = 645.
- (2R,5S)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-5-imidazol-1-ylmethyl-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: [M+H]⁺ = 577.
- (2R,5S)-5-(2,4-Dimethyl-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: [M+H]⁺ = 605.
- (2R,5R)-5-(2-Chloro-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: [M+H]⁺ = 611.

(2R,5S)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(5-methyl-2-oxo-2H-pyridin-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 618$.

(2R,5S)-5-(4-Chloro-2-methyl-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 625$.

(2R,5S)-5-(4-Cyano-2-methyl-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 616$.

(2R,5S)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(4-methyl-imidazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester and (2R,5S)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(5-methyl-imidazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 591$.

(2R,5R)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(5-methyl-[1,2,3]triazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 592$; and (2R,5R)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(4-methyl-[1,2,3]triazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 592$; regioisomer mixture separated by flash chromatography.

(2R,5S)-5-[4-(tert-Butyl-dimethyl-silanyloxymethyl)-2-methyl-imidazol-1-ylmethyl]-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester and (2R,5S)-5-[5-(tert-Butyl-dimethyl-silanyloxymethyl)-2-methyl-imidazol-1-ylmethyl]-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 735$.

(2R,5R)-5-(3,4-Dimethyl-pyrazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester and (2R,5R)-5-(4,5-Dimethyl-pyrazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 605$.

(2R,5R)-4-{2-[6-(4-Fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-5-(5-methyl-[1,2,4]triazol-1-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester; MS: $[M+H]^+ = 592$.

Preparation 21: 6-Butyl-3,3-dimethyl-5-oxy-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester

A degassed mixture of 6-chloro-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (2.82 g, 10 mmol), lithium bromide (2.58 g, 30 mmol), (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl)palladium (II) dichloride (0.136 g, 0.2 mmol), butylzinc bromide (0.5 M in THF; 40 mL, 20 mmol), THF (30 mL) and NMP (30 mL) was stirred under nitrogen at 20 °C for 18 h. Mixture was poured into water (200 mL) and extracted with ether. Aqueous phase was treated with 10% aqueous citric acid (30 mL) then re-extracted with ether (100 mL). The combined ether layers were treated with petrol (50 mL) then washed with water (3 x 80 mL). The organic phase was dried (MgSO₄) and evaporated to give a pale yellow oil (2.90 g). A mixture of this material and 3-chloroperbenzoic acid (3.0 g, 13.4 mmol) in DCM was stirred at 20 °C for 2 h. Further 3-chloroperbenzoic acid (1.0 g, 7.7 mmol) was added and stirring continued for 1 h. The mixture was then applied directly to a pre-packed silica cartridge. Chromatography (SiO₂ gradient elution, 0 - 20%, EtOAc in petrol) gave the title compound (1.725 g). MS: [M+H]⁺ = 321.

Preparation 22: 6-(1-Hydroxy-butyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester

A mixture of 6-butyl-3,3-dimethyl-5-oxy-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (1.72 g, 5.4 mmol) and acetic anhydride (10 mL) was stirred at 100 °C for 2 h then poured into ice-water (50 g). Resulting mixture was stirred for 1 h then treated with NaHCO₃. The mixture was extracted with DCM (3 x 50 mL) and the combined extracts were dried and evaporated to give an oil. This material was treated with water (2 mL), methanol (10 mL) and sodium hydroxide (0.28 g) and the mixture stirred for 2 h at 20 °C. Mixture was poured into brine and extracted with DCM (3 x 50 mL). Combined organic extracts were dried and evaporated to give an oil. Chromatography (SiO₂, 0 – 50% ether in petrol gradient) gave the title compound (1.44 g). MS: [M+H]⁺ = 321.

Preparation 23: 6-(1,1-Difluoro-butyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester

A mixture of 6-(1-hydroxy-butyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (1.44 g, 4.5 mmol) and manganese (IV) oxide (3.92, 45 mmol) in dichloromethane (30 mL) was stirred at 20 °C for 18 h. Solids were removed by filtration and filtrate evaporated to give a solid (1.19 g). A solution of this material in DCM (4 mL) was added to a stirred solution of DAST (3.61 g, 22.5 mmol) in DCM (8 mL) at -78 °C under nitrogen. Mixture was stirred at -70 °C for 1 h then at 20 °C for 40 h. Mixture was slowly poured into ice – water (~80 g) and resulting two phase mixture neutralised with NaHCO₃. Resulting mixture was extracted with DCM (3 x 30 mL) and combined extracts dried and

evaporated to give an oil. Chromatography (SiO₂, 0 – 40% ether in petrol gradient) gave the title compound (1.113 g). MS: [M+H]⁺ = 341.

Preparation 24: 6-(1,1-Difluoro-butyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine

A mixture of 6-(1,1-difluoro-butyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (1.113 g, 3.3 mmol) methanol (20 mL) and 5 M aqueous HCl (20 mL) was stirred at 20 °C for 72 h then evaporated *in vacuo*. The residue from evaporation was converted to the free base by partition between DCM and aqueous sodium hydrogen carbonate to give the title compound (0.799 g) as an oil. MS: [M+H]⁺ = 241.

Preparation 25: (Z)-2-*tert*-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)-acrylic acid methyl ester

To (+/-)-Boc- α -phosphonoglycine trimethyl ester (16.5 g, 55.5 mmol) in dichloromethane (100 mL) was added DBU (7.64 mL, 51.1 mmol) and the mixture stirred for 10 minutes. 2,5-Dimethyl-2H-pyrazole-3-carbaldehyde (5.76 g, 46.4 mmol; ChemCollect) was added as a solution in dichloromethane (100 mL) over a period of 20 minutes. The mixture was stirred at RT overnight. The mixture was diluted with EtOAc (200 mL), washed with dilute aqueous KH₂PO₄ (~ 400 mL), brine and then dried (Na₂SO₄). The mixture was concentrated *in vacuo* and the residue purified by SiO₂ chromatography (eluting with 25-75% EtOAc – hexanes) to give a white crystalline solid (10.8 g). Of this material, 8.8 g was dissolved in EtOAc and then washed with dilute aqueous Na₂CO₃, brine and dried (MgSO₄). The solution was evaporated, redissolved in MeOH (120 mL) and treated with 10% Pd/C (1.7 g). The mixture was stirred overnight, filtered and evaporated. The resulting solid was recrystallized (20% EtOAc/heptane) to give the first batch of the title compound as a fine crystalline solid (4.78 g). MS: m/z = 296 (M+H)⁺. Evaporation of the filtrate and subsequent recrystallization (iPr₂O) gave a second crop of the title compound (2.5g).

Preparation 26: (S)-2-*tert*-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)propionic acid methyl ester

(Z)-2-*tert*-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)-acrylic acid methyl ester (preparation 25) (7.28 g, 24.7 mmol) and 1,2-bis[(2S,5S)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I)trifluoromethanesulfonate [(S,S)-Et-DUPHOS-Rh] (1.4 g) were dissolved in MeOH (100 mL) and shaken for 16 hours under an atmosphere of hydrogen (60 psi). The solution was evaporated and the residue purified by SiO₂ chromatography (eluting with 25-100 % EtOAc – hexanes) to give the title compound as a colourless oil (6.96 g). MS: m/z = 298 (M+H)⁺.

Preparation 27: (S)-2-tert-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)propionic acid

(S)-2-tert-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)propionic acid methyl ester (Preparation 26) (6.81 g, 22.9 mmol) was dissolved in a mixture of MeOH (30 mL) and THF (100 mL) and then treated with 1N aqueous LiOH (35 mL, 1.5 mol. eq). The mixture was stirred for 2 hours at RT and then concentrated *in vacuo*. The mixture was partitioned between water and Et₂O. The aqueous layer was then acidified by slow addition of 5N aqueous HCl and then extracted with EtOAc (x3). The combined EtOAc layers were washed with brine, dried (MgSO₄) and evaporated to give the title compound as colourless crystalline solid (5.64 g). MS: m/z = 284 (M+H⁺)⁺.

Preparation 28: (R)-2-[(S)-2-tert-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)-propionylamino]-propionic acid methyl ester

(S)-2-tert-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)propionic acid (Preparation 27) (2.47 g, 8.73 mmol), HOBt (1.4 g, 1.2 mol. eq.) and D-alanine methyl ester hydrochloride (1.45 g, 1.2 mol. eq.) were dissolved in DMF (25 mL). *N,N*-Diisopropylethylamine (1.8 mL, 1.2 mol. eq.), followed by EDC (2.0 g, 1.2 mol. eq.), were added and the mixture stirred for 2 hours at RT. The mixture was concentrated *in vacuo* and then partitioned between dichloromethane (120 mL) and water (30 mL). The dichloromethane layer was washed with dilute aqueous Na₂CO₃, dilute aqueous KH₂PO₄ and dried (MgSO₄). The solution was evaporated and the residue was purified by SiO₂ chromatography (eluting with 50-100 % EtOAc – hexanes) to give the title compound (3.27 g) as a colorless gum. MS: m/z = 369 (M+H⁺)⁺.

Preparation 29: (R)-2-[(S)-2-Amino-3-(2,5-dimethyl-2H-pyrazol-3-yl)-propionylamino]-propionic acid methyl ester hydrochloride

(R)-2-[(S)-2-tert-Butoxycarbonylamino-3-(2,5-dimethyl-2H-pyrazol-3-yl)-propionylamino]-propionic acid methyl ester (Preparation 28) (2.27 g, 6.17 mmol) was dissolved in EtOAc (10 mL), cooled to ~ 0 °C, and then treated with HCl (4N in 1,4-dioxane; 22 mL). The mixture was then stirred at RT for 90 min. the mixture was evaporated to dryness to give the title product (2.21 g) as a colourless solid. MS: m/z = 269 (M+H⁺)⁺.

Preparation 30: (3R,6S)-3-Methyl-6-(5-methyl-2H-pyrazol-3-ylmethyl)-piperazine-2,5-dione

(R)-2-[(S)-2-Amino-3-(2,5-dimethyl-2H-pyrazol-3-yl)-propionylamino]-propionic acid methyl ester hydrochloride (Preparation 29) (1.72 g, 5.6 mmol) and triethylamine (2.3 mL, 3 mol.

eq.) were dissolved in MeOH (50 mL) and heated at reflux overnight. The mixture was then allowed to cool whereupon product precipitated. The first batch of the title compound (315 mg) was collected by filtration. MS: $m/z = 237 (M+H)^+$.

The filtrate was concentrated to a slurry, to which was added methylethylketone (8 mL) and hexanes (8 mL). The heterogeneous mixture was stirred for 10 minutes and then collection by filtration to give the second batch of the title compound (871 mg) as a colourless solid (containing 1 mol. eq. of triethylamine hydrochloride)

Preparation 31: (2S,5R)-2-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-5-methyl-piperazine hydrochloride

(3R,6S)-3-Methyl-6-(5-methyl-2H-pyrazol-3-ylmethyl)-piperazine-2,5-dione (Preparation 30) (460 mg, 1.95 mmol) was dissolved in borane (1N in THF; 14 mL, 7 mol. eq.) and heated at 75 °C overnight. The mixture was cooled and then MeOH (4 mL) was added carefully. 5N aqueous HCl (1 mL) was then added and the mixture heated at 70 °C for 2 hours. The mixture was cooled and concentrated to ~ 3 mL of slurry. The solid (mainly boric acid) was collected by filtration. The filtrate was evaporated to dryness to give the title compound (580 mg) as a colourless solid. ¹H NMR (400 MHz, Me-d₃-OD): 6.68 (1H, s), 4.28-4.13 (1H, m), 4.08 (3H, s), 3.96-3.84 (1H, m), 3.84-3.66 (2H, m), 3.59 (1H, dd), 3.51-3.38 (3H, m), 2.45 (3H, s), 1.48 (3H, d).

Preparation 32: (2R,5S)-5-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester

(2S,5R)-2-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-5-methyl-piperazine hydrochloride (Preparation 32) (580 mg) and triethylamine (2 mL) were dissolved in MeOH/H₂O (15 mL; 1:1) and then cooled to ~ 0 °C. Boc₂O (348 mg as a solution in THF) was added and then the mixture stirred at RT overnight. The mixture was concentrated and partitioned between dichloromethane and dilute aqueous Na₂CO₃. The organic layer was dried (MgSO₄) and evaporated. The residue was purified by SiO₂ chromatography (eluting with 0-20 % MeOH – dichloromethane) to give the title compound (200 mg) as a colorless gum. MS: $m/z = 309 (M+H)^+$.

Preparation 33: (2R,5S)-4-{2-[6-(2,4-Difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-5-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester

(2R,5S)-5-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester (195 mg, 0.63 mmol), 2-chloro-1-[6-(2,4-difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-ethanone hydrochloride (243 mg, 1.1 mol. eq.), KI (210 mg, 2 mol.

eq.) and K_2CO_3 (350 mg, 4 mol, eq.) were stirred together in MeCN (5 mL) at RT overnight. The mixture was partitioned between dichloromethane and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by SiO_2 chromatography (eluting with 0-10 % MeOH – EtOAc) gave the title compound (330 mg) as a colourless gum. MS: $[M+H]^+ = 623$.

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The following compounds were prepared using an analogous method to preparation 33:

(2R,5S)-4-{2-[6-(1,1-Difluoro-butyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl]-2-oxo-ethyl}-5-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; $[M + H]^+ = 589$.

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(2R,5S)-4-{2-[6-(2,4-Difluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl]-2-oxo-ethyl}-5-(2,5-dimethyl-2H-pyrazol-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid tert-butyl ester; $[M + H]^+ = 623$.

15 Preparation 34: 2-Methyl-4-cyanoimidazole

2-methyl-4-carbaldehyde imidazole (0.8g, 7.27 mmol), trityl chloride (3.04g, 10.91 mmol) and Et_3N (2.02 ml, 14.55 mmol) were combined in DCM (7 mL) and stirred at room temperature overnight. Mixture was diluted with DCM and washed with water. Solvent was evaporated to give a white powder. Recrystallation from toluene gave 1-trityl-2-methyl-1H-imidazole -4-carbaldehyde (750 mg) as white powder. This material was dissolved in pyridine (10 mL) and $NH_2OH.HCl$ (0.22 g, 3.20 mmol) was added and the reaction stirred at room temperature for 1 h. Ac_2O (8 ml) was added and the mixture heated to 80 °C for 3 h. Water (50 ml) was added and mixture extracted with DCM (2 x 20 mL), and extracts were dried and evaporated. Residue was triturated with EtOAc/Petrol (1:4) and product collected by filtration (350 mg).

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The filtrate was concentrated and purified by column chromatography (0-50% EtOAc/Petrol gradient) to give further product as a white powder (250 mg). The resulting 1-trityl-2-methyl-1H-imidazole-4-carbonitrile (600 mg) was dissolved in MeOH/AcOH (1:1, 20 mL) and heated at reflux for 2 h. Water (30 ml) was added followed by 2 M HCl until pH 2 was attained.

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Mixture was washed with EtOAc (2 x 20 ml) then aqueous layer was basified with K_2CO_3 and extracted with DCM. DCM phase was dried and evaporated to give the title compound as a white powder. 1H NMR (400 MHz, Me- d_3 -OD): 7.71 (1H, s), 2.40 (3H, s).

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Preparation 35: 4-[(tert-Butyldimethylsilyl)oxy]methyl}-2-methyl-1H-imidazole

A mixture of 4-hydroxymethylimidazole (500 mg, 4.46 mmol), triethylamine (0.81 mL, 5.80 mmol) and TBDMS-Cl (739 mg, 4.90 mmol) was dissolved in DMF (5 mL) and stirred at rt overnight. After this time, water (25 mL) and EtOAc (10 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). The collected organic phase was washed with brine (25

35

mL), dried over Na₂SO₄, filtered and concentrated to give the title compound (972 mg, 96% yield) as orange oil, used as crude in the next step. MS: [M+H] 227.

Preparation 36: 2-(5-Chloro-3-fluoro-pyridin-2-yl)-2-methyl-propionitrile

- 5 A solution of sodium bis(trimethylsilyl)amide (610 mL, 40% in tetrahydrofuran, 1.326 mole) was added to a cooled solution of 5-chloro-2,3-difluoropyridine (198.2 g, 1.326 mole) and isobutyronitrile (238 mL, 2.65 mole) in toluene (2 L). The mixture was stirred under nitrogen at RT overnight before addition of saturated aqueous ammonium chloride (1 L). Phases were separated and the aqueous extracted with ethyl acetate (2 x 1 L). Combined organics
10 were dried (MgSO₄) and concentrated *in vacuo* at 40 °C to give the title compound (259.8 g, 95%) ¹H NMR (400 MHz, DMSO-d₆): 8.57 (1H, dd), 8.24 (1H, dd), 1.74 (6H, bd).

Preparation 37: 2-(5-Chloro-3-fluoropyridin-2-yl)-2-methylpropylamine

- Borane-tetrahydrofuran complex (1 M, 1.37 L, 1.365 mole) was added to a cooled solution of
15 2-(5-chloro-3-fluoropyridin-2-yl)-2-methylpropionitrile (135.6 g, 0.683 mole) in tetrahydrofuran (670 mL). The mixture was stirred under nitrogen at room temperature overnight before cooling in ice. The mixture was quenched by the addition of 5 M hydrochloric acid (335 mL). The resulting mixture was basified with 40% aqueous potassium hydroxide (460 mL) and the phases were separated. The basic aqueous phase was extracted with ethyl acetate (2 x 670
20 mL) and the combined organic extracts were washed with brine (670 mL), dried (MgSO₄) and concentrated *in vacuo* at 40 °C to give the title compound (102.9g, 74%) ¹H NMR (400 MHz, DMSO-d₆): 8.44 (1H, t), 7.95 (1H, dd), 2.85 (2H, d), 1.29 (6H, d).

Preparation 38: 6-Chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine

- 25 A mixture of 2-(5-chloro-3-fluoropyridin-2-yl)-2-methylpropylamine (33 g, 0.163 mole), potassium carbonate (122 g) and NMP (100 mL) were heated to 150 °C for 4 hours. The cooled mixture was diluted with water (330 mL) and extracted with toluene (3 x 300 mL). The combined organic extracts were washed with brine (160 mL), dried (MgSO₄) and concentrated *in vacuo* at 40 °C to give crude material (24.8 g). Chromatography on silica
30 eluting with 5-30% ethyl acetate / petrol gave the title compound (21 g, 71%) ¹H NMR (400 MHz, DMSO-d₆): 7.61 (1H, d), 6.75 (1H, d), 6.06 (1H, bs), 3.31 (2H, s), 1.21 (6H, s).

Preparation 39: 6-Chloro-3,3-dimethyl-2,3-dihydropyrrolo[3,2-b]pyridine-1-carboxylic acid tert-butyl ester

- 35 Di-tertbutyldicarbonate (3.7 g, 17.1 mmol) was added to a mixture of 6-chloro-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine (2.6 g, 14.2 mmol), tetrahydrofuran (26 mL) and 2 M sodium hydroxide (11.4 mL, 22.8 mmol) with stirring over the weekend. The biphasic mixture

was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* at 40 °C to give crude material (6.02 g). Chromatography on silica eluting with 5 - 30% ethyl acetate / petrol gave the title compound (2.23g, 55%); ¹H NMR (400 MHz, DMSO-d₆): 8.11 (1H, d), 7.85 (1H, bs), 3.77 (2H, s), 1.52 (9H, s), 1.28 (6H, s).

Preparation 40: 6-Bromo-3,3-dimethyl-2,3-dihydropyrrolo[3,2-b]pyridine-1-carboxylic acid tert-butyl ester (alternative procedure)

The title compound was synthesised from 5-bromo-2,3-difluoropyridine following analogous methods to those of Preparations 36 – 40 inclusive; analytical data were consistent with those obtained previously.

Preparation of Compounds of Formula (I)

Compounds of formula (I) are prepared using deprotection methods analogous to those detailed below:

Method 1

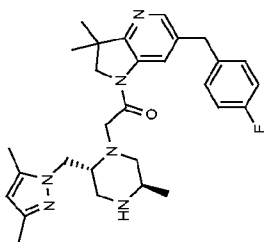
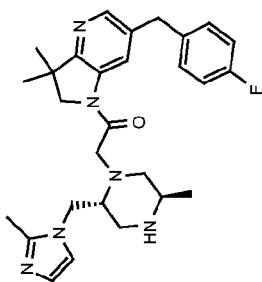
A mixture of (2R,5S)-5-(4-Chloro-2-methyl-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester (0.11 mmol), ethyl acetate (3 mL) and HCl – dioxane (4 M; 5 mL) was stirred at 20 °C for 18 h and resulting solid collected by filtration to give 2-[(2R,5R)-2-[(4-chloro-2-methyl-1H-imidazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one dihydrochloride (Example 11)

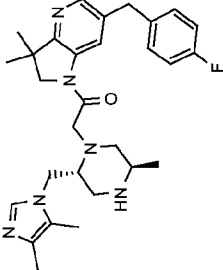
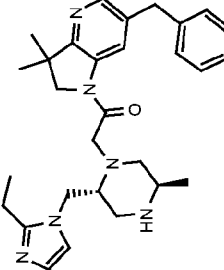
Method 2

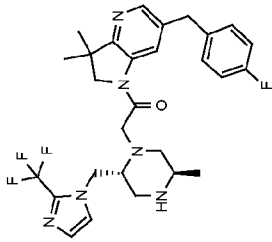
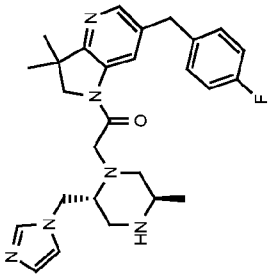
(2R,5S)-5-(2-Cyano-imidazol-1-ylmethyl)-4-{2-[6-(4-fluoro-benzyl)-3,3-dimethyl-2,3-dihydro-pyrrolo[3,2-b]pyridin-1-yl]-2-oxo-ethyl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester (0.10 mg, 0.17 mmol) was dissolved in a mixture of TFA and DCM (1:1; 5 mL), stirred for 2 h, then evaporated *in vacuo* and partitioned between DCM and aqueous NaHCO₃. The organic layer was dried and evaporated to give an oil. This material was dissolved in EtOAc and treated with 1 molar equivalent of L-lactic acid. The mixture was then evaporated to give 1-[[[(2R,5R)-1-(2-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl]-2-oxoethyl)-5-methylpiperazin-2-yl]methyl]-1H-imidazole-2-carbonitrile L-lactate (Example 10; 0.11 g) as a colourless solid.

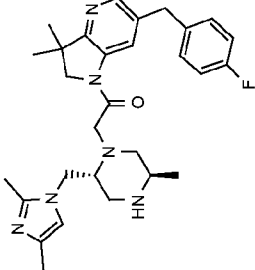
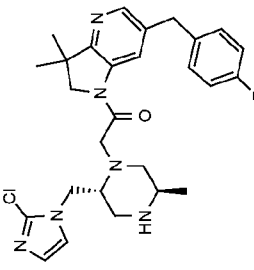
EXAMPLES 1 to 22, 30 to 31 and 38

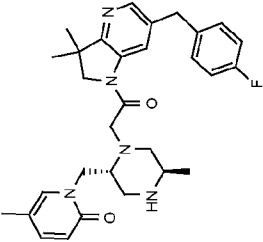
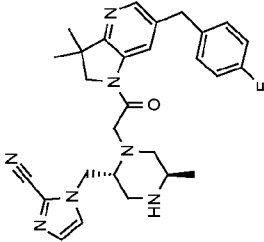
By following methods similar and/or analogous to those described above, the compounds set out in the Table below were prepared from the corresponding N-Boc protected derivatives, with any significant variations indicated below except where otherwise stated. Precursors for the N-Boc protected derivatives are identified (by preparation number or name) in the table below. The title compounds were either isolated directly as the free base or appropriate salt without further purification, or purified for example using mass-directed preparative HPLC, crystallization or trituration.

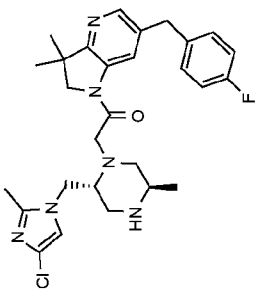
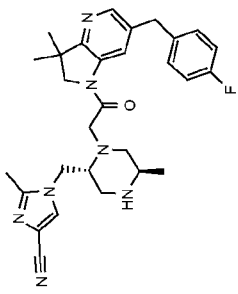
Example	Structure	Name	Synthesis of Boc derivative	Deprotection Method	NMR Data	MS Data [M+H] ⁺
1		2-[(2R,5R)-2-[(3,5-Dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 3,5-dimethyl-1H-pyrazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.78 (1H, s), 8.43-8.32 (1H, m), 7.35 (2H, dd), 7.11 (2H, t), 6.29 (1H, s), 4.70 (1H, dd), 4.43 (1H, dd), 4.33-4.07 (5H, m), 4.07-3.86 (2H, m), 3.56-3.45 (1H, m), 3.32-3.22 (2H, m), 3.10-2.91 (2H, m), 2.43 (4H, d), 2.33 (3H, s), 1.62 (6H, d), 1.34 (3H, d).	505
2		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-[(2-methyl-1H-imidazol-1-yl)methyl]piperazin-1-yl]ethan-1-one, dihydrochloride	19 + 2-methyl-1H-imidazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.83 (1H, s), 8.35 (1H, s), 7.68 (1H, s), 7.51 (1H, s), 7.41-7.30 (2H, m), 7.12 (2H, t), 4.70 (1H, d), 4.42-4.29 (1H, m), 4.22 (4H, s), 4.10-3.94 (3H, m), 3.43 (1H, d), 3.24 (2H, t), 3.08-2.92 (2H, m), 2.71 (3H, s), 1.62 (7H, d), 1.33 (3H, d).	491

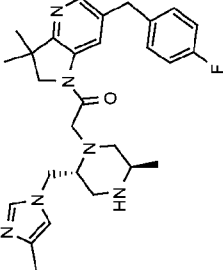
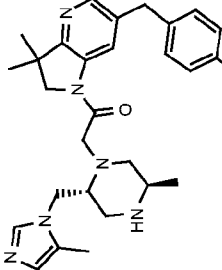
3		2-[(2R,5R)-2-[(4,5-Dimethyl-1H-imidazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[[4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 4,5-dimethyl-1H-imidazole, See Preparation 20	1	1H NMR (400 MHz, Me-d3-OD): 8.97 (1H, s), 8.77-8.69 (1H, m), 8.32 (1H, s), 7.33 (2H, dd), 7.14-7.06 (2H, m), 4.64-4.54 (1H, m), 4.45-4.33 (1H, m), 4.18 (4H, s), 4.15-4.00 (2H, m), 4.00-3.87 (2H, m), 3.43 (1H, s), 3.29-3.18 (2H, m), 3.05-2.89 (2H, m), 2.29 (6H, s), 1.59 (6H, d), 1.32 (3H, d).	505
4		2-[(2R,5R)-2-[(2-Ethyl-1H-imidazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[[4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 2-ethyl-1H-imidazole, See Preparation 20	1	1H NMR (400 MHz, Me-d3-OD): 8.79 (1H, s), 8.35 (1H, s), 7.71 (1H, d), 7.54 (1H, d), 7.42-7.29 (2H, m), 7.18-7.05 (2H, m), 4.79-4.65 (1H, m), 4.37 (1H, dd), 4.21 (4H, s), 4.01-3.94 (2H, m), 3.47-3.38 (2H, m), 3.28-3.17 (2H, m), 3.17-3.04 (2H, m), 2.99 (2H, q), 1.61 (7H, d), 1.40 (3H, t), 1.33 (3H, d).	505

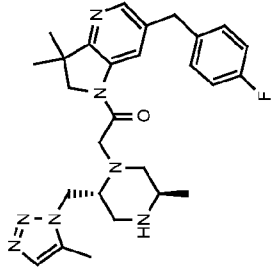
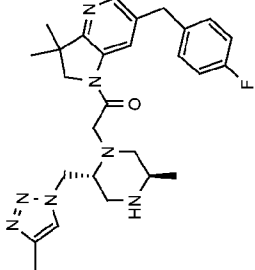
5		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-{[2-(trifluoromethyl)-1H-imidazol-1-yl]methyl}piperazin-1-yl]ethan-1-one, dihydrochloride	19 + 2-(trifluoromethyl)-1H-imidazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.73 (1H, s), 8.32 (1H, s), 7.58 (1H, d), 7.41-7.28 (2H, m), 7.17 (1H, d), 7.14-7.04 (2H, m), 4.65 (1H, dd), 4.31 (1H, dd), 4.19 (2H, s), 4.14-4.06 (2H, m), 4.01-3.88 (3H, m), 3.46-3.36 (2H, m), 3.18 (1H, dd), 3.09-2.99 (2H, m), 2.91 (1H, t), 1.57 (6H, s), 1.30 (3H, d).	545
6		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-2-(1H-imidazol-1-ylmethyl)-5-methylpiperazin-1-yl]ethan-1-one, dihydrochloride	19 + 1H-imidazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 9.15 (1H, s), 8.85 (1H, s), 8.35 (1H, s), 7.76 (1H, s), 7.68-7.60 (1H, m), 7.35 (2H, t), 7.11 (2H, t), 4.77-4.61 (2H, m), 4.32-4.05 (5H, m), 3.98-3.79 (2H, m), 3.54-3.34 (3H, m), 3.30-3.12 (1H, m), 2.93 (1H, t), 2.80 (1H, t), 1.68-1.55 (6H, m), 1.31 (3H, d).	477

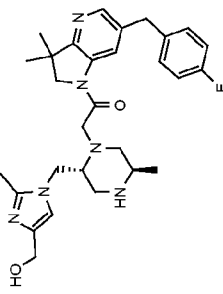
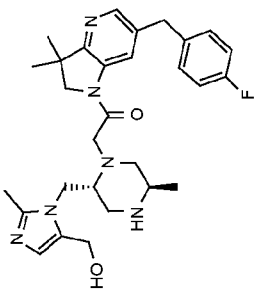
7		2-[(2R,5R)-2-[(2,4-Dimethyl-1H-imidazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[[4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 2,4-dimethyl-1H-imidazole, See Preparation 20	1, purification by HPLC, ^a then HCl salt formation	1H NMR (400 MHz, Me-d3-OD): 8.80 (1H, s), 8.34 (1H, s), 7.40-7.29 (3H, m), 7.11 (2H, t), 4.62 (1H, dd), 4.26 (1H, dd), 4.21 (4H, s), 4.08-3.88 (3H, m), 3.64-3.47 (1H, m), 3.42 (1H, d), 3.29-3.13 (2H, m), 3.07-2.90 (2H, m), 2.69-2.60 (3H, m), 2.31 (3H, s), 1.61 (6H, d), 1.32 (3H, d).	505
8		2-[(2R,5R)-2-[(2-Chloro-1H-imidazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[[4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 2-chloro-1H-imidazole, See Preparation 20	1	1H NMR (400 MHz, Me-d3-OD): 8.81 (1H, s), 8.38-8.31 (1H, m), 7.76 (1H, d), 7.49 (1H, d), 7.34 (2H, dd), 7.11 (2H, t), 4.65 (1H, dd), 4.41 (1H, dd), 4.20 (4H, d), 4.15-3.89 (3H, m), 3.59-3.35 (2H, m), 3.30-3.11 (1H, m), 3.06-2.93 (2H, m), 1.61 (6H, d), 1.32 (3H, d).	511

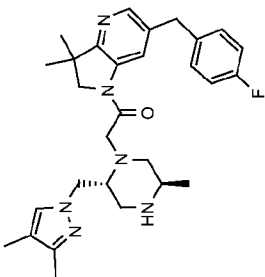
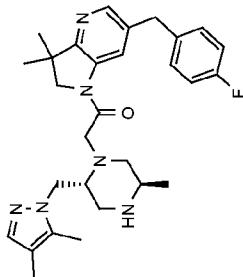
9		1-[[[(2R,5R)-1-(2-{6-[[4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl]-2-oxoethyl)-5-methylpiperazin-2-yl]methyl]-5-methyl-1,2-dihydropyridin-2-one, dihydrochloride	19 + 5-methyl-1,2-dihydropyridin-2-one, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.77 (1H, s), 8.37 (1H, s), 7.55 (1H, s), 7.47-7.28 (3H, m), 7.11 (2H, t), 6.50 (1H, d), 4.53 (1H, d), 4.38-3.96 (7H, m), 3.90 (1H, s), 3.58 (1H, s), 3.45 (1H, d), 3.30-3.06 (2H, m), 2.10 (3H, s), 1.62 (6H, d), 1.35 (3H, d).	518
10		1-[[[(2R,5R)-1-(2-{6-[[4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl]-2-oxoethyl)-5-methylpiperazin-2-yl]methyl]-1H-imidazole-2-carbonitrile, L-lactate	See Preparation 20	2	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.24 (1H, s), 8.14-8.02 (1H, m), 7.60 (1H, s), 7.25 (2H, t), 7.18 (1H, s), 7.04 (2H, t), 4.62 (1H, dd), 4.42-4.27 (1H, m), 4.18-3.83 (7H, m), 3.72 (2H, d), 3.22-3.06 (2H, m), 3.00-2.75 (2H, m), 1.41 (6H, d), 1.36 (5H, d), 1.24 (3H, d).	502

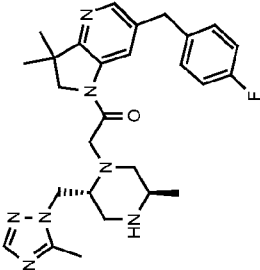
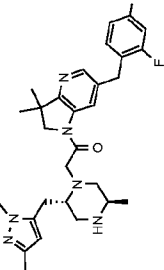
11		2-[(2R,5R)-2-[(4-Chloro-2-methyl-1H-imidazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + -(4-chloro-2-methyl-1H-imidazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.84 (1H, s), 8.35 (1H, s), 7.79 (1H, s), 7.35 (2H, t), 7.11 (2H, t), 4.65 (1H, d), 4.37 (1H, d), 4.23 (4H, s), 4.10-4.01 (1H, m), 3.95 (2H, d), 3.45 (1H, s), 3.21 (1H, d), 2.99 (2H, t), 2.68 (3H, s), 1.65-1.59 (6H, m), 1.33 (3H, d).	525
12		1-[[[(2R,5R)-1-(2-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-oxoethyl)-5-methylpiperazin-2-yl]methyl]-2-methyl-1H-imidazole-4-carbonitrile, dihydrochloride	19 + 2-methyl-1H-imidazole-4-carbonitrile, See Preparation 20	2, then HPLC purification, followed by HCl salt formation	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.78 (1H, d), 8.34 (1H, s), 8.14 (1H, s), 7.35 (2H, s), 7.11 (2H, t), 4.56-4.46 (1H, m), 4.19 (5H, s), 3.97 (2H, s), 3.41 (2H, d), 3.29-2.99 (3H, m), 2.93 (1H, d), 2.79 (1H, s), 2.52 (2H, s), 1.61 (6H, d), 1.32 (3H, d).	516

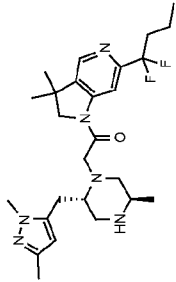
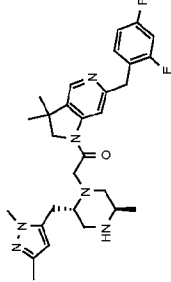
13		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-[(4-methyl-1H-imidazol-1-yl)methyl]piperazin-1-yl]ethan-1-one, dihydrochloride	19 + 4-methyl-1H-imidazole, See Preparation 20	1, HPLC ^b separation of regioisomers (faster eluting), then salt formation	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.98 (1H, d), 8.81 (1H, s), 8.35 (1H, s), 7.44 (1H, s), 7.41-7.29 (2H, m), 7.18-7.05 (2H, m), 4.68-4.53 (2H, m), 4.31-4.08 (5H, m), 3.97-3.77 (2H, m), 3.39 (3H, d), 3.21 (1H, dd), 2.98-2.74 (2H, m), 2.37 (3H, s), 1.61 (6H, d), 1.31 (3H, d).	491
14		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-[(5-methyl-1H-imidazol-1-yl)methyl]piperazin-1-yl]ethan-1-one, dihydrochloride	19 + 4-methyl-1H-imidazole, See Preparation 20	1, HPLC ^b separation of regioisomers (slower eluting), then salt formation	¹ H NMR (400 MHz, Me-d ₃ -OD): 9.11 (1H, s), 8.75 (1H, s), 8.33 (1H, s), 7.47-7.28 (4H, m), 7.18-7.05 (2H, m), 4.69-4.56 (1H, m), 4.47 (1H, dd), 4.20 (5H, s), 3.54-3.39 (2H, m), 3.30-3.17 (2H, m), 3.06-2.87 (2H, m), 2.40 (3H, s), 1.60 (7H, d), 1.32 (3H, d).	491

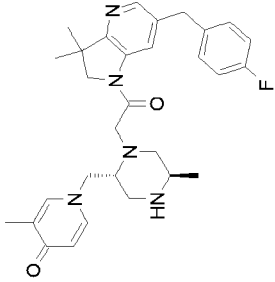
15		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-[(5-methyl-1H-1,2,3-triazol-1-yl)methyl]piperazin-1-yl]ethan-1-one, dihydrochloride	19 + 4-methyl-1H-1,2,3-triazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.82 (1H, d), 8.37 (1H, s), 7.39 (3H, d), 7.11 (2H, s), 4.70 (2H, d), 4.25 (3H, s), 3.92 (2H, d), 3.39 (2H, s), 3.20 (3H, s), 2.21 (3H, d), 1.82-1.46 (9H, m), 1.46-1.25 (3H, m).	492
16		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-[(4-methyl-1H-1,2,3-triazol-1-yl)methyl]piperazin-1-yl]ethan-1-one, dihydrochloride	19 + 4-methyl-1H-1,2,3-triazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.78 (1H, s), 8.35 (1H, s), 7.40 (1H, s), 7.34 (2H, s), 7.10 (2H, s), 4.67 (2H, d), 4.31-4.15 (4H, m), 4.11-3.94 (2H, m), 3.89 (2H, s), 3.10 (2H, s), 2.29-2.12 (3H, m), 1.59 (9H, s), 1.34-1.16 (3H, m).	492

17		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-2-{[4-(hydroxymethyl)-2-methyl-1H-imidazol-1-yl]methyl}-5-methylpiperazin-1-yl]ethan-1-one, dihydrochloride	19 + 35, See Preparation 20	1, HPLC ^c separation of regioisomers (faster eluting), then salt formation	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.83 (1H, s), 8.34 (1H, s), 7.47 (1H, d), 7.36 (2H, s), 7.18-7.10 (2H, m), 4.68 (2H, d), 4.36-4.24 (1H, m), 4.21 (4H, d), 4.16-4.06 (2H, m), 4.02 (2H, d), 3.83-3.64 (1H, m), 3.64-3.41 (2H, m), 3.15 (3H, s), 2.74 (3H, d), 1.61 (6H, s), 1.34 (4H, d).	521
18		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-2-{[5-(hydroxymethyl)-2-methyl-1H-imidazol-1-yl]methyl}-5-methylpiperazin-1-yl]ethan-1-one, dihydrochloride	19 + 35, See Preparation 20	1, HPLC ^c separation of regioisomers (slower eluting), then salt formation	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.80 (1H, s), 8.34 (1H, s), 7.55 (1H, s), 7.35 (2H, s), 7.12 (2H, d), 4.60 (2H, d), 4.38-4.25 (1H, m), 4.20 (5H, s), 4.01 (4H, d), 3.43 (1H, s), 3.28-3.11 (2H, m), 3.11-2.92 (2H, m), 2.69 (3H, d), 1.61 (6H, s), 1.33 (4H, s).	521

19		2-[(2R,5R)-2-[(3,4-Dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 3,4-dimethyl-1H-pyrazole, See Preparation 20	1, HPLC ^d separation of regioisomers (slower eluting), then salt formation	505 1H NMR (400 MHz, Me-d3-OD): 8.77 (1H, s), 8.35 (1H, s), 7.60 (1H, s), 7.34 (2H, dd), 7.11 (2H, t), 4.49 (1H, dd), 4.34 (1H, dd), 4.20 (2H, s), 4.17-4.11 (2H, m), 4.11-3.86 (2H, m), 3.86-3.71 (1H, m), 3.49-3.36 (1H, m), 3.25-3.12 (2H, m), 3.09-2.83 (2H, m), 2.18 (3H, s), 1.97 (3H, s), 1.59 (6H, d), 1.31 (4H, d).
20		2-[(2R,5R)-2-[(4,5-Dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one, dihydrochloride	19 + 3,4-dimethyl-1H-pyrazole, See Preparation 20	1, HPLC ^d separation of regioisomers (faster eluting), then salt formation	505 1H NMR (400 MHz, Me-d3-OD): 8.73 (1H, s), 8.35 (1H, s), 7.41-7.29 (3H, m), 7.17-7.06 (2H, m), 4.61-4.45 (1H, m), 4.25-4.06 (5H, m), 4.06-3.87 (3H, m), 3.83-3.74 (1H, m), 3.74-3.65 (1H, m), 3.47-3.37 (1H, m), 3.25-3.14 (1H, m), 3.14-2.86 (3H, m), 2.23 (2H, s), 1.91 (2H, s), 1.59 (6H, d), 1.31 (4H, d).

21		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-5-methyl-2-[(5-methyl-1H-1,2,4-triazol-1-yl)methyl]piperazin-1-yl]ethan-1-one	19 + 3-methyl-1H-1,2,4-triazole, See Preparation 20	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.82 (1H, d), 8.72 (1H, s), 8.35 (1H, s), 7.35 (2H, s), 7.10 (2H, s), 4.25 (4H, s), 4.18-4.09 (1H, m), 4.09-3.97 (2H, m), 3.89 (2H, d), 3.42 (2H, s), 3.30-3.22 (2H, m), 3.07 (2H, s), 2.80 (1H, s), 2.53 (2H, s), 1.62 (6H, s), 1.33 (3H, s).	492
22		1-{6-[(2,4-Difluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one, dihydrochloride	See Preparation 33	1	¹ H NMR (400 MHz, Me-d ₃ -OD): 8.86 (1H, s), 8.38 (1H, s), 7.54-7.41 (1H, m), 7.09-6.96 (2H, m), 6.70 (1H, s), 4.34-4.06 (8H, m), 4.02 (3H, s), 3.76-3.56 (1H, m), 3.48-3.35 (2H, m), 3.28-3.11 (3H, m), 2.43 (3H, s), 1.62 (6H, d), 1.37 (3H, d).	523

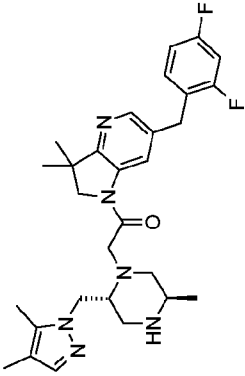
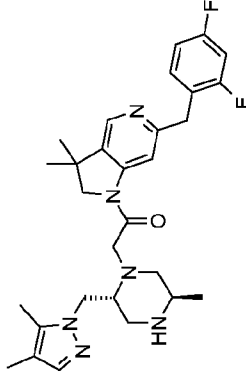
30 	1-[6-(1,1-Difluorobutyl)-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl]-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one dihydrochloride	17D + 32, see preparation 33	1	1H NMR (400 MHz, Me-d3-OD): 8.56 (1H, s), 8.22-8.14 (1H, m), 7.57-7.45 (1H, m), 7.14-7.02 (2H, m), 6.63 (1H, s), 4.39 (2H, s), 4.23-3.87 (8H, m), 3.49 (1H, d), 3.31-3.19 (2H, m), 3.18-2.97 (3H, m), 2.47-2.35 (3H, m), 1.52 (6H, d), 1.34 (3H, d). 523
31 	1-[6-(1,1-Difluorobutyl)-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl]-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one dihydrochloride	17B + 32, see preparation 33	1	1H NMR (400 MHz, Me-d3-OD): 8.69 (1H, s), 8.61-8.48 (1H, m), 6.65 (1H, s), 4.23 (2H, s), 4.16-4.06 (2H, m), 4.00 (4H, s), 3.58-3.37 (2H, m), 3.23-2.98 (3H, m), 2.50-2.24 (5H, m), 1.56 (8H, d), 1.36 (3H, d), 1.05 (3H, t). 489

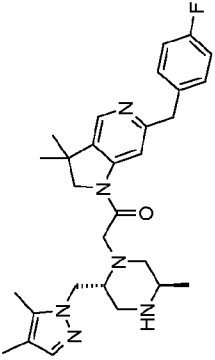
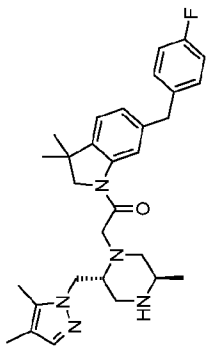
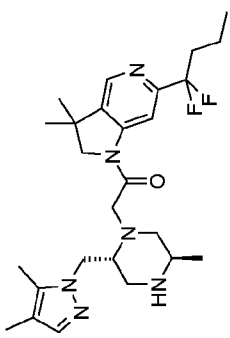
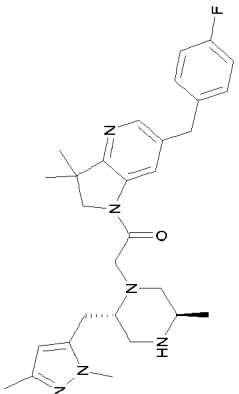
38		1-[(2R,5R)-1-(2-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-oxoethyl)-5-methylpiperazin-2-yl]methyl-3-methyl-1,4-dihydropyridin-4-one, dihydrochloride	19 + 3-methyl-1,4-dihydropyridin-4-one, See Preparation 20	1	¹H NMR (400 MHz, Me-d₃-OD): 8.84 (1H, s), 8.58 (2H, d), 8.36 (1H, s), 7.35 (2H, t), 7.25 (1H, d), 7.11 (2H, t), 4.67 (1H, dd), 4.33-4.13 (3H, m), 3.92 (2H, d), 3.68 (4H, s), 3.44 (1H, s), 3.22 (1H, dd), 2.93 (2H, t), 2.29 (3H, s), 1.70-1.53 (6H, m), 1.32 (3H, d).	518
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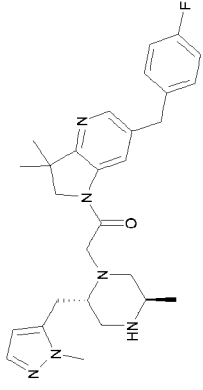
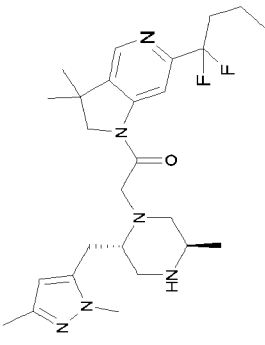
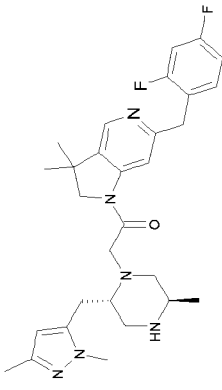
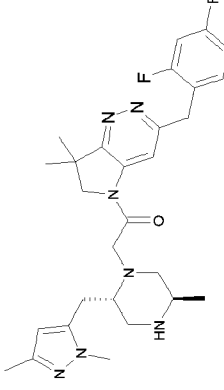
Examples 23 – 37

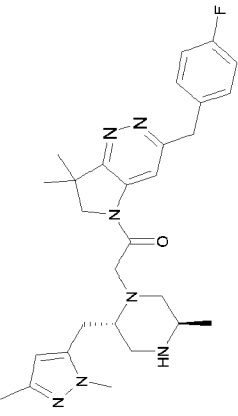
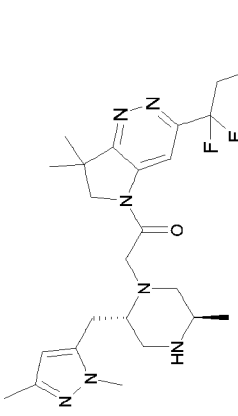
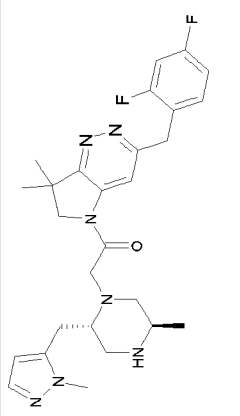
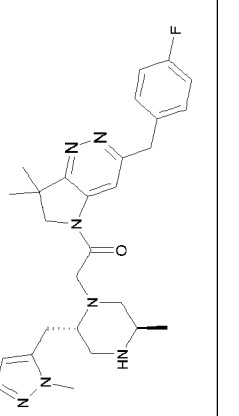
The following compounds can be made using the methods described herein.

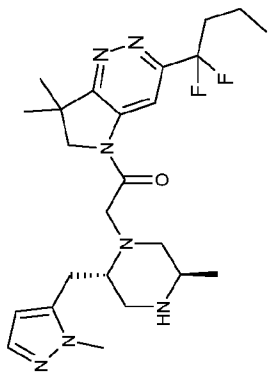
- 5 In particular Preparation 20 and Preparation 33 could be used with the appropriate intermediates. The required intermediates are commercially available or can be synthesised using the methods analogous to those described herein.

Prophetic Example	Compound Structure	Name
23		1-{6-[(2,4-Difluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2R,5R)-2-[(4,5-dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one
24		1-{6-[(2,4-Difluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl}-2-[(2R,5R)-2-[(4,5-dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one

25		2-[(2R,5R)-2-[(4,5-Dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl}ethan-1-one
26		2-[(2R,5R)-2-[(4,5-Dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl}ethan-1-one
27		1-[6-(1,1-Difluorobutyl)-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl]-2-[(2R,5R)-2-[(4,5-dimethyl-1H-pyrazol-1-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one
28		2-[(2S,5R)-2-[(1,3-Dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]-1-{6-[(4-fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}ethan-1-one

29		1-{6-[(4-Fluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-b]pyridin-1-yl}-2-[(2S,5R)-5-methyl-2-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazin-1-yl]ethan-1-one
30		1-[6-(1,1-Difluorobutyl)-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl]-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one
31		1-{6-[(2,4-Difluorophenyl)methyl]-3,3-dimethyl-1H,2H,3H-pyrrolo[3,2-c]pyridin-1-yl}-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one
32		1-{3-[(2,4-Difluorophenyl)methyl]-7,7-dimethyl-5H,6H,7H-pyrrolo[3,2-c]pyridazin-5-yl}-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one

33		2-[(2S,5R)-2-[(1,3-Dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]-1-{3-[(4-fluorophenyl)methyl]-7,7-dimethyl-5H,6H,7H-pyrrolo[3,2-c]pyridazin-5-yl}ethan-1-one
34		1-[3-(1,1-Difluorobutyl)-7,7-dimethyl-5H,6H,7H-pyrrolo[3,2-c]pyridazin-5-yl]-2-[(2S,5R)-2-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5-methylpiperazin-1-yl]ethan-1-one
35		1-[3-[(2,4-Difluorophenyl)methyl]-7,7-dimethyl-5H,6H,7H-pyrrolo[3,2-c]pyridazin-5-yl]-2-[(2S,5R)-5-methyl-2-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazin-1-yl]ethan-1-one
36		1-[3-[(4-Fluorophenyl)methyl]-7,7-dimethyl-5H,6H,7H-pyrrolo[3,2-c]pyridazin-5-yl]-2-[(2S,5R)-5-methyl-2-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazin-1-yl]ethan-1-one

37		1-[3-(1,1-Difluorobutyl)-7,7-dimethyl-5H,6H,7H-pyrrolo[3,2-c]pyridazin-5-yl]-2-[(2S,5R)-5-methyl-2-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazin-1-yl]ethan-1-one
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Biological Assays

Expression and purification of XIAP, cIAP-1 and cIAP-2 BIR3 domains

The recombinant BIR3 domain of human XIAP (residues 252-350) fused to a His-tag, human cIAP-1 (residues 267-363) fused to a GST-tag and human cIAP-2 (residues 244-337) fused to a His-tag were overexpressed from *Escherichia coli* cells grown in TB medium. Protein was isolated from lysates using Ni-NTA affinity chromatography (XIAP/cIAP-2) or glutathione sepharase 4B affinity chromatography (cIAP-1). Affinity tags for XIAP and cIAP-1 were cleaved with thrombin in 25mM HEPES pH 7.5, 100mM NaCl, 50μM Zn(OAc)₂ and 1mM Ca(OAc)₂ followed by purification of BIR3 domains by size-exclusion chromatography. The His-tag was uncleaved for cIAP-2 and the protein was not concentrated above 3 mg/ml due to aggregation induced covalent self-oligomerization issues. The purified protein was stored in 25mM Tris pH 7.5, 100mM NaCl at -80°C.

XIAP, cIAP-1 and cIAP-2 *In vitro* Competitive Displacement Binding Assays

Modified SMAC peptides and compounds were tested for their ability to displace the fluorescent tracer from either XIAP, cIAP-1 or cIAP-2. BIR3 domains of cIAP-1, cIAP-2 and XIAP were incubated with test compounds or SMAC based peptides and their respective peptide probes (Peptide Protein Research) in assay buffer (50mM Hepes pH 7.5, 0.025% Tween-20, 0.01% BSA, and 1mM DTT). Positive controls consisted of BIR3 proteins and tracer (no inhibition) and negative controls contained tracer only (100% inhibition). The samples were incubated at room temperature for 1hr (XIAP and cIAP-2) or 3hrs (cIAP-1) prior to being read in the BMG Pherastar in Fluorescence Polarization mode (FP 485nm, 520nm, 520nm). IC₅₀ values were determined from dose-response plots using nonlinear least-squares analysis.

Final conditions for XIAP, cIAP-1 and cIAP-2 assays

Protein	Protein Conc	Peptide Probe	Peptide Conc
XIAP	20nM	AbuRPFK(5&6FAM)-amide	5nM
cIAP-1	4nM	AbuRPFK(5&6FAM)-amide	2nM
cIAP-2	20nM	AVPWK(5&6FAM)-amide	2nM

The compounds of Examples 1-9, 13-16, 21, 22, 30, 31 and 38 have IC₅₀ values of less than 1 μM or provide at least 50% inhibition of the activity at a concentration of 1 μM in the XIAP assay and have IC₅₀ values of less than 0.1 μM or provide at least 50% inhibition of the activity at a concentration of 0.1 μM in the cIAP1 assay. Preferred compounds of the

invention have IC₅₀ values of less than 0.01 µM against XIAP and/or cIAP1 and/or cIAP2. Data for the compounds of the invention in the above assays are provided in Table 1.

Anti-proliferative Activity

- 5 Inhibition of cell growth is measured using the Alamar Blue assay (Nociari, M. M, Shalev, A., Benias, P., Russo, C. *Journal of Immunological Methods* 1998, 213, 157-167). The method is based on the ability of viable cells to reduce resazurin to its fluorescent product resorufin. For each proliferation assay cells are plated onto 96 well plates and allowed to recover for 16 hours prior to the addition of inhibitor compounds (in 0.1% DMSO v/v) for a further 72 hours.
- 10 At the end of the incubation period 10% (v/v) Alamar Blue is added and incubated for a further 6 hours prior to determination of fluorescent product at 535nm ex / 590nm em. The anti-proliferative activities of compounds of the invention can be determined by measuring the ability of the compounds to inhibit growth in 3 cancer cell lines:
- EVSA-T (human breast carcinoma) DSMZ cat. no. ACC 433
 - 15 • MDA-MB-231 (human breast carcinoma) ECACC cat. no. 92020424
 - HCT116 (human colon carcinoma) ECACC cat. no. 91091005 (insensitive cell line used as a control for non-specific cytotoxicity)

- Many compounds of the invention were found to have EC₅₀ values of less than 0.01 µM in
- 20 EVSA-T cell line assays (and less than 0.1 µM against the MDA-MB-231 cell line) and preferred compounds have EC₅₀ values of less than 0.001 µM in EVSA-T cell assays (and less than 0.01 µM against the MDA-MB-231 cell line) and EC₅₀ > 10 µM against HCT116 cells. In an assay using the cell line EVSA-T, Examples 1 to 22, 30, 31 and 38 have an EC₅₀ of less than 1µM. Data for the compounds of the invention in the above assays are provided
- 25 in Table 1.

HEK293-XIAP-Caspase-9 Immunoprecipitation (IP) MSD Assay Protocol

- Stable HEK293-XIAP-Caspase-9 cells were plated out into 96-well plates [200 µl/well at 1 x10⁶ cells/ml in cultured complete medium (DMEM + 10% FBS + 0.5 mg/ml Geneticin
- 30 (Invitrogen)] and left overnight at 37 °C to recover. Compounds were added to duplicate wells in 0.1% DMSO for 2 h at 37 °C. Cells were lysed in 50 µl 1 x MSD lysis buffer (1% Triton X-100 in 20 mM Tris.Cl (pH 7.6), 150 mM NaCl including protease inhibitors) for 20 min rocking at room temperature. Streptavidin high bind MSD plate (L15SB-2) were coated with biotinylated anti-FLAG M2 antibody (Sigma F9291) at 25 µl/well with a 5 µg/ml dilution of
- 35 antibody in PBS for 1 h, shaking; followed by blocking for 1 h with 150 µl 3% BSA/TBST. Cell lysate (25 µl) was added to the 96-well anti-FLAG coated MSD plate and placed on

shaker for 4 h at room temperature. After washing 4 times with 150 μ l TBST (20 mM Tris.Cl (pH 7.6), 150 mM NaCl, 0.1% Tween-20), anti-Caspase-9 [CST#9505] diluted to 5 μ l/ml in MSD blocking buffer (3% BSA/TBST) was added overnight at 4° C. After washing plates 4 times with 150 μ l TBST, anti-rabbit-sulfo tag (MSD cat no. R32AB-1), diluted to 2 μ g/ml in MSD blocking buffer, was added for 2 hours at RT. Plates were washed 4 times with 150 μ l TBST, and 150 μ l/well 1 x MSD read buffer (R92TC-2) added before reading each plate.

EC₅₀ values were determined from dose-response plots using nonlinear least-squares analysis. Many compounds of the invention were found to have EC₅₀ values of less than 1 μ M in and preferred compounds have EC₅₀ values of less than 0.1 μ M.

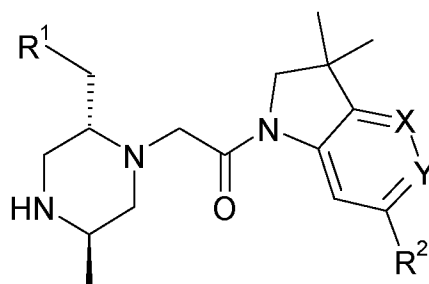
Table 1

Example	Xiap IC50 or PI μ M	clAP1 IC50 or PI μ M	EVSA-T prolif μ M
1	0.091	98%@0.012	0.0043
2	65%@0.12	100%@0.012	0.0016
3	34%@0.04	99%@0.012	0.0016
4	35%@0.04	96%@0.012	0.0026
5	0.11	96%@0.012	0.0004
6	54%@0.12	89%@0.012	0.0055
7	41%@0.04	100%@0.012	0.0029
8	36%@0.04	100%@0.012	0.0026
9	35%@0.04	92%@0.012	0.01
10			0.0064
11			0.0018
12			0.0013
13	38%@0.04	97%@0.012	0.0099
14	38%@0.04	98%@0.012	0.0059
15	0.22	85%@0.012	0.0094
16	52%@0.12	93%@0.012	0.0085
17			0.027
18			0.028
19			0.008
20			0.0021
21	61%@0.12	95%@0.012	0.0038
22	47% at 0.04	98% at 0.012	0.00082
30	59% at 0.04	81% at 0.012	0.015
31	64% at 0.04	100% at 0.012	0.0013
38	48% at 0.04	94% at 0.012	0.064

Where more than one data point has been obtained, the table above shows an average (e.g. geometric mean) of these data points (to 2 significant figures).

CLAIMS

1. A compound of formula (I):



(I)

or tautomeric or stereochemically isomeric forms, N-oxides, pharmaceutically acceptable salts or the solvates thereof; wherein

X is CH and Y is CR³, or one of X or Y is CR³ and the other is nitrogen or X and Y are nitrogen;

R¹ is selected from

(i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile,

(ii) C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a

substituent selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile,

(iii) imidazolyl which is optionally substituted with one or two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile,

(iv) pyridinyl which is substituted with two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile, and

(v) triazolyl substituted with one substituent selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, =O and nitrile or two substituents independently selected from halogen, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile;

R² is selected from: benzyl optionally substituted on the phenyl group by one or two substituents selected from fluorine and nitrile, and optionally substituted on the methylene by hydroxyl; and C₂₋₄ alkyl substituted by one or two substituents selected from fluorine and hydroxyl; and

R³ is selected from hydrogen and nitrile.

2. A compound as defined in claim 1, wherein X and Y are both nitrogen; X is nitrogen and Y is CH; or X is CH and Y is nitrogen.

5

3. A compound as defined in claim 2, wherein X is nitrogen and Y is CH.

4. A compound as defined in claim 2, wherein X is CH and Y is nitrogen.

10 5. A compound as defined in any one of claims 1 to 4, wherein R¹ is selected from:

(i) C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile;

15 (ii) C-linked imidazolyl which is optionally substituted with one or two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile;

(iii) C-linked pyridinyl which is substituted with one or two substituents independently selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile; and

20 (iv) C-linked triazolyl substituted with one substituent selected from halogen, C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, =O and nitrile or two substituents independently selected from halogen, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile.

25

6. A compound as defined in any one of claims 1 to 4, wherein R¹ is selected from:

(i) N-linked pyrazolyl which is substituted on any of the carbon atoms with two substituents independently selected from methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile;

30 (iii) N-linked imidazolyl which is optionally substituted with one or two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile; and

(iv) N-linked pyridinyl which is substituted with two substituents independently selected from fluorine, chlorine, methyl, ethyl, isopropyl, hydroxyl, hydroxymethyl, methoxy, monofluoromethyl, trifluoromethyl, =O and nitrile.

35

7. A compound as defined in any one of claims 1 to 4, wherein R¹ is selected from:
- (i) N-linked pyrazolyl which is substituted on two of the carbon atoms with a methyl substituent;
 - (iii) N-linked imidazolyl which is optionally substituted with one or two substituents
- 5 independently selected from chlorine, methyl, ethyl, hydroxymethyl, trifluoromethyl and nitrile; and
- (iv) N-linked pyridinyl which is substituted with two substituents selected from methyl and =O.
- 10 8. A compound as defined in any one of claims 1 to 4, wherein R¹ is selected from:
- (i) N-linked pyrazolyl which is substituted on two of the carbon atoms with a methyl substituent;
 - (iii) N-linked imidazolyl which is substituted with one or two substituents independently
- 15 selected from chlorine, methyl, ethyl, hydroxymethyl, trifluoromethyl and nitrile; and
- (iv) N-linked pyridinyl which is substituted with two substituents selected from methyl and =O.
9. A compound as defined in claim 5, wherein R¹ is a C-linked pyrazolyl which is optionally substituted on a nitrogen atom with a substituent selected from C₁₋₄ alkyl,
- 20 hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile.
10. A compound as defined in claim 9, wherein when R¹ represents a C-linked pyrazolyl
- 25 which is substituted on a nitrogen atom with a substituent, said substituent is selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl, and further optionally substituted on the carbon atoms with one or two substituents independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile.
- 30 11. A compound as defined in claim 10, wherein when R¹ represents a C-linked pyrazolyl, said pyrazolyl is substituted on one nitrogen atom by a C₁₋₄ alkyl substituent and optionally substituted on one carbon atom by a C₁₋₄ alkyl substituent.
12. A compound as defined in claim 11, wherein when R¹ represents a C-linked pyrazolyl,
- 35 said pyrazolyl is substituted on one nitrogen atom by a methyl substituent and substituted on one carbon atom by a methyl substituent.

13. A compound as defined in claim 12, wherein when R^1 represents a C-linked pyrazolyl, said R^1 group is 1,3-dimethyl-1H-pyrazol-5-yl.

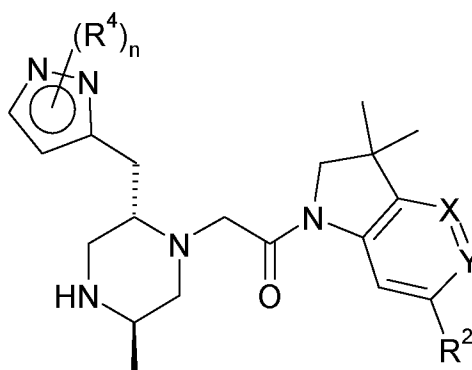
14. A compound as defined in any one of claims 1 to 13, wherein R^2 is selected from 4-fluorobenzyl, 2,4-difluorobenzyl or 2-cyano-4-fluorobenzyl.

15. A compound as defined in any one of claims 1 to 13, wherein R^2 is selected from 1,1-difluoropropyl and 1,1-difluorobutyl.

16. A compound as defined in claim 14, wherein R^2 is 2,4-difluorobenzyl.

17. A compound as defined in claim 15 wherein R^2 is 1,1-difluorobutyl.

18. A compound as defined in claim 1, wherein the compound of formula (I) is a compound of formula (Ie):

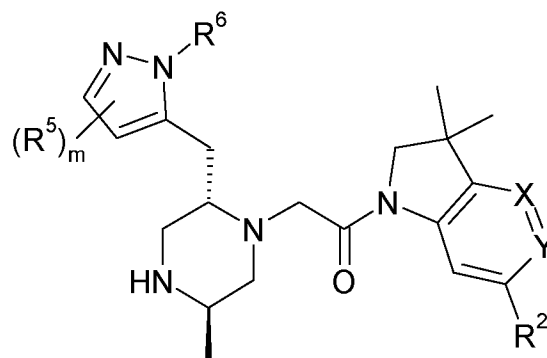


(Ie)

or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein R^2 is as defined in any one of claims 1 or 14 to 17, R^4 is independently selected from C_{1-4} alkyl, hydroxy C_{1-4} alkyl and halo C_{1-4} alkyl when on a nitrogen atom and selected from C_{1-4} alkyl, hydroxyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl, methoxymethyl, =O and nitrile when on a carbon atom; and n is 0, 1, 2 or 3.

19. A compound as defined in claim 1, wherein the compound of formula (I) is a compound of formula (If):



(If)

or tautomeric or stereochemically isomeric forms, *N*-oxides, pharmaceutically acceptable salts or the solvates thereof;

wherein R² is as defined in any one of claims 1 or 14 to 17, R⁶ is selected from C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl and haloC₁₋₄ alkyl; R⁵ is independently selected from C₁₋₄ alkyl, hydroxyl, hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxy, haloC₁₋₄ alkyl, methoxymethyl, =O and nitrile; and m is selected from 0, 1 and 2.

20. A compound as defined in claim 1, wherein the compound is selected from Examples 1 to 38 or a tautomeric or stereochemically isomeric form, *N*-oxide, pharmaceutically acceptable salt or the solvate thereof.

21. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 20.

22. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 20, in combination with one or more therapeutic agents.

23. A compound as defined in any one of claims 1 to 20 for use in therapy.

24. A compound as defined in any one of claims 1 to 20 for use in the prophylaxis or treatment of a disease state or condition mediated by IAP, such as an XIAP and/or cIAP.

25. A compound as defined in any one of claims 1 to 20 for use in the prophylaxis or treatment of a disease state or condition which overexpresses IAP, such as XIAP and/or cIAP.

26. A compound as defined in any one of claims 1 to 20 for use in the prophylaxis or treatment of a disease state or condition as described herein.
27. A compound as defined in any one of claims 1 to 20 for use in the prophylaxis or
5 treatment of cancer.
28. A compound of formula (I) as defined in any one of claims 1 to 20 in combination with one or more (e.g. 1 or 2) other therapeutic agents (e.g. anticancer agents).
- 10 29. A compound of formula (I) as defined in any one of claims 1 to 20 in combination with one or more (e.g. 1 or 2) other therapeutic agents (e.g. anticancer agents) for use in therapy, such as in the prophylaxis or treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/052721

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D403/14 C07D471/04 C07D519/00 A61K31/437 A61P35/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K		
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 practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2012/143726 A1 (ASTEX THERAPEUTICS LTD [GB]; WOOLFORD ALISON JO-ANNE [GB]; HOWARD STEV) 26 October 2012 (2012-10-26) claims; examples 112,138,142,143,147,171,233; table 8; compounds	1-29
A	----- FLYGARE JOHN A ET AL: "Small-molecule pan-IAP antagonists: a patent review", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 20, no. 2, 1 February 2010 (2010-02-01), pages 251-267, XP009140763, ISSN: 1354-3776 figure 6; examples ----- -/--	1-29
☒ Further documents are listed in the continuation of Box C. ☒ 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 application or patent 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 16 December 2013		Date of mailing of the international search report 20/12/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2013/052721

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/045905 A1 (NOVARTIS AG [CH]; CHAREST MARK G [US]; CHEN CHRISTINE HIU-TUNG [US]; C) 17 April 2008 (2008-04-17) claims; examples -----	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2013/052721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012143726 A1	26-10-2012	AU 2012246081 A1 CA 2831346 A1 TW 201309673 A WO 2012143726 A1	03-10-2013 26-10-2012 01-03-2013 26-10-2012
WO 2008045905 A1	17-04-2008	AU 2007307763 A1 CA 2666112 A1 CN 101595121 A EP 2102229 A1 JP 5190062 B2 JP 2010506847 A KR 20090065548 A RU 2009117701 A US 2011015232 A1 WO 2008045905 A1	17-04-2008 17-04-2008 02-12-2009 23-09-2009 24-04-2013 04-03-2010 22-06-2009 20-11-2010 20-01-2011 17-04-2008