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(71) Applicant: **CTxT PTY LIMITED** [AU/AU]; 343 Royal Parade, Parkville, Victoria 3052 (AU).

(72) Inventors: **STUPPLE, Paul Anthony**; Monash Institute of Pharmaceutical Sciences, 381 Royal Parade, Parkville, Victoria 3052 (AU). **WALKER, Scott Raymond**; Monash Institute of Pharmaceutical Sciences, 381 Royal Parade, Parkville, Victoria 3052 (AU). **CAMERINO, Michelle Ang**; Monash Institute of Pharmaceutical Sciences, 381 Royal Parade, Parkville, Victoria 3052 (AU).

(74) Agents: **WATSON, Robert** et al.; Mewburn Ellis LLP, City Tower, 40 Basinghall Street, London, Greater London EC2V 5DE (GB).

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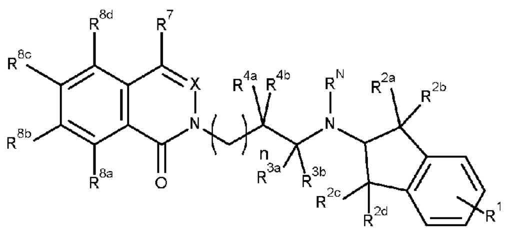
(54) Title: PRMT5 INHIBITORS



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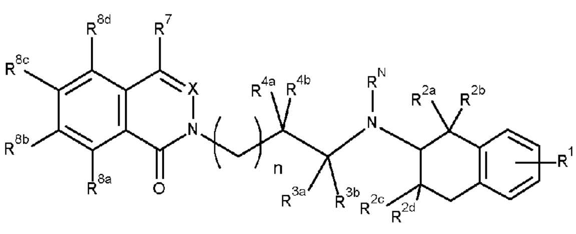

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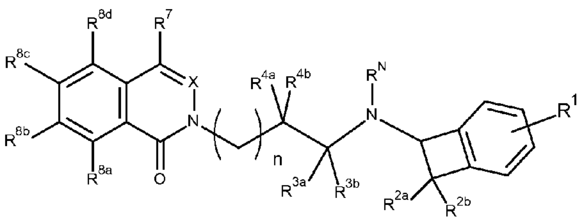

(Ic)

(57) Abstract: A compound of formula (Ia), (Ib) or (Ic) wherein: n is 1 or 2; R^N is H or Me; R^1 is optionally one or more halo or methyl groups; R^{2a} and R^{2b} are independently selected from the group consisting of: (i) F; (ii) H; (iii) Me; and (iv) CH_2OH; R^{2c} and R^{2d} (if present) are independently selected from the group consisting of: (i) F; (ii) H; (iii) Me; and (iv) CH_2OH; R^{3a} and R^{3b} are independently selected from H and Me; R^{4a} is selected from OH, $-NH_2$, $-C(=O)NH_2$, and $-CH_2OH$; R^{4b} is either H or Me; X is either N or CH; R^7 is selected from H and C_{1-4} alkyl; (a) one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, NHC_{1-4} alkyl; (b) another of R^{8a}, R^{8b}, R^{8c} and R^{8d} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, acylamidomethyl, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4} alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl; (c) the others of R^{8a}, R^{8b}, R^{8c} and R^{8d} are H.

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PRMT5 INHIBITORS

The present invention relates to amino-bicyclic compounds and their use as pharmaceuticals, and in particular, in treating cancer and hemoglobinopathies.

Background to the Invention

Post-translational modification of proteins is a hallmark of signal transduction where cells are able to react quickly to changes or events in the cellular environment. Post-translational modification of proteins expands the structural and functional diversity of the proteome. The role of acetylation and phosphorylation of proteins has been extensively studied as highly reversible reactions for fine- tuning responses to external stimuli or changes in the environmental conditions. Recently, the importance of other types of protein modifications, including ubiquitination and methylation has begun to be recognized.

The methylation of proteins and the enzymes that carry out these reactions has increased the dimensions of gene regulation by marking genes that are transcriptionally active or silenced. Protein methylation can occur on amino acids such as lysine, arginine, histidine, or proline, and on carboxy groups.

Arginine methylation of mainly nuclear proteins is an important post-translational modification process involved in structural remodelling of chromatin, signal transduction, cellular proliferation, nucleocytoplasmic shuttling, translation, gene transcription, DNA repair, RNA processing, or mRNA splicing.

Methylation of proteins at arginine residues is catalysed by Protein Arginine Methyltransferase enzymes. The Protein Arginine Methyl Transferase (PRMT) family of enzymes are evolutionarily conserved between organisms but differ in the number of members in different organisms.

There are eleven members of the human PRMT family, eight of which have known enzymatic activity and target substrates. With the exception of PRMT2 and two recently identified putative PRMT genes (PRMT10 and PRMT11), all remaining proteins of the family possess enzymatic arginine methylation activity.

PRMTs are subdivided into two types based on the methylation that they catalyse at the guanidinium group of arginine residues of substrate proteins. There are three nitrogens in the guanidinium group, potentially all of which could be methylated; the two Ψ-guanidino nitrogen atoms and the internal δ-guanidino nitrogen atom. Mono-methylation and dimethylation of arginine (MMA and DMA) is found in mammalian cells at one or both of the two Ψ-guanidino nitrogen atoms; dimethylation may be either symmetric or asymmetric. The third methylated arginine is generated by monomethylation of the internal δ-guanidino nitrogen atom of arginine and has so far been documented only in yeast proteins. Type I PRMT enzymes catalyse the formation of MMA and asymmetric dimethylarginine by di-methylating the same nitrogen atom of the guanidinium group, whereas Type II PRMT enzymes catalyse the formation of MMA and symmetric di-methylarginine by mono-methylating each of the terminal nitrogen atoms. Type III enzymes methylate the internal δ-guanidino nitrogen atom. Of the eight well characterised human PRMTs, PRMT1, 3, 4, 6 and 8 are Type I enzymes, and PRMT5, 7 and 9 are Type II enzymes.

PRMTs catalyse the methylation of the guanidino nitrogen atoms of arginine residues through the transfer of a methyl group from S-adenosyl methionine (SAM). A by-product of the enzymatic methylation step is S-adenosyl-L-homocysteine (AdoHcy), which is hydrolyzed to adenosine and homocysteine by AdoHcy hydrolase (Krause et al., 2007).

<u>PRMT5</u>

PRMT5 (aka JBP1, SKB1, IBP72, SKB1his and HRMTIL5) is a Type II arginine methyltransferase, and was first identified in a two-hybrid search for proteins interacting with the Janus tyrosine kinase (Jak2) (Pollack et al., 1999).

PRMT5 plays a significant role in control and modulation of gene transcription. Inter alia, PRMT5 is known to methylate histone H3 at Arg-8 (a site distinct from that methylated by PRMT4) and histone H4 at Arg-3 (the same site methylated by PRMT1) as part of a complex with human SWI/SNF chromatin remodelling components BRG1 and BRM.

In addition to direct repressive histone marks induced by PRMT5, the enzyme's role in gene silencing is also mediated through the formation of multiprotein repressor complexes that include NuRD components, HDACs, MDB proteins and DNA methyltransferases, (Rank et al., 2010; Le Guezennec et al., 2006; Pal et al., 2003).

PRMT5 is involved in the methylation and functional modulation of the tumour suppressor protein p53. See (Berger, 2008; Durant et al., 2009; Jansson et al., 2008; Scoumanne et al., 2009). Most of the physiological functions of p53 are attributable to its role as a transcriptional activator, responding to agents that damage DNA. p53 status is wild type in approximately half of human cancer cases. These include 94% in cervix, 87% in blood malignancies, 85% in bones and endocrine glands, and 75% of primary breast cancer. Restoration of p53 in cancer cells harbouring wild type p53, by way of inhibiting mechanisms that suppress its function leads to growth arrest and apoptosis, and is regarded as a potentially effective means of tumour suppression.

p53 target genes have two alternative downstream effects: either they pause the cell cycle, allowing the DNA to be repaired, or, if repair is not possible, they activate processes leading to apoptosis (programmed cell death). How p53 'chooses' between these distinct outcomes is a central question in the field of tumour biology.

p53 is replete with post-translational modifications. Phosphorylation was one of the first post-translational modifications to be clearly defined on p53. In the last decade it has become additionally clear that p53 is modified not only by phosphorylation, but that it is extensively modified by lysine acetylation and methylation, among other modifications. Indeed, besides histone proteins p53 is the most common protein substrate known for these post-translational modifications. However, despite the plethora of post-translational modifications, p53 has not been identified, until recently, as a substrate for arginine methylation.

Jansson et al (Jansson et al., 2008) discovered that PRMT5 is physically associated with a p53 cofactor called Strap. A co-factor complex that contains Strap et al binds to p53 in response to DNA damage. Jansson et al demonstrated that PRMT5 methylates p53 in vitro, and mapped the sites of methylation (R333, R335 and R337). They developed an antibody that specifically detects p53 methylated on these sites and confirmed that p53 is methylated in vivo. Jansson et al went on to show that p53 methylation requires PRMT5 and is increased in response to etoposide, a DNA damaging agent.

The role of PRMT5 and p53 arginine methylation on cell cycle regulation and DNA damage response have been explored by both Jansson et al and Scoumanne et al (Jansson et al., 2008; Scoumanne et al., 2009). Although some differences are evident between the results from the two groups in respect of cell cycle regulation in unperturbed cells (which may be ascribed to cell type specific effects and/or the actual nature of the experimental arrangements), both groups report similar results with respect to the DNA damage response.

In response to DNA damage, caused by a variety of agents, including doxorubicin, camptothecin and UV light, and also in response to treatment with Nutlin-3, knockdown of PRMT5 results in an increase in sub-G1 population and concomitant reduction in G1 cells and, in the presence of p53, a significant increase in apoptosis. Knockdown of PRMT5 also resulted in a reduced level of p21, a key p53 target gene that regulates cell cycle arrest during the p53 response and MDM2, a p53 E3 ubiquitin ligase, but not PUMA, NOXA, AIP1 & APAF1, p53 target genes linked to apoptosis.

Knockdown of PRMT5 (but not PRMT1 or CARM1/PRMT4) results in decreased p53 stabilisation, decreased basal p53 levels, and decreased p53 oligomerisation, and also decreased expression of eIF4E a major component of translational machinery involved in ribosome binding to mRNA. Indeed, eIF4E is a potent oncogene, which has been shown to promote malignant transformation in vitro and human cancer formation.

Knockdown of PRMT5 would be expected to lead to a reduction in the level of arginine methylated p53. Consistent with arginine methylation status of p53 influencing the p53 response (reduced arginine methylation biasing the response to proapoptotic), Jannson et al showed that a p53 mutant in which each of the three critical arginine residues were substituted with lysine (p53KKK) retained the ability to induce apoptosis but its cell cycle arrest activity was significantly compromised.

Moreover, pS3KKK also has a significantly reduced ability to induce transcription of p21, by contrast with APAF1. The promoter binding specificity of wild-type p53 to key target genes is also significantly affected by arginine methylating status: Knockdown of PRMT5 results in decreased p53 binding to the promoter regions of the p21 and (intriguingly) PUMA genes, but does not affect p53 binding to the promoter regions of NOXA or APAF1.

Taken together, it would seem that PRMT5 is a pro-survival factor, which regulates cell proliferation in unstressed conditions and modulates the p53 response during DNA damage. In particular, knockdown of PRMT5, leading to a reduction in the levels of arginine methylated p53, appears to bias the p53 DNA damage response to proapoptotic as opposed to cell cycle arrest.

PRMT5 is further linked to cancers in that it is aberrantly expressed in around half of human cancer cases. PRMT5 overexpression has been observed in patient tissue samples and cell lines of Prostate cancer (Gu et al., 2012), Lung cancer (Zhongping et al., 2012), Melanoma cancer (Nicholas et al., 2012), Breast cancer (Powers et al., 2011), Colorectal cancer (Cho et al., 2012), Gastric cancer (Kim et al., 2005), Esophagus and Lung carcinoma (Aggarwal et al., 2010) and B-Cell lymphomas and leukemia (Wang, 2008). Moreover, elevated expression of PRMT5 in Melanoma, Breast and Colorectal cancers has been demonstrated to correlate with a poor prognosis.

Lymphoid malignancies including CLL are associated with over-expression of PRMT5. PRMT5 is over-expressed (at the protein level) in the nucleus and cytosol in a number of patient derived Burkitt's lymphoma; mantle cell lymphoma (MCL); in vitro EBV-transformed lymphoma; leukaemia cell lines; and B-CLL cell lines, relative to normal CD19+ B lymphocytes (Pal et al., 2007; Wang et al., 2008). Intriguingly, despite elevated levels of PRMT5 protein in these tumour cells, the levels of PRMT5 mRNA are reduced (by a factor of 2 - 5). Translation of PRMT5 mRNA is however, enhanced in lymphoma cells, resulting in increased levels of PRMT5 (Pal et al., 2007; Wang et al., 2008).

In addition to genomic changes, CLL, like almost all cancers, has aberrant epigenetic abnormalities characterised by global hypomethylation and hot-spots of repressive hypermethylation of promoters including tumour suppressor genes. While the role of epigenetics in the origin and progression of CLL remains unclear, epigenetic changes appear to occur early in the disease and specific patterns of DNA methylation are associated with worse prognosis (Chen et al., 2009; Kanduri et al., 2010). Global symmetric methylation of histones H3R8 and H4R3 is increased in transformed lymphoid cell lines and MCL clinical samples (Pal et al., 2007), correlating with the overexpression of PRMT5 observed in a wide variety of lymphoid cancer cell lines and MCL clinical samples.

PRMT5 is therefore a target for the identification of novel cancer therapeutics.

PRMT5 Function and Hemoglobinopathies

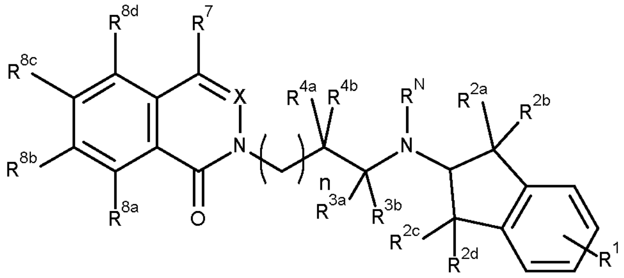
Hemoglobin is a major protein in red blood cells and is essential for the transport of oxygen from the lungs to the tissues. In adult humans, the most common hemoglobin type is a tetramer called hemoglobin A, consisting of two α and two β subunits. In human infants, the hemoglobin molecule is made up of two α and two γ chains. The gamma chains are gradually replaced by subunits as the infant grows. The developmental switch in human ß-like globin gene subtype from foetal (γ) to adult (ß) that begins at birth heralds the onset of the hemoglobinopathies ß-thalassemia and sickle cell disease (SCD). In ß-thalassemia the adult chains are not produced. In SCD a point mutation in the coding sequence in the ß globin gene leads to the production of a protein with altered polymerisation properties. The observation that increased adult γ-globin gene expression (in the setting of hereditary persistence of foetal hemoglobin (HPFH) mutations) significantly ameliorates the clinical severity of ß-thalassemia and SCD has prompted the search for therapeutic strategies to reverse γ-globin gene silencing. To date, this has been achieved through pharmacological induction, using compounds that broadly influence epigenetic modifications, including DNA methylation and histone deacetylation. The development of more targeted therapies is dependent on the identification of the molecular mechanisms underpinning foetal globin gene silencing. These mechanisms have remained elusive, despite exhaustive study of the HPFH mutations, and considerable progress in many other aspects of globin gene regulation.

PRMT5 plays a critical role in triggering coordinated repressive epigenetic events that initiate with dimethylation of histone H4 Arginine 3 (H4R3me2s), and culminate in DNA methylation and transcriptional silencing of the γ-genes (Rank et al., 2010). Integral to the synchronous establishment of the repressive markers is the assembly of a PRMT5-dependent complex containing the DNA methyltransferase DNMT3A, and other repressor proteins (Rank et al., 2010). DNMT3A is directly recruited to bind to the PRMT5-induced H4R3me2s mark, and loss of this mark through shRNA-mediated knock-down of PRMT5, or enforced expression of a mutant form of PRMT5 lacking methyltransferase activity leads to marked upregulation of γ-gene expression, and complete abrogation of DNA methylation at the γ-promoter. Treatment of human erythroid progenitors with non-specific methyltransferase inhibitors (Adox and MTA) also resulted in upregulation of γ-gene expression (He Y, 2013). Inhibitors of PRMT5 thus have potential as therapeutics for hemoglobinopathies such as ß-thalassemia and Sickle Cell Disease (SCD).

The present inventors have developed particular substituted β-hydroxy amides inhibit the activity of PRMT5 and therefore may be of use in treating conditions ameliorated by the inhibition of the activity of PRMT5.

Summary of the Invention

A first aspect of the present invention provides a compound of formula Ia, Ib or Ic:



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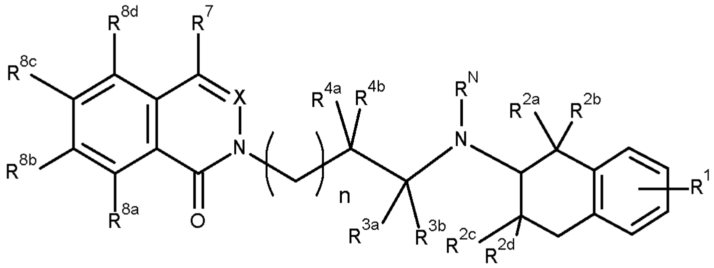

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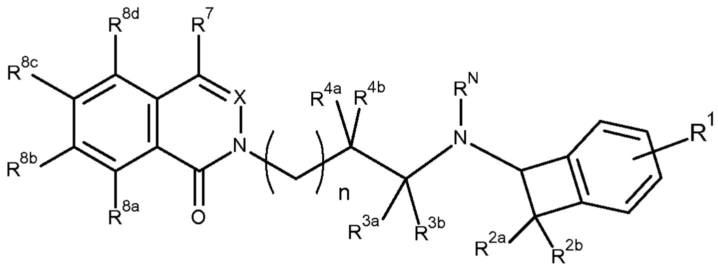


(Ic)

wherein:

n is 1 or 2;

R^N is H or Me;

R^1 is optionally one or more halo or methyl groups;

R^{2a} and R^{2b} are independently selected from the group consisting of:

(i) F;

(ii) H;

(iii) Me; and

(iv) CH_2OH;

R^{2c} and R^{2d} (if present) are independently selected from the group consisting of:

(i) F;

(ii) H;

(iii) Me; and

(iv) CH_2OH;

R^{3a} and R^{3b} are independently selected from H and Me;

R^{4a} is selected from OH, $-NH_2$, $-C(=O)NH_2$, and $-CH_2OH$;

R^{4b} is either H or Me;

X is either N or CH;

R^7 is selected from H and C_{1-4} alkyl;

(a) one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, NHC_{1-4} alkyl;

(b) another of R^{8a}, R^{8b}, R^{8c} and R^{8d} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, acylamidomethyl, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4} alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl;

(c) the others of R^{8a}, R^{8b}, R^{8c} and R^{8d} are H.

A second aspect of the present invention provides a compound of the first aspect for use in a method of therapy. The second aspect also provides a pharmaceutical composition comprising a compound of the first aspect and a pharmaceutically acceptable excipient.

A third aspect of the present invention provides a method of treatment of cancer, comprising administering to a patient in need of treatment, a compound of the first aspect of the invention or a pharmaceutical composition of the first aspect of the invention. The third aspect of the present invention also provides the use of a compound of the first aspect of the invention in the manufacture of a medicament for treating cancer, and a compound of the first aspect of the invention or pharmaceutical composition thereof for use in the treatment of cancer.

As described below, the compound of the first aspect may be administered simultaneously or sequentially with radiotherapy and/or chemotherapy in the treatment of cancer.

A fourth aspect of the present invention provides a method of treatment of hemoglobinopathies, comprising administering to a patient in need of treatment, a compound of the first aspect of the invention or a pharmaceutical composition of the first aspect of the invention. The fourth aspect of the present invention also provides the use of a compound of the first aspect of the invention in the manufacture of a medicament for treating hemoglobinopathies, and a compound of the first aspect of the invention or pharmaceutical composition of the first aspect of the invention for use in the treatment of hemoglobinopathies.

Definitions

C_{1-4} alkyl: The term “C_{1-4} alkyl” as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a saturated hydrocarbon compound having from 1 to 4 carbon atoms.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), and butyl (C_4).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), and n-butyl (C_4).

Examples of saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4) and tert-butyl (C_4).

C_{1-4} fluoroalkyl: The term “C_{1-4} fluoroalkyl” refers to a C_{1-4} alkyl group as defined above where one of more of the hydrogen atoms is replaced by a fluoro. Examples of C_{1-4} fluoroalkyl include, but are not limited to, $-CF_3$, CF_2H, $-C_2F_5$, and $-C_2F_4H$.

C_{3-6} cycloalkyl: the term ‘C_{3-6} cycloalkyl’ as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a saturated cyclic core having 3, 4, 5 or 6 atom in the cyclic core all of which are carbon atoms. Examples of C_{3-6} cycloalkyl include, but are not limited to, cyclopropyl, cyclohexyl and cyclopentyl.

C_{3-4} cycloalkyl: the term ‘C_{3-4} cycloalkyl’ as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a saturated cyclic core having 3 or 4 atoms in the cyclic core all of which are carbon atoms. Examples of C_{3-4} cycloalkyl include cyclopropyl and cyclobutyl.

C_{5-6} heteroaryl: the term C_{5-6} heteroaryl as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of an aromatic structure having between one and three atoms that are not carbon forming part of said ring. Wherein, those atoms that are not carbon can be chosen independently from the list nitrogen, oxygen and sulphur. The group may be substituted by one or more C_{1-4} alkyl groups.

Examples of C_{5-6} heteroaryl groups include, but are not limited to, groups derived from:
N_1: pyridine (C_6);

N_1O_1: oxazole (C_5), isoxazole (C_5);
N_2O_1: oxadiazole (furazan) (C_5);
N_2S_1: thiadiazole (C_5)
N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);
N_3: triazole (C_5).

C_{5-6} heteroaryl methyl: -CH_2-(C_{5-6} heteroaryl), wheren C_{5-6} heteroaryl is as defined above.

C_{4-6} heterocyclyl: The term "C_{4-6} heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a monocyclic heterocyclic compound, which moiety has from 4 to 6 ring atoms; of which from 1 to 2 atoms are heteroatoms, chosen from oxygen or nitrogen.

In this context, the prefixes (e.g. C_{4-6}) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms.

Examples of C_{4-6} heterocyclyl groups include, but are not limited to, those derived from:
N_1: azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
N_2: diazetidine (C_4), imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
O_1: oxetane (C_4), tetrahydrofuran (C_5); oxane (C_6);
O_2: dioxetane (C_4), dioxolane (C_5); dioxane (C_6);
N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6).

Those C_{4-6} heterocyclyl groups which include a N atom may be substituted on this atom by an acyl group, and in particular, by -C(=O)Me.

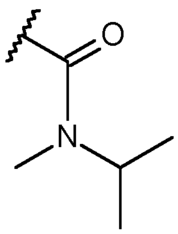
C_{4-6} heterocyclyl methyl: -CH_2-(C_{4-6} heterocyclyl), wherein C_{4-6} heterocyclyl is as defined above.

Phenyl: -C_6H_5, wherein the phenyl may itself be optionally substituted by one or more C_{1-4} alkyl groups, one or more C_{1-4} fluoroalkyl groups, one or more C_{1-4} alkoxy groups, one or more halo substituents and one or more cyano substituents.

Benzyl: -CH_2-Phenyl, wherein phenyl is as defined above.

Halo: The term “halo” as used herein, refers to a group selected from fluoro, chloro, bromo and iodo.

Amido: -(C=O)NRR’ wherein R and R’ are independently selected from H, C_{1-4} alkyl and C_{4-6} heterocyclyl as defined above, or together form a group selected from (-CH_2-)$_n$ and -$(CH_2)_m$-X-$(CH_2)_p$-, where n=3-6, m and p=0-4, and X=O or NH. X may also be N-$S(=O)_2$, S or $S(=O)_2$. The cyclic amido groups may also be bridged by a further group selected from (-CH_2-)$_{n1}$ and -$(CH_2)_{m1}$-X-$(CH_2)_{p1}$-, where n1 is 1-3 and m1 and p1 are 1-3. The cyclic amido groups may also be further substituted by one, two or more hydroxy, oxo, C_{1-2} alkyl, C_{1-2} alkyl-C_{1-2} alkoxy, C_{1-2} alkyl-hydroxy and C_{1-2} alkoxy groups or one spiro C_{4-6} heteroaryl or spiro C_{4-6} cycloalkyl group or be fused to an C_{5-7} aromatic ring. Examples of amido groups include, but are not limited to, -C(=O)NH_2, -C(=O)NMe_2, -C(=O)NHMe, -C(=O)NHCH$(CH_3)_2$,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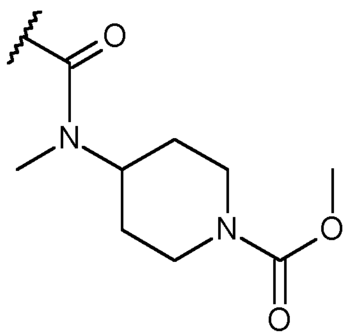
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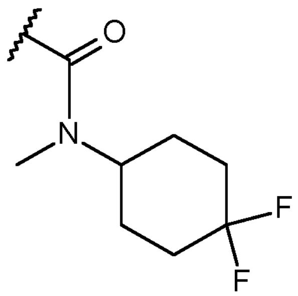
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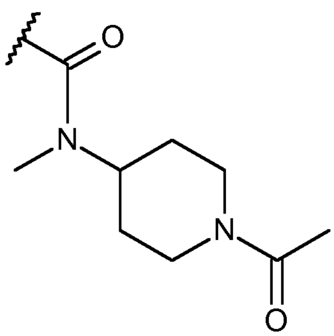
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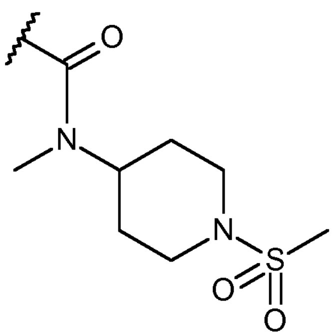
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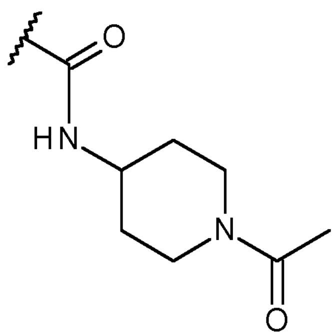
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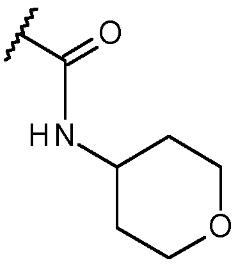
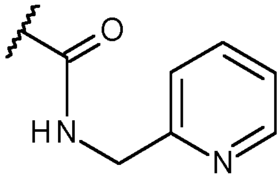
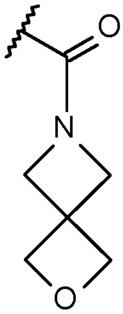
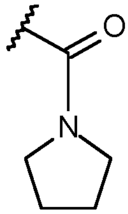
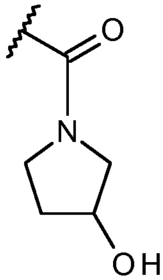
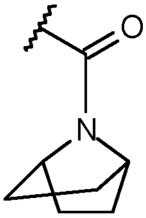
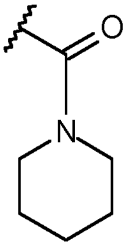
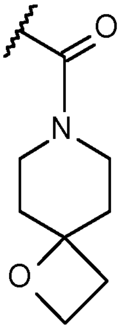
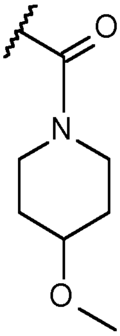
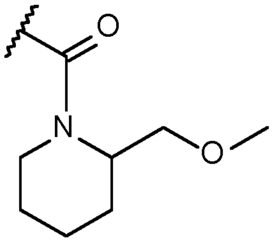
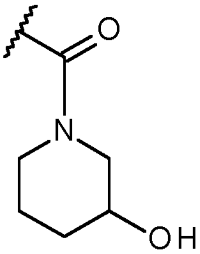
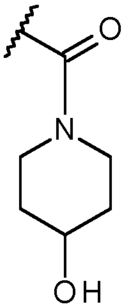
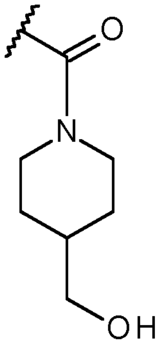
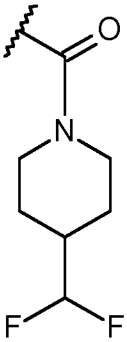
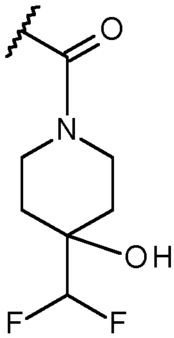
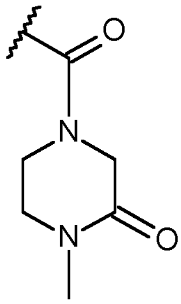
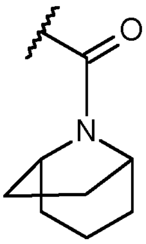
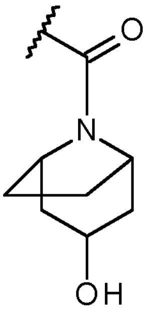
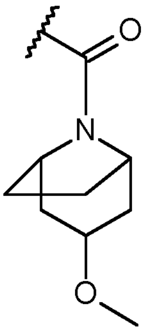
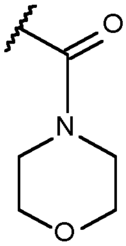
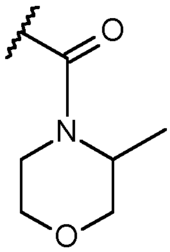
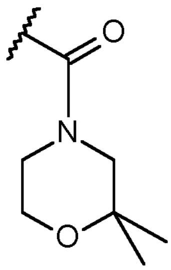
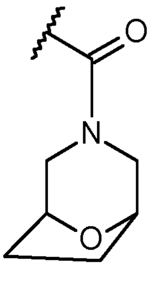
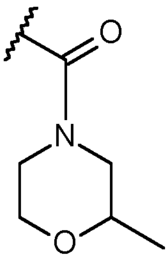
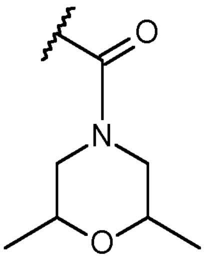
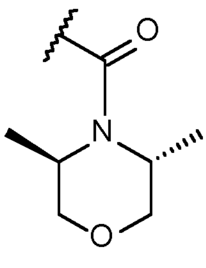
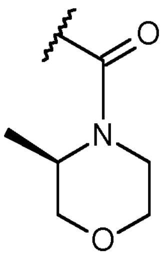
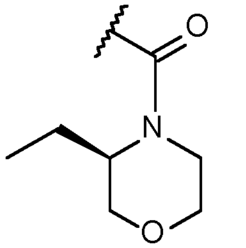
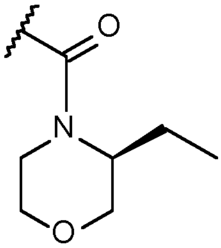
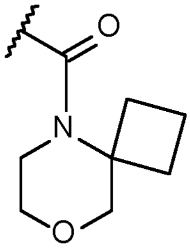
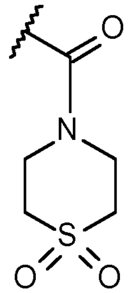
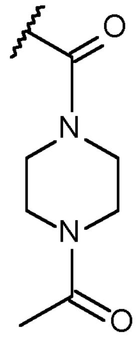
, , , , ,

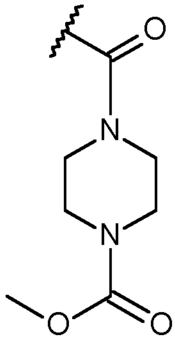
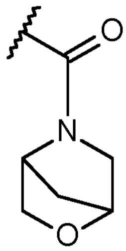
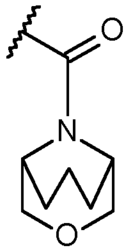
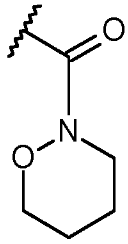
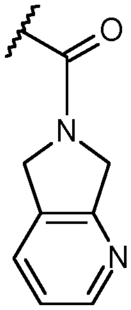
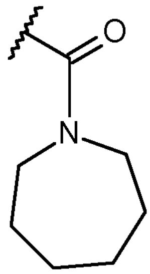
, , , , ,

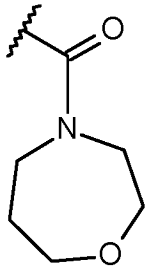
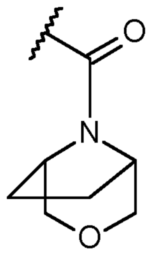
, , , , , ,

, , , , , ,

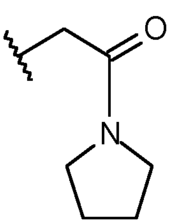
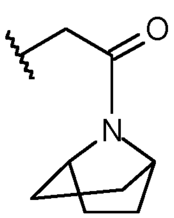
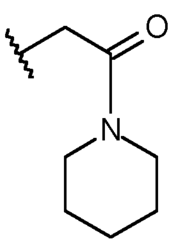
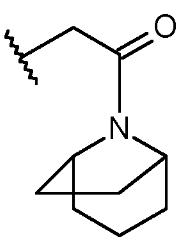
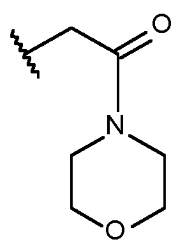
, , , , ,

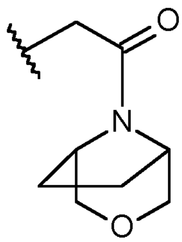
, , , , ,

, , , , , ,

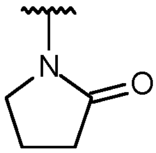
 and .

Amidomethyl: $-CH_2$-amido, where amido is as defined above, Examples of amidomethyl groups include, but are not limited to, $-CH_2-C(=O)NH_2$, $-CH_2-C(=O)NMe_2$, $-CH_2-C(=O)NHMe$,

, , , , 

and  .

Acylamido: -NR(C=O)R’ wherein R and R’ are independently selected from H, C_{1-4} alkyl and C_{1-4} fluoro alkyl as defined above. R’ may also be $-(CH_2)_n-$, where n is 3 or 4. Examples of an acylamido group include, but are not limited to, $-N(H)C(=O)CF_3$, -N(H)C(=O)Me, and:



Acylamidomethyl: $-CH_2$-acylamido, where acylamido is as defined above, Examples of acylamidomethyl groups include, but are not limited to $-CH_2-N(H)C(=O)Me$ and $-CH_2-N(H)C(=O)CF_3$.

C_{1-4} alkyl ester: -C(=O)OR, wherein R is a C_{1-4} alkyl group. Examples of C_{1-4} alkyl ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, and $-C(=O)OC(CH_3)_3$.

C_{1-4} alkyl ester methyl: $-CH_2-(C_{1-4}$ alkyl ester), where C_{1-4} alkyl ester is as defined above. Examples of C_{1-4} alkyl ester methyl groups include, but are not limited to, $-CH_2-C(=O)OCH_3$, $-CH_2-C(=O)OCH_2CH_3$, and $-CH_2-C(=O)OC(CH_3)_3$.

C_{1-4} alkyl carbamoyl: -NHC(=O)OR wherein R is a C_{1-4} alkyl group as defined above. Examples of C_{1-4} alkyl carbamoyl include, but are not limited to, $-N(H)C(=O)OCH_3$, $-N(H)C(=O)OCH_2CH_3$, and $-N(H)C(=O)OC(CH_3)_3$.

C_{1-4} alkyl carbamoyl methyl: $-CH_2-(C_{1-4}$ alkyl carbamoyl), where C_{1-4} alkyl carbamoyl is as defined above. Examples of C_{1-4} alkyl carbamoyl methyl include, but are not limited to, $-CH_2-N(H)C(=O)OCH_3$, $-CH_2-N(H)C(=O)OCH_2CH_3$, and $–CH_2-N(H)C(=O)OC(CH_3)_3$.

C_{1-4} alkylacyl: -C(=O)R, wherein R is a C_{1-4} alkyl group as defined above. Examples of C_{1-4} alkylacyl groups include, but are not limited to, -C(=O)CH_3 (acetyl), -C(=O)CH_2CH_3 (propionyl) and -C(=O)C$(CH_3)_3$ (t-butyryl).

C_{1-4} alkylacyl methyl: -CH_2-(C_{1-4} alkylacyl), where C_{1-4} alkylacyl is as defined above. Examples of C_{1-4} alkylacylmethyl groups include, but are not limited to, -CH_2-C(=O)CH_3, -CH_2-C(=O)CH_2CH_3, and -CH_2-C(=O)C$(CH_3)_3$.

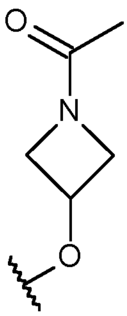
Phenylcarbonyl: -C(=O)-phenyl, where phenyl is as defined above.

Carboxy (carboxylic acid): -C(=O)OH

Carboxymethyl: -CH_2-C(=O)OH.

Ether: -OP, wherein P is chosen from one of the following substituents: C_{1-4} alkyl, benzyl, phenyl, C_{1-4} fluoroalkyl, C_{5-6} heteroaryl, -CH_2-C_{5-6} heteroaryl, C_{4-6} heterocyclyl, and -CH_2-C_{4-6} heterocyclyl as defined above. Examples of an ether include, but are not limited to, -OPh, -OBn, -OCF_3, -OCH_2CF_3, -OCH$(CH_3)_2$, -OCH_2-cyclopropyl,

-O-(N-acetyl)azetidinyl, e.g.



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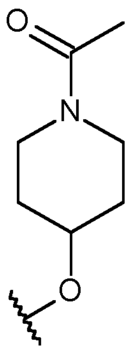
-O-(N-acetyl)piperidinyl, e.g.



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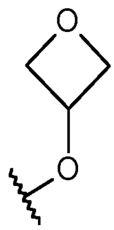
-O-oxetanyl, e.g.;



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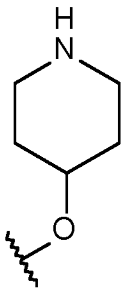
Piperidyloxy, e.g



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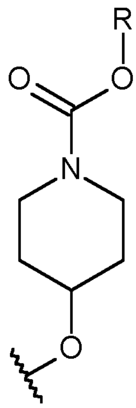
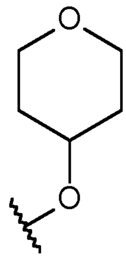
-O-(N-carboxylate)piperidinyl, e.g.



where R is methyl, isopropyl, isobutyl;

-O-tetrahydropyranyl, e.g.;



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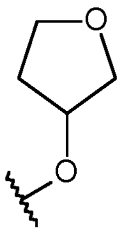
-O-tetrahydrofuranyl, e.g.;



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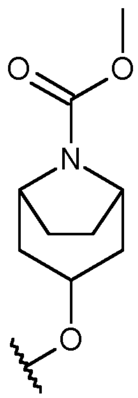
(8-methoxycarbonyl-8-azabicyclo[3.2.1]octan-3-yl)oxy:



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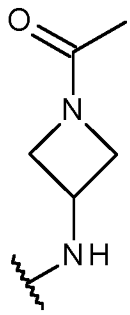
Amino: -NPP', wherein P and P' are independently chosen from H, C_{1-4} alkyl, C_{4-6} heterocyclyl, phenyl and C_{5-6} heteroaryl as defined above. Examples of an amine include, but are not limited to, $-NH_2$,-N(H)pyridazinyl,

-NH-(N-acetyl)azetidinyl, e.g.



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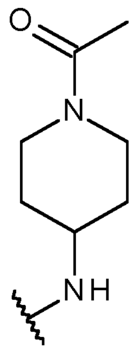
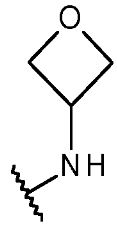
-NH-(N-acetyl)piperidinyl, e.g.



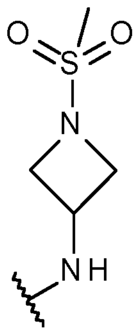
;

-NH-oxetanyl, e.g.;



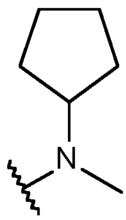
.

(1-methylsulfonylazetidin-3-yl)amino;



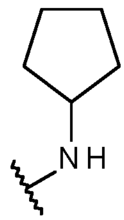
;

cyclopentyl(methyl)amino;



;

cyclopentylamino;



Aminomethyl: -CH_2-Amino, where amino is as defined above. Examples of aminomethyl include, but are not limited to, -CH_2-NH_2 and –CH_2-N(H)pyridazinyl.

Sulfonamido: -SO_2NRR’ wherein R and R’ are independently selected from H, C_{1-4} alkyl, phenyl and C_{5-6} heteroaryl as defined above. Examples of sulfonamido groups include, but are not limited to, -SO_2N$(Me)_2$ and -SO_2NPhMe.

Sulfonamino: -NHSO_2R wherein R is selected from C_{1-4} alkyl, phenyl and C_{5-6} heteroaryl as defined above. Examples of sulfonamino groups include, but are not limited, to -NHSO_2Me and -NHSO_2Ph

Sulfone: -SO_2R, wherein R is selected from C_{1-4} alkyl and C_{1-4} fluoroalkyl as defined above. Example of sulfone groups includes but is not limited to SO_2CF_3.

Sulfoxide: -SOR, wherein R is selected from C_{1-4} alkyl and C_{1-4} fluoroalkyl as defined above. Example of sulfoxide groups includes but is not limited to $SOCF_3$.

Nitrile: -CN.

Nitrilemethyl: $-CH_2-CN$

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge, *et al.*, *J. Pharm. Sci.*, **66**, 1-19 (1977).

For example, 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 a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e. NH_4^+) and substituted ammonium ions (e.g. NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, 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 $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g. $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids:

hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, trifluoroacetic acid and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Solvates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term “solvate” is used herein in the conventional sense to refer to a complex of solute (e.g. active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

Isomers

Certain compounds of the invention may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as “isomers” (or “isomeric forms”).

The term “chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

The term “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

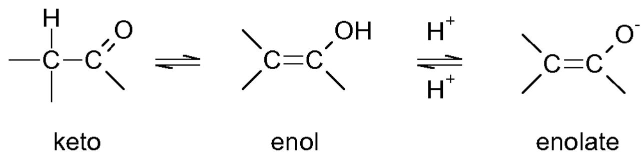
“Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Note that, except as discussed below for tautomeric forms, specifically excluded from the term “isomers”, as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g. C_{1-7} alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, 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/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

Note that specifically included in the term “isomer” are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, and ^{125}I. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 13C, and 14C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labelled or substituted therapeutic compounds of the invention may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent. The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Therapeutic Indications

Compounds disclosed herein may provide a therapeutic benefit in a number of disorders, in particular, in the treatment or prevention of cancers and hemoglobinopathies.

<u>Cancer</u>

Modulators of PRMT5 mediated post-translational arginine methylation of p53 may regulate a pro-apoptotic p53 response, and may therefore be useful as therapeutic agents, for example in the treatment of cancer. Such agents may also be useful as therapeutic agents for the treatment of cancers which exhibit overexpression of PRMT5.

A "cancer" may be any form of cancer. In particular, a cancer can comprise any one or more of the following: leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), non-Hodgkin's lymphoma, Hodgkin's disease, prostate cancer, lung cancer, melanoma, breast cancer, colon and rectal cancer, colon cancer, squamous cell carcinoma and gastric cancer.

Alternatively, the cancer may comprise adrenocortical cancer, anal cancer, bladder cancer, blood cancer, bone cancer, brain tumor, cancer of the female genital system, cancer of the male genital system, central nervous system lymphoma, cervical cancer, childhood rhabdomyosarcoma, childhood sarcoma, endometrial cancer, endometrial sarcoma, esophageal cancer, eye cancer, gallbladder cancer, gastrointestinal tract cancer, hairy cell leukemia, head and neck cancer, hepatocellular cancer, hypopharyngeal cancer, Kaposi's sarcoma, kidney cancer, laryngeal cancer, liver cancer, malignant fibrous histiocytoma, malignant thymoma, mesothelioma, multiple myeloma, myeloma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, nervous system cancer, neuroblastoma, oral cavity cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pituitary tumor, plasma cell neoplasm, primary CNS lymphoma, rectal cancer, respiratory system, retinoblastoma, salivary gland cancer, skin cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, stomach cancer, testicular cancer, thyroid cancer, urinary system cancer, uterine sarcoma, vaginal cancer, vascular system, Waldenstrom's macroglobulinemia and/or Wilms' tumor. Cancers may be of a particular type. Examples of types of cancer include lymphoma, melanoma, carcinoma (e.g. adenocarcinoma, hepatocellular carcinoma, medullary carcinoma, papillary carcinoma, squamous cell carcinoma), astrocytoma, glioma, medulloblastoma, myeloma, meningioma, neuroblastoma, sarcoma (e.g. angiosarcoma, chrondrosarcoma, osteosarcoma).

The cancer may be a PRMT5 overexpressing cancer. The cancer may over express PRMT5 protein relative to non-cancerous tissue. In some cases, the cancer overproduces PRMT5 mRNA relative to non-cancerous tissue.

Alternatively or additionally, the cancer may be a p53 overexpressing cancer. The cell may overexpress p53 protein relative to non-cancerous tissue. It may overproduce p53 mRNA as compared to non-cancerous tissue. In some cases, the level of p53 protein and/or mRNA in the cell is at a level approximately equivalent to that of a non-cancerous cell.

The agents described herein may be useful in combination with other anti-cancer therapies. They may act synergistically with chemo- or radiotherapy, and/or with p53 targeted drugs.

An inhibitor of PRMT5 would in all likelihood augment the effects of drugs (such as the nutlins) that restore p53. Inhibition of PRMT5, resulting in decreased arginine-methylated p53, may sensitize tumour cells to chemo- and radiotherapy by switching, or at least biasing, the cellular outcome to apoptosis.

Combination therapies

p53 is activated by DNA damage. PRMT5 is part of the complex of proteins that activate and modulate p53 activity in response to DNA damage. It is likely that inhibition of PRMT5, resulting in decreased arginine-methylated p53, would sensitize tumour cells to chemo- and radiotherapy by switching or at least biasing the cellular outcome to apoptosis. PRMT5 inhibition is likely to synergize well with low dose chemo- or radiotherapy, by stabilizing p53, and biasing the cellular outcome to apoptosis.

Biasing the p53 response towards apoptosis would in all likelihood be of benefit, and an agent that so biases the response would be expected to augment the effect of a p53 resurrecting drug. Thus, in some cases, a PRMT5 modulator disclosed herein may be administered in conjunction with a radiotherapeutic or chemotherapeutic regime. It may be administered in conjunction with a drug that resurrects cellular p53 activity, for example, a p53 agonist. The PRMT5 modulator may be administered simultaneously or sequentially with radio and/or chemotherapy. Suitable chemotherapeutic agents and radiotherapy protocols will be readily appreciable to the skilled person. In particular, the compound described herein may be combined with low dose chemo or radio therapy. Appropriate dosages for “low dose” chemo or radio therapy will be readily appreciable to the skilled practitioner.

Hemoglobinopathies

The compounds disclosed herein may be useful in the treatment or prevention of conditions that may benefit from the increased expression of γ-globin genes, for example, due to the release of repressive methylation of these genes. The compounds disclosed herein may be useful in the treatment or prevention of hemoglobinopathies. A hemoglobinopathy is a condition associated with the presence of abnormal hemoglobin in the blood of a subject. Such conditions include ß-thalassemia and Sickle Cell Disease, α-thalassemia and δ-thalassemia.

Hemoglobinopathies treatable by the compounds disclosed herein may be ameliorated by the re-activation of the subjects γ-globin genes (γ genes). In such cases, the subject is not a fetal mammal.

Methods of Treatment

The compounds of the present invention may be used in a method of therapy. Also provided is a method of treatment, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of the invention. The term "therapeutically effective amount" is an amount sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors.

As described above, the anti cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and docetaxel (Taxotere) and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5*-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661 and and 4-((2,4-dichloro-5-methoxyphenyl)amino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinoline-3-carbonitrile (bosutinib, SKI-606; Cancer research (2003), 63(2), 375-81), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [HerceptinT], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic and antilymphangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor A (VEGFA) antibody bevacizumab (AvastinT), the anti vascular endothelial cell growth factor A (VEGFA) antibody ranibizumab, the anti-VEGF aptamer pegaptanib, the anti vascular endothelial growth factor receptor 3 (VEGFR3) antibody IMC-3C5, the anti vascular endothelial cell growth factor C (VEGFC) antibody VGX-100, the anti vascular endothelial cell growth factor D (VEGFD) antibody VGX-200, the soluble form of the vascular endothelial growth factor receptor 3 (VEGFR3) VGX-300 and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (vandetanib; ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (cediranib; AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985), pazopanib (GW786034), axitinib (AG013736), sorafenib and sunitinib (SU11248; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as cytokine transfected dendritic cells, approaches using cytokine transfected tumour cell lines and approaches using anti idiotypic antibodies

Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intravitreal and intrasternal; by implant of a depot, for example, subcutaneously, intravitreal or intramuscularly. The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orang-utan, gibbon), or a human.

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) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term “pharmaceutically acceptable” as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, 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.

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington’s Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990.

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

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, losenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g. by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica); disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g. sodium lauryl sulfate); and preservatives (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active compound in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/mL to about 10 μg/mL, for example from about 10 ng/ml to about 1 μg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, 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. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the compound, and compositions comprising the compound, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the active compound is in the range of about 100 ng to about 25 mg (more typically about 1 μg to about 10 mg) per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 100 mg, 3 times daily.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 150 mg, 2 times daily.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 200 mg, 2 times daily.

However in one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 50 or about 75 mg, 3 or 4 times daily.

In one embodiment, the active compound is administered to a human patient according to the following dosage regime: about 100 or about 125 mg, 2 times daily.

Treatment

The term “treatment,” as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of 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, regression of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis, prevention) is also included.

The term “therapeutically-effective amount,” as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Similarly, the term “prophylactically-effective amount,” as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired prophylactic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The Subject/Patient

The subject/patient may be an animal, mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus. In one preferred embodiment, the subject/patient is a human.

General synthesis methods

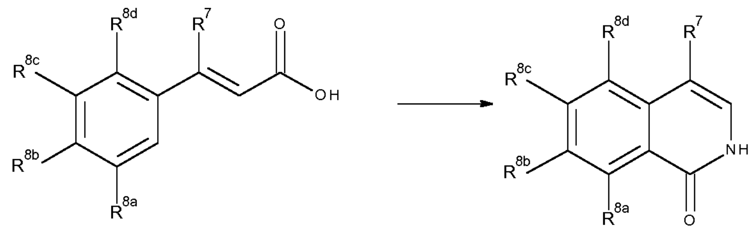
The compounds of the invention can be prepared employing the following general methods and using procedures described in detail in the examples. The reaction conditions referred to are illustrative and non-limiting, for example one skilled in the art may use a diverse range of synthetic methods to synthesis the desired compounds such as but not limited to methods described in literature (for example but not limited to March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 7th Edition or Larock’s Comprehensive Organic Transformations: Comprehensive Organic Transformations: A Guide to Functional Group Preparations).

Compounds of formula I as described above, can be prepared by synthetic strategies outlined below, wherein the definitions above apply. The synthetic strategies could be applied to the use of racemic or single enantiomer starting materials.

Preparation of heteroarene precursors

X=CH, R^7 = H, C_{1-4} alkyl

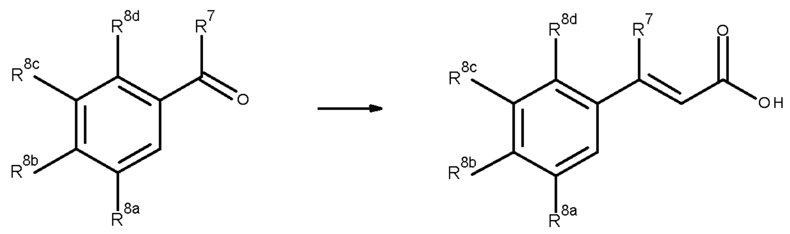
Isoquinolinones suitable for use in the methods below may be prepared by a variety of methods. For example, suitable cinnamic acid derivatives may be cyclised by conversion of the acid to the acyl azide with for example DPPA, followed by rearrangement and cyclisation by for example heating.



G1 G2a

Scheme 1

Cinnamic acid derivatives suitable for conversion to isoquinolinones may be prepared by a variety of methods. For example, a suitable carbonyl compounds may be treated with a malonic acid derivative to afford the corresponding cinnamic acid derivative by a Knoevenagel reaction

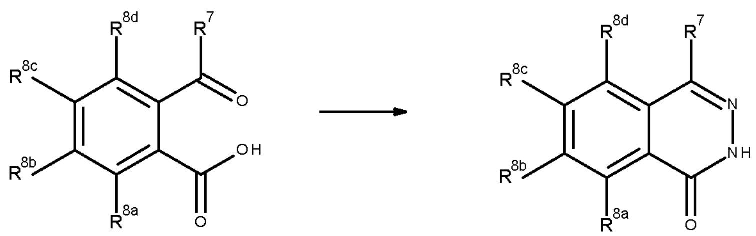


G3 G1

Scheme 2

X=N, R^7 = H, C_{1-4} alkyl

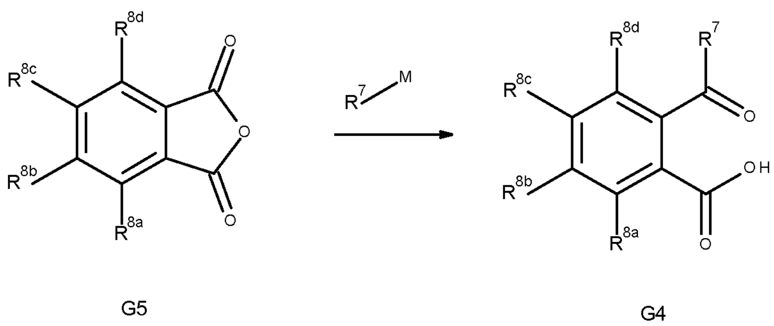
Phthalazin-1(2*H*)-ones suitable for use in the methods below may be prepared by a variety of methods. For example, a suitable ortho-acyl carbonyl compound can be activated by treatment with for example carbonyl diimidazole, and cyclised by treatment with hydrazine.



G4 G2b

Scheme 3

The required ortho-acyl carbonyl compound can be prepared by variety of methods. For example, for R^7= C_{1-4} alkyl, the addition of a suitable organometallic reagent such as for example a Grignard reagent to a phthalic anhydride derivative. For R^7=H the required ortho-acyl carbonyl compound can be prepared by for example treatment of a suitable phthalic anhydride derivative with a suitable reducing agent such as for example lithium tri-*tert*-butoxyaluminum hydride

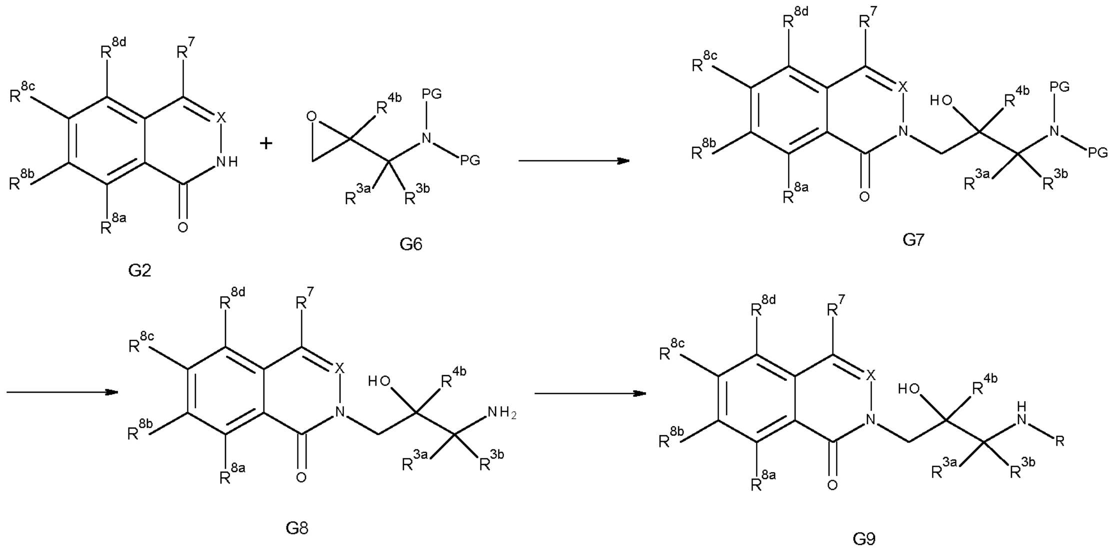


Scheme 4

<u>General synthesis method 1 (for n=1)</u>

A bicyclic heteroaromatic **G2** can be alkylated using a suitable epoxide of formula **G6** (PG is a Protecting Group or H) in a substitution reaction which may be performed in the presence of a suitable base, e.g. potassium carbonate, sodium hydride and potassium t-butoxide. The epoxide **G6** should possess an amino substituent which bears a suitable protecting group (PG), e.g. phthalimide or Boc. The product of the substitution reaction **G7** is an alcohol, which bears the protected amine. If this protecting group is a phthalimide, deprotection can be effected using hydrazine in a suitable solvent, or if it is Boc then the use of acid, e.g. trifluoroacetic acid or HCl in a suitable solvent to give the amine **G8**. Alkylation of **G8** can be performed using a reductive alkylation reaction with a suitable ketone in the presence of a suitable reducing agent, e.g. sodium triacetoxyborohydride, sodium cyanoborohydride or sodium borohydride optionally in the presence of an additional reagent such as acetic acid or titanium isopropoxide.

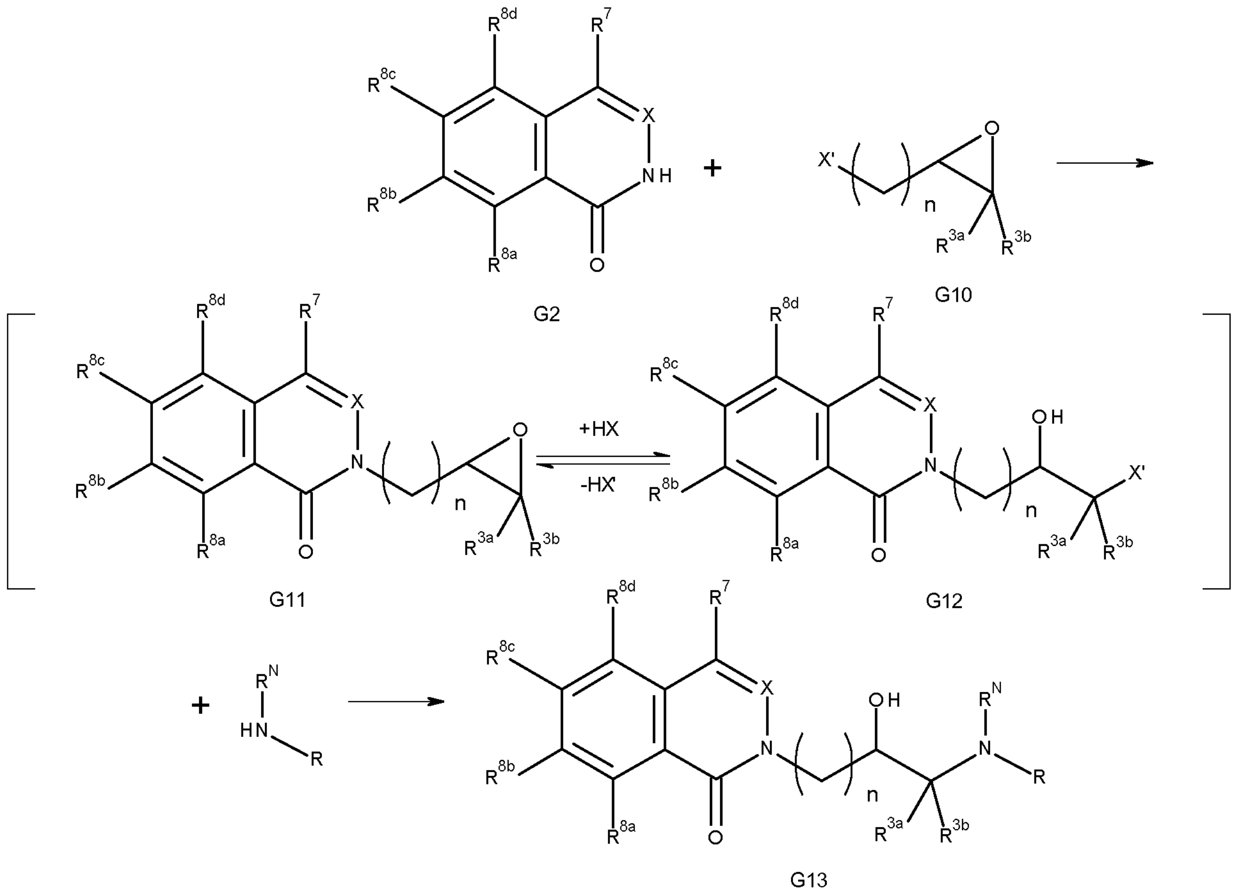
Enantiomerically pure forms of epoxide **G6** can be used to allow for enantiomerically pure products to be prepared.



Scheme 5

General synthesis method 2 (for n=1 or 2)

Scheme 6 illustrates how to form amine substitutions such as shown in **G13**. The bicyclic heteroaromatic **G2** is reacted with a halo-epoxide **G10** or similar and the resultant mixture reacted on with a desired amine (HNR^NR) resulting in a product **G13**. The group denoted (X') can be but is not limited to halogen, mesylate, tosylate, nosylate or similar.

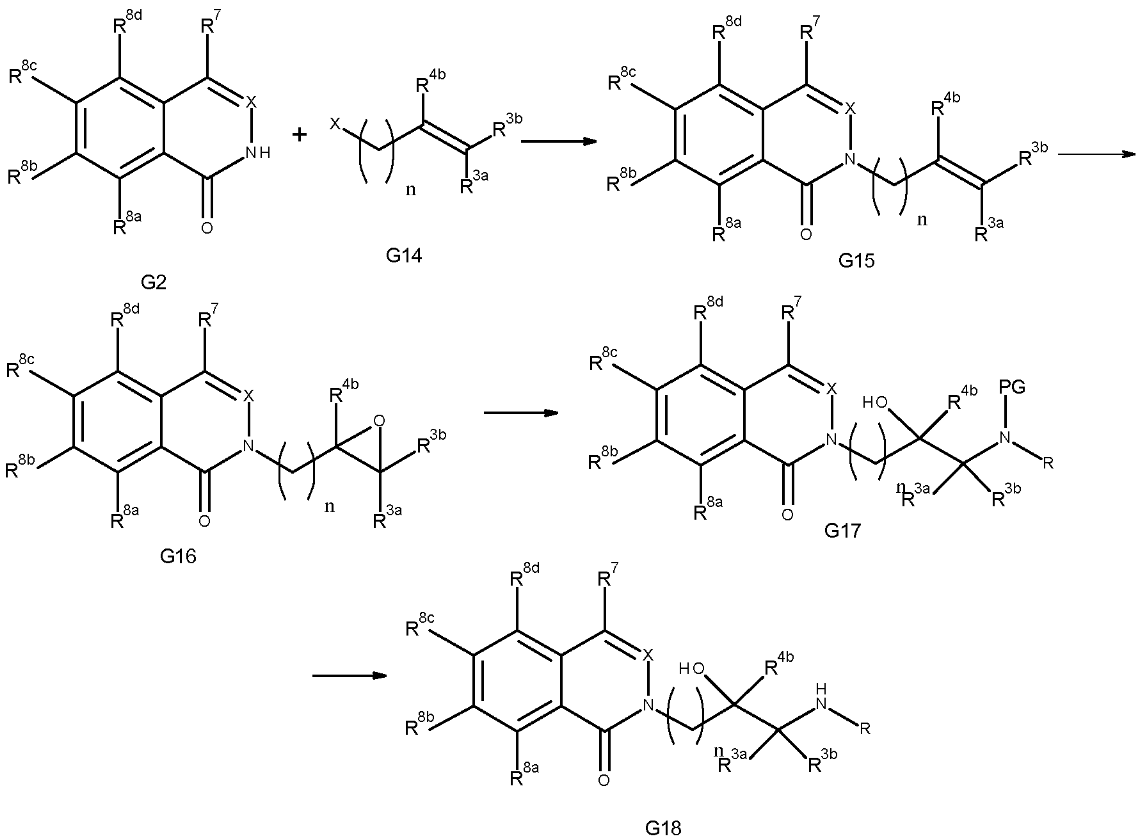


Scheme 6

Enantiomerically pure forms of the epoxide **G10**, e.g. epichlorohydrin, can be used to obtain the products **G13** in enantiomerically pure form.

<u>General synthesis method 3 (n=1 or 2)</u>

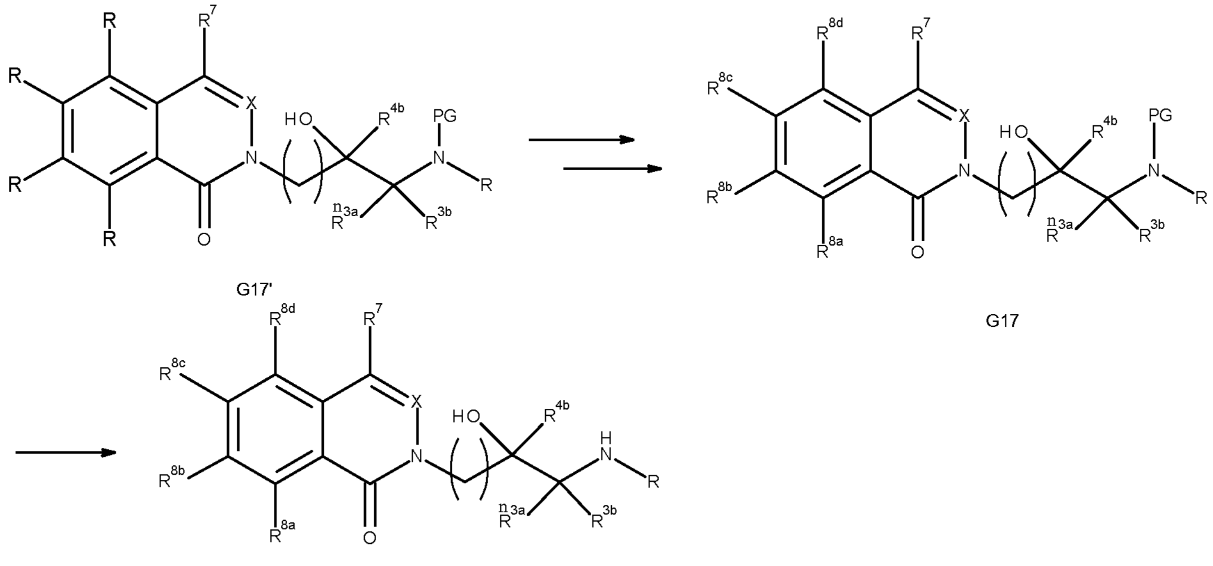
Scheme 7 shows alkylation of a bicyclic heteroaromatic **G2** with a suitable olefin-containing alkylating agent **G14**, in a substitution reaction, where X is a suitable leaving group, e.g. bromo, iodo, mesylate and tosylate to give **G15**. Epoxidation of the olefin of **G15** with a suitable reagent, e.g. *meta*-chloro peroxybenzoic acid allows access to epoxide **G16**. The epoxide can be opened with a suitable nucleophile, e.g. a primary amine or a secondary amine, which may include an appropriate protecting group, e.g. 2,4-dimethoxybenzyl, to give **G17**. Removal of the protecting group, in the case of 2,4-dimethoxybenzyl using an acid gives the required amino substituent in **G18**.



Scheme 7

General synthesis method 4

An intermediate **G17'** as shown in Scheme 8 can be prepared using the methods described above which contains suitable functionality on the bicyclic heteroaromatic to allow functional group interconversions to be performed to access to **G17**, which possesses a suitable protecting group which could be removed to give **G18**. Examples of R might include halo, tosylate, boronic acid, boronic ester and phenol which could allow for transition metal catalysed reactions to be performed, e.g. Suzuki coupling, Negishi coupling, S_NAr reaction, Ullman coupling, Chan Lam coupling, an alkylation reaction e.g. S_N2 or S_N1, a Mitsonobu reaction, a C-H activation reaction, a Kumada coupling , a Buchwald reaction etc.

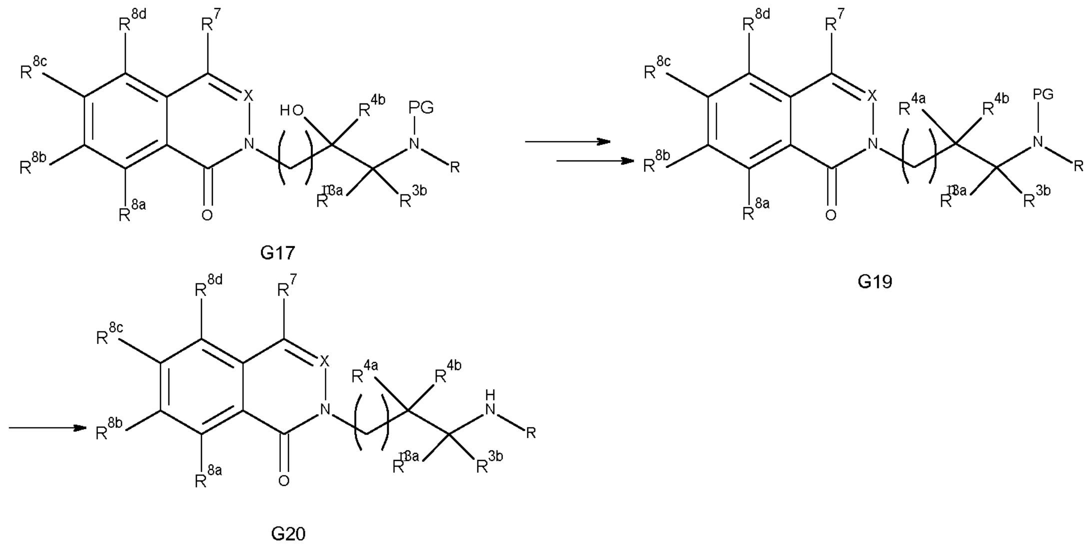


G17' G17 G18

Scheme 8

<u>General synthesis method 5</u>

The alcohol group that is present in **G17** in Scheme 9 can be transformed through a range of functional group interconversions that are known to those skilled in the art. For example R^{4a} = NH2 can be introduced using a reagents such as DPPA and DBU to give the azide, which can then be reduced using triphenylphosphine. R^{4a} = CN can be introduced via activation of the alcohol to a suitable leaving group, e.g. R^{4a} = mesylate, tosylate or halogen and then treatment with a suitable source of cyanide, e.g. sodium cyanide. The resulting cyano compound can be hydrolysed to the primary amide R^{4a} = $CONH_2$ using acidic or basic conditions. Under more forcing acid or basic conditions, the carboxylic acid could be formed, i.e. R^{4a} = CO_2H. The carboxylic acid could be reduced to the corresponding primary alcohol, R^{4a} = CH_2OH using a suitable reducing agent, e.g. BH_3, or alternatively through activation of the acid to a mixed anhydride, R^{4a} = CO_2COR, where R = alkyl, and then treatment with a suitable reducing agent, e.g. sodium borohydride.



G17 G19 G20

Scheme 9

Further Embodiments

n

In some embodiments, n is 1. In some embodiments, n is 2.

R^N

In some embodiment, R^N is H. In other embodiments, R^N is Me.

R^1

In some embodiments, there may be no R^1 substituents. In some embodiments, R^1 represents one to four Me or halo groups, preferably one to three Me or halo groups and more preferably one or two Me or halo groups. In some of these embodiments, R^1 may represent F. In others of these embodiments, R^1 may represent Me groups.

R^2

R^{2a}, R^{2b}, R^{2c} and R^{2d} (if present) are independently selected from H, F, CH_2OH and Me. In some of these embodiments, R^{2a}, R^{2b}, R^{2c} and R^{2d} (if present) are independently selected from H, Me and CH_2OH. In further of these embodiments, R^{2a}, R^{2b}, R^{2c} and R^{2d} (if present) are independently selected from H and Me.

In some embodiments R^{2a}, R^{2b}, R^{2c} and R^{2d} (if present) are all H.

In some of those embodiments where R^{2a}, R^{2b}, R^{2c} and R^{2d} are all present (i.e. formulae Ia and Ib), they may be comprised of three H and one Me or CH_2OH group. It may be preferred in these embodiments that R^{2a} is Me and R^{2b}, R^{2c} and R^{2d} are H. It may be preferred in these embodiments that R^{2c} is Me or CH_2OH and R^{2a}, R^{2b} and R^{2d} are H.

In some of those embodiments where R^{2a}, R^{2b}, R^{2c} and R^{2d} are all present (i.e. formulae Ia and Ib), they may be comprised of two H and two Me groups. It may be preferred in these embodiments that R^{2a} and R^{2c} are Me and R^{2b} and R^{2d} are H. It may be preferred in these embodiments that R^{2a} and R^{2b} are Me and R^{2c} and R^{2d} are H. It may also be preferred in these embodiments that R^{2c} and R^{2d} are Me and R^{2a} and R^{2b} are H.

In some of those embodiment where only R^{2a} and R^{2b} are present (i.e. formula Ic), they may be comprised of one H and one Me or CH_2OH group.

In some of those embodiment where only R^{2a} and R^{2b} are present (i.e. formula Ic), they may both be a Me or CH_2OH group.

R^3

R^{3a} and R^{3b} are independently selected from H and Me. In some embodiments R^{3a} is H and R^{3b} is Me. In some embodiments R^{3a} and R^{3b} are both H. In some embodiments R^{3a} and R^{3b} are both Me.

R^{4a}

In some embodiments R^{4a} is OH.

In other embodiments, R^{4a} is $-NH_2$. In other embodiments R^{4a} is $-C(=O)NH_2$. In other embodiments R^{4a} is $-CH_2OH$.

It may be preferred that R^{4a} is OH.

R^{4b}

In some embodiments R^{4b} is H. In some embodiments R^{4b} is Me.

Enantiomers

The carbon to which R^{4a} and R^{4b} are attached is a chiral centre.

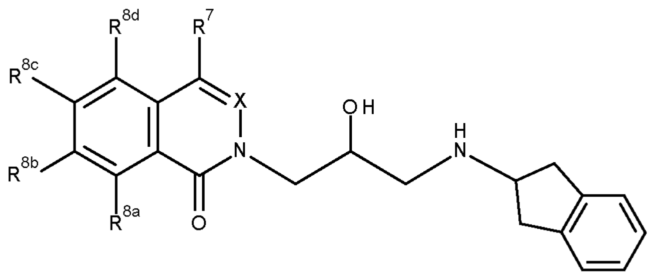
When the compound contains this chiral centre, in some embodiments, the compound is a racemate.

When the compound contains this chiral centre, in some embodiments, the compound is a single enantiomer. In some of these embodiments, the compound is the *(R)*-enantiomer. In others of these embodiments, the compound is the *(S)*-enantiomer.

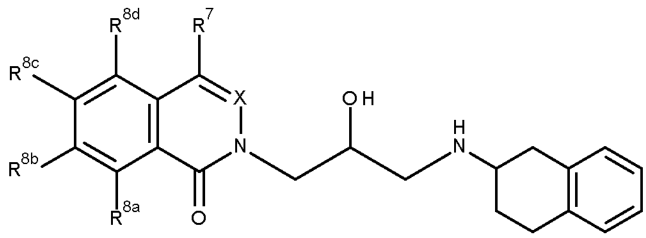
The compound may also include further chiral centres, for example, in compounds of formula Ia, in tetrahydronaphthalenyl group. In some embodiments, the compound is a racemate. In other embodiments, the compound is a single enantiomer. In some of these embodiments, the compound is the *(R)*-enantiomer. In others of these embodiments, the compound is the *(S)*-enantiomer.

R^1-R^4 & n

In some embodiments, R^N, R^1, R^{2a}, R^{2b}, R^{2c} (if present), R^{2d} (if present), R^{3a}, R^{3b} and R^{4b} are all H, R^{4a} is OH and n is 1, and thus the compound of formula Ia is of formula Ia1, the compound of formula Ib is of formula Ib1, and the compound of formula Ic is of formula Ic1:



(Ia1)



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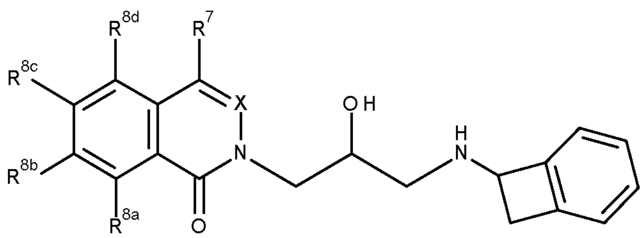
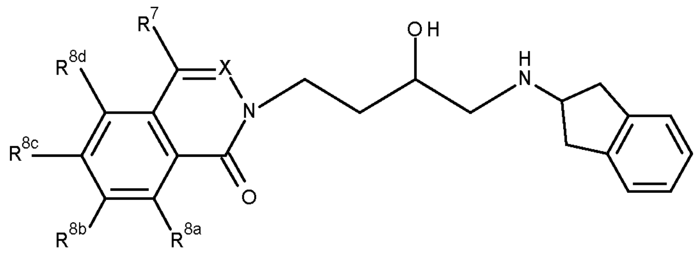
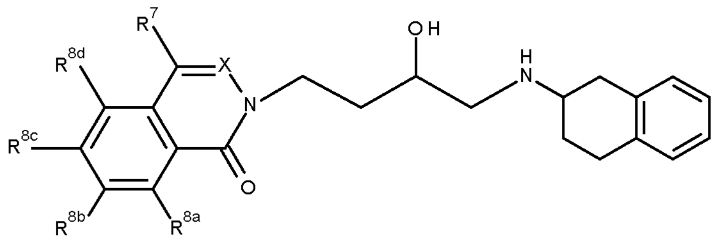


(Ic1)

In some embodiments, R^N, R^1, R^{2a}, R^{2b}, R^{2c} (if present), R^{2d} (if present), R^{3a}, R^{3b} and R^{4b} are all H, R^{4a} is OH and n is 2, and thus the compound of formula Ia is of formula Ia2, the compound of formula Ib is of formula Ib2, and the compound of formula Ic is of formula Ic2:



(Ia2)



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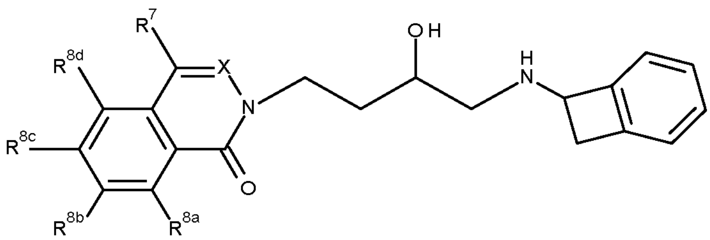


(Ic2)

X

In some embodiments, X is N.

In some embodiments, X is CH.

R^7

In some embodiments, R^7 is H.

In other embodiments, R^7 is C_{1-4} alkyl. In some of these embodiments, R^7 is methyl. In other of these embodiments, R^7 is ethyl.

R^{8a}, R^{8b}, R^{8c} and R^{8d}

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} alkyl, it may be preferably selected from methyl, ethyl, *i*-Pr, *t*-Bu.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} fluoroalkyl, it may preferably be selected from $-CF_3$ and $-CF_2H$.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{5-6} heteroaryl, it may be substituted by one or more C_{1-4} alkyl groups. These groups may preferably be on one or more of the nitrogen ring atoms (if present). These groups may also preferably be methyl.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{5-6} heteroaryl, it may preferably be selected from pyridizinyl, pyrimidinyl, pyridinyl, pyrazolyl, pyrazinyl, oxadiazolyl, isoxazolyl, triazolyl, imidazolyl, benzimidazolyl and thiadiazolyl.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{5-6} heteroaryl methyl, it may preferably be selected from $-CH_2$-imidazolyl and $-CH_2$-triazolyl.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{5-6} heterocyclyl, it may preferably be morpholino.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{5-6} heterocyclyl methyl, it may preferably be selected from $-CH_2$-morpholino and $-CH_2$-piperazinyl.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is phenyl, it may be substituted by one or more C_{1-4} alkyl groups. These groups may preferably be methyl.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is phenyl, it may be substituted by one or more C_{1-4} fluoroalkyl groups. These groups may preferably be trifluoromethyl.

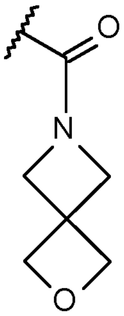
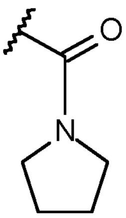
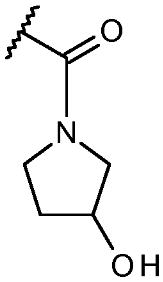
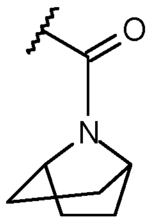
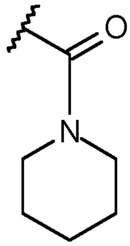
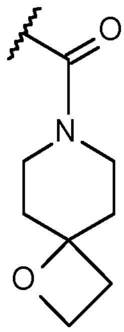
When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is phenyl, it may be substituted by one or more C_{1-4} alkoxy groups. These groups may preferably be methoxy.

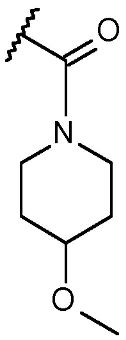
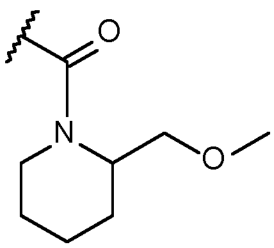
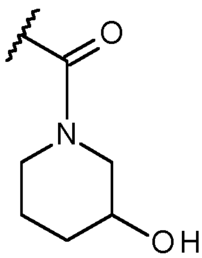
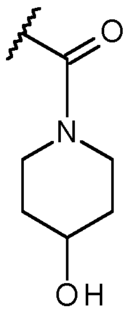
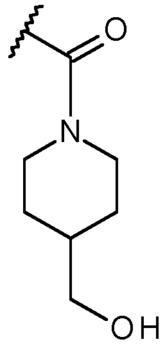
When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is phenyl, it may be substituted by one or more halo substituents. These groups may preferably be fluoro or chloro, more preferably fluoro.

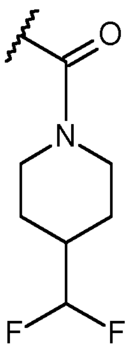
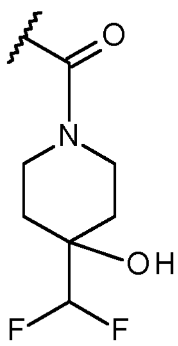
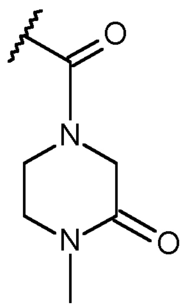
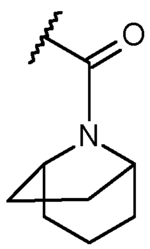
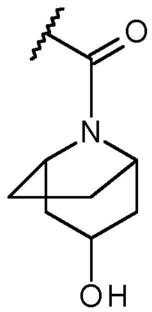
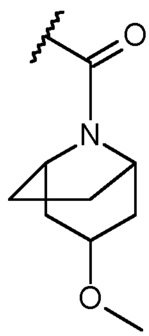
When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is phenyl, it may be substituted by one or more cyano groups. It may be preferred that there is a single cyano substituent.

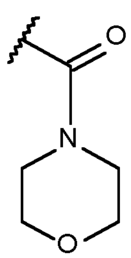
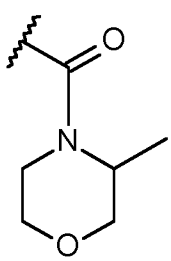
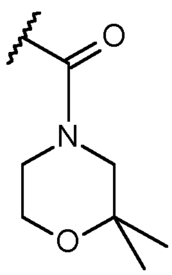
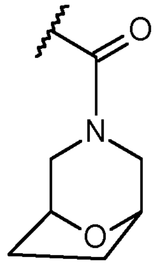
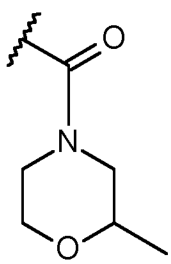
When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is halo, it may preferably be selected from F, Cl and Br.

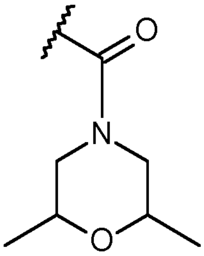
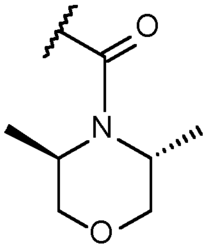
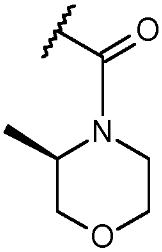
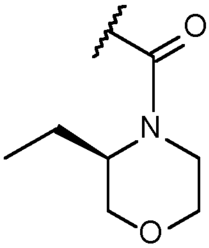
When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is amido, the amido substituent groups R and R' may preferably form a ring, which ring may also be bridged or substituted. If the amido group is not cyclic, it may preferably be selected from -C(=O)NH_2, -C(=O)NMeH, -C(=O)NMe_2 and -C(=O)N^{i}PrH. If the amido group is cyclic, it may preferably be selected from -C(=O)-piperidinyl, -C(=O)-hydroxypiperidinyl, -C(=O)-methoxypiperidinyl, -C(=O)-pyrrolidinyl,-C(=O)-morpholino, -C(=O)-methylmorpholino, -C(=O)-dimethylmorpholino and -C(=O)-azetidinyl. Further cyclic amido groups include:

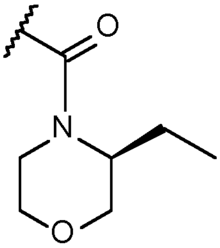
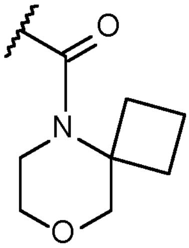
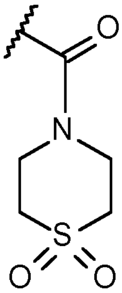
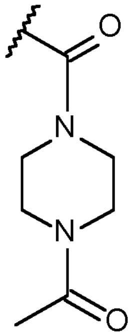
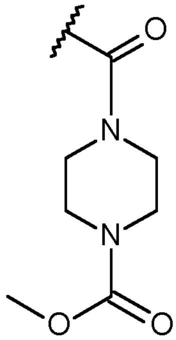
, , , , , ,

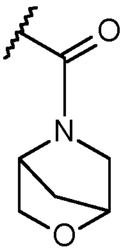
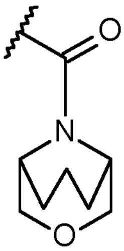
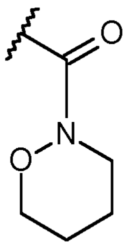
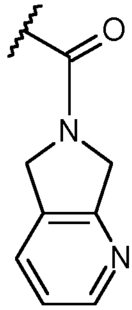
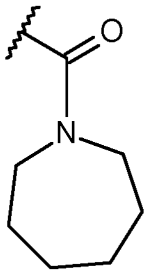
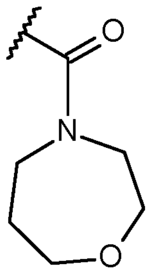
, , , , ,

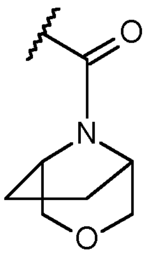
, , , , , ,

, , , , ,

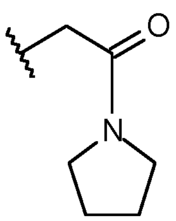
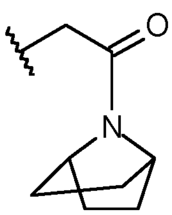
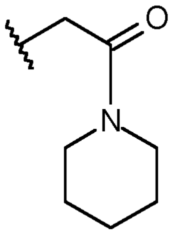
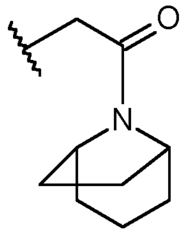
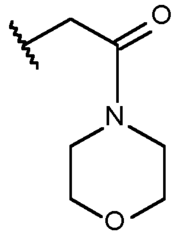
, , , ,

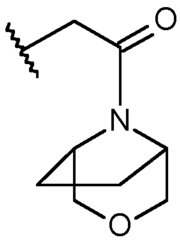
, , , , ,

, , , , ,  and

.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is amidomethyl, the amido substituent groups R and R' may preferably form a ring, which ring may also be bridged or substituted. If the amido group is not cyclic, the amidomethyl group may preferably be selected from $-CH_2C(=O)NH_2$, $-CH_2C(=O)NMeH$ and $-CH_2C(=O)N^iPrH$. If the amindo group is cyclic, the amidomethyl group may preferably be selected from $-CH_2C(=O)$-pyrrolidinyl $-CH_2C(=O)$-morpholino, , -C(=O)-hydroxypiperidinyl, -C(=O)-methoxypiperidinyl, -C(=O)-methylmorpholino and $CH_2C(=O)$-azetidinyl . Further cyclic amidomethyl groups include:

, , , ,  and



When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is acylamido, it may preferably be γ-lactam.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is acylamidomethyl, it may preferably be selected from $-CH_2NHC(=O)Me$, $-CH_2NHC(=O)CF_3$.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} alkyl ester, it may preferably be -C(=O)-OMe.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} alkyl ester methyl, it may preferably be $-CH_2-C(=O)-OMe$.

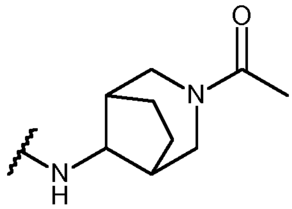
When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} alkyl carbamoyl methyl, it may preferably be $-CH_2NHC(=O)OMe$.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} alkylacyl, it may preferably be selected from -C(=O)Me and -C(=O)Et.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is C_{1-4} alkylacylmethyl, it may preferably be $-CH_2C(=O)Me$.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is phenylcarbonyl, it may preferably be -C(=O)-Ph.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is ether, it may preferably be selected from methoxy, ethoxy, -OBn, -OPh, $-OCF_3$,$-OCF_2H$, $-O-(C_6H_4)-CN$, -O-oxanyl, $-OCH_2$pyridinyl, $-OCH_2$-oxadiazolyl, $-OCH_2$-isoxazole, When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is amino, the amino substituent may be a C_{5-6} heteroaryl group, in which case the amino group may preferably be selected from -NH-pyrazinyl, -NH-pyrimidine. In other embodiments, the amino substituent may be a C_{4-6} heterocyclyl group, such as optionally N-substituted azetidinyl, optionally N-substituted piperidinyl and oxetanyl. A further amino group may be:



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When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is aminomethyl, it may preferably be $-CH_2NH_2$. Alternatively, the amino substituent may be as defined above

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is sulfonamido it may preferably be selected from $-SO_2NMePh$, $-SO_2NMe_2$, and $-SO_2NHEt$.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is sulfonamino, it may preferably be selected from $-NHSO_2Ph$ and $-NHSO_2Me$.

When one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is sulfone, it may preferably be $-SO_2CF_3$.

The R^{8a}, R^{8b}, R^{8c} and R^{8d} that is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, NHC_{1-4} alkyl

In some embodiments, the R^{8a}, R^{8b}, R^{8c} and R^{8d} that is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy and NHC_{1-4} alkyl is selected from halo, C_{1-4} alkyl, methoxy or ethoxy. In further of these embodiments, the group is either chloro or ethoxy.

In some embodiments, R^{8a} is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy and NHC_{1-4} alkyl.

In some embodiments, R^{8a} is selected from halo, C_{1-4} alkyl, methoxy or ethoxy.

In some embodiments, R^{8a} is either chloro or ethoxy.

The R^{8a}, R^{8b}, R^{8c} and R^{8d} that is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4}

alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl

In some embodiments, this group is selected from C_{1-4} alkyl, fluoro, chloro, bromo, acetyl, methoxy, ethoxy, -C(=O)Me, -C(=O)Et, $-CH_2C(=O)Me$, phenyl, $-CF_3$, $-CF_2H$, -CN, $-CH_2CN$, -OBn, -OPh, $-OCF_3$,$-OCF_2H$, -O-(C_6H_4)-CN, -COOH, $-CH_2COOH$, -C(=O)OMe, $-C(=O)NH_2$, -C(=O)NMeH, $-C(=O)NMe_2$, $-C(=O)N^iPrH$, -C(=O)-piperidinyl, -C(=O)-pyrrolidinyl,-C(=O)-morpholino (which may be bridged or substituted with one or two methyl groups), -C(=O)-azetidinyl, $-CH_2C(=O)NH_2$, $-CH_2C(=O)$-azetidinyl, $-CH_2C(=O)NMeH$, $-CH_2C(=O)N^iPrH$, -$CH_2C(=O)$-pyrrolidinyl, $-CH_2C(=O)$-morpholino, $-CH_2$-morpholino, $-CH_2$-methylpiperazinyl, -OCH_2pyridinyl, $-OCH_2$-methyloxadiazolyl, $-CH_2$-imidazolyl, -O-tetrahydropyranyl, $-CH_2$-tetraydropyanyl,-NH-methylpyrazinyl, $-CH_2$-triazolyl, $-NHSO_2Ph$, $-NHSO_2Me$, $-SO_2NMePh$, $-SO_2NMe_2$, $-SO_2NHEt$, $-SO_2CF_3$,- γ-lactam, $-CH_2NHC(=O)Me$, $-CH_2NHC(=O)OMe$, -$CH_2NHC(=O)CF_3$, morpholino, $-CH_2NH_2$, -C(=O)Ph, $-OCH_2$-isoxazolyl, -NH-pyrimidinyl, pyridizinyl, pyrimidinyl, pyridinyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, pyrazinyl, pyridazinyl , methyloxadiazolyl, oxadiazolyl, dimethyloxadiazolyl, isoxazolyl, dimethyltriazolyl, imidazolyl, benzimidazolyl and thiadiazolyl.

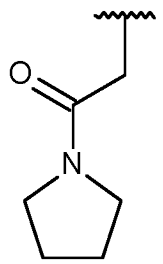
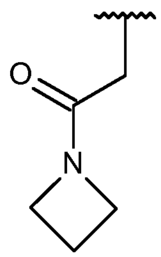
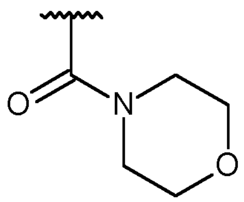
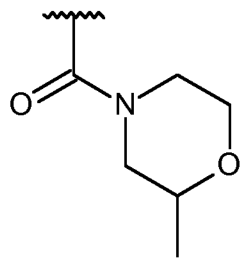
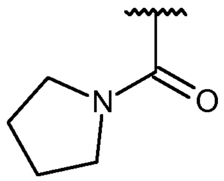
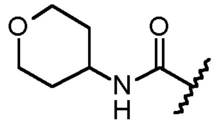
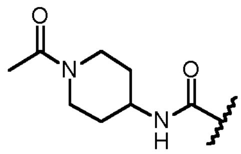
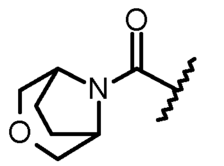
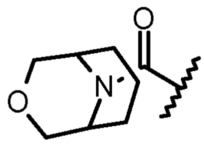
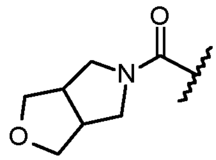
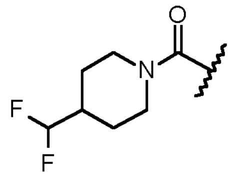
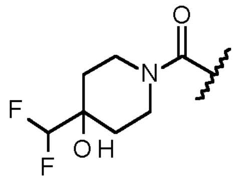
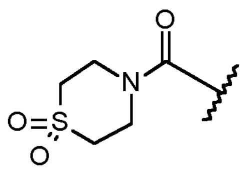
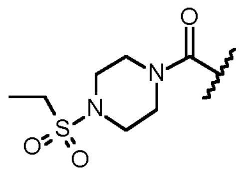
In some embodiments, one of R^{8b}, R^{8c} and R^{8d} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4} alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl.

In further of these embodiments, one of R^{8b}, R^{8c} and R^{8d} is selected from C_{1-4} alkyl, fluoro, chloro, bromo, acetyl, methoxy, ethoxy, -C(=O)Me, -C(=O)Et, $-CH_2C(=O)Me$, phenyl, $-CF_3$, -CF_2H, -CN, $-CH_2CN$, -OBn, -OPh, $-OCF_3$,$-OCF_2H$, -O-(C_6H_4)-CN, -COOH, $-CH_2COOH$, -C(=O)OMe, $-C(=O)NH_2$, -C(=O)NMeH, $-C(=O)NMe_2$, $-C(=O)N^iPrH$, -C(=O)-piperidinyl, -C(=O)-pyrrolidinyl,-C(=O)-morpholino (which may be bridged or substituted with one or two methyl groups), -C(=O)-azetidinyl, $-CH_2C(=O)NH_2$, $-CH_2C(=O)$-azetidinyl, $-CH_2C(=O)NMeH$, $-CH_2C(=O)N^iPrH$, $-CH_2C(=O)$-pyrrolidinyl, $-CH_2C(=O)$-morpholino, $-CH_2$-morpholino, $-CH_2$-methylpiperazinyl, $-OCH_2$pyridinyl, $-OCH_2$-methyloxadiazolyl, $-CH_2$-imidazolyl, -O-tetrahydropyranyl, $-CH_2$-tetraydropyanyl,-NH-methylpyrazinyl, $-CH_2$-triazolyl, $-NHSO_2Ph$, -$NHSO_2Me$, $-SO_2NMePh$, $-SO_2NMe_2$, $-SO_2NHEt$, $-SO_2CF_3$,- γ-lactam, $-CH_2NHC(=O)Me$, -$CH_2NHC(=O)OMe$, $-CH_2NHC(=O)CF_3$, morpholino, $-CH_2NH_2$, -C(=O)Ph, $-OCH_2$-isoxazolyl, -

NH-pyrimidinyl, pyridizinyl, pyrimidinyl, pyridinyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, pyrazinyl, pyridazinyl , methyloxadiazolyl, oxadiazolyl, dimethyloxadiazolyl, isoxazolyl, dimethyltriazolyl, imidazolyl, benzimidazolyl and thiadiazolyl.

In further of these embodiments, one of R^{8b} and R^{8d} is selected from C_{1-4} alkyl, amino or C_{5-6} heteroaryl.

In other further embodiments, R^{8c} is selected from amido or amidomethyl. In particular, R^{8c} may be selected from:

EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), *n*-propyl (nPr), isopropyl (iPr), *n*-butyl (nBu), *tert*-butyl (tBu), phenyl (Ph), benzyl (Bn), methoxy (MeO), ethoxy (EtO), trimethylsilyl (TMS), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), deuterated methanol (d_4-MeOD) ethanol (EtOH), isopropanol (*i*-PrOH), ether or diethyl ether (Et_2O), ethyl acetate (EtOAc), acetic acid (AcOH), acetonitrile (MeCN), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), dimethylsulfoxide (DMSO), deuterated chloroform ($CDCl_3$), diethylamine (DEA), deuterated dimethylsulfoxide (d_6-DMSO), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI.HCl, EDCI), *meta*-chloroperoxybenzoic acid (mCPBA), 1,1'-bis(diphenylphosphino)ferrocene (dppf), *tert*-butyloxycarbonyl (Boc, BOC), 2-(trimethylsilyl)ethoxymethyl (SEM), triethylamine (Et_3N or TEA), 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 4-dimethylaminopyridine (DMAP), *N,N*-diisopropylethylamine (DIPEA or DIEA), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) ($PdCl_2$(dppf)), *trans*-dichlorobis(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$), tris(dibenzylideneacetone) dipalladium(0) ($Pd_2(dba)_3$), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), propylphosphonic anhydride (T3P), hexamethylphosphoramide (HMPA), 1,2-dichloroethane (DCE), benzyl (Bn) and 1-hydroxybenzotriazole (HOBt).
In addition, TLC refers to thin layer chromatography.

General Experimental Details

Unless otherwise stated the following generalisations apply. ^1H NMR spectra were recorded on a Bruker Ultrashield Plus (400 MHz) or a Bruker AVANCE (400 MHz). The multiplicity of a signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; br, broad; m, multiplet. All observed coupling constants, *J*, are reported in Hertz.

LCMS data was generated using either an Agilent 6100 Series Single Quad LCMS (LCMS-A), an Agilent 1260 Infinity Series UPLC/MS (LCMS-B), an Agilent 1200 Series G6110A Quadrupole LCMS or Waters 2695 alliance (LCMS-C). Chlorine isotopes are reported as ^{35}Cl, Bromine isotopes are reported as either ^{79}Br or ^{81}Br or both $^{79}Br/^{81}Br$.

LCMS Method A (LCMS-A):

Instrument: Agilent 6100 Series Single Quad LC/MS

Agilent 1200 Series HPLC

Pump: 1200 Series G1311A Quaternary pump

Autosampler: 1200 Series G1329A Thermostatted Autosampler

Detector: 1200 Series G1314B Variable Wavelength Detector

LC conditions:

Reverse Phase HPLC analysis

Column: Luna C8 (2) 5 µm 50 × 4.6 mm 100 Å

Column temperature: 30 °C

Injection Volume: 5 µL

Solvent A: Water 0.1 % Formic Acid

Solvent B: MeCN 0.1 % Formic Acid

Gradient: 5-100 % solvent B over 10 min

Detection: 254 nm or 214 nm

MS conditions:

Ion Source: Quadrupole

Ion Mode: Multimode-ES

Drying gas temp: 300 °C

Vaporizer temperature: 200 °C

Capillary voltage (V): 2000 (positive)

Capillary voltage (V): 4000 (negative)

Scan Range: 100-1000

Step size: 0.1 sec

Acquisition time: 10 min

LCMS Method B (LCMS-B):

Instrument: Agilent 1260 Infinity Series UPLC/MS

Pump: 1260 Infinity G1312B Binary pump

Autosampler: 1260 Infinity G1367E 1260 HiP ALS

Detector: 1290 Infinity G4212A 1290 DAD

LC conditions:

Reverse Phase HPLC analysis

Column: Poroshell 120 EC-C18 2.7 µm 50 × 3.0 mm

Column temperature: 35 °C

Injection Volume: 1 µL

Solvent A: Water 0.1 % Formic Acid

Solvent B: MeCN 0.1 % Formic Acid

Gradient: 5-100 % solvent B over 3.8 min

Detection: monitored at 254 nm and 214 nm

MS conditions:

Ion Source: Quadrupole

Ion Mode: API-ES

Drying gas temp: 350 °C

Capillary voltage (V): 3000 (positive)

Capillary voltage (V): 3000 (negative)

Scan Range: 100-1000

Step size: 0.1 sec

Acquisition time: 5 min

LCMS Method C (LCMS-C):

Instrument: Agilent 1200 Series G6110A Quadrupole

Pump: Binary pump

Detector: DAD

LC conditions:

Reverse Phase HPLC analysis

Column: Xbridge-C18, 2.5 µm, 2.1×30 mm

Column temperature: 30 °C

Injection Volume: 1-10 µL

Solvent A: Water 0.07 % Formic acid

Solvent B: Methanol

Gradient: 30-95 % solvent B over 3.5 min (for medium polarity samples) or 10-95% solvent B over 3.7 min (for large polarity samples)

Detection: monitored at 254 nm and 214 nm

MS conditions:

Ion Source: Quadrupole

Ion Mode: ES+

Drying gas temp: 350 °C

Drying gas flow: 10 L/min

Nebulizer pressure: 35 psi

Capillary voltage (V): 3500 (positive)

Scan Range: 50-900

Or

Instrument: Waters 2695 alliance

Pump: Quaternary Pump

Detector: 2996 Photodiode Array Detector

MS model: Micromass ZQ

LC conditions:

Column: Xbridge-C18, 3.5μm, 2.1×50 mm

Column temperature: 30 °C

Injection volume: 1-10 μL

Acquisition of wavelength: 214 nm, 254 nm

Solvent A: 0.07% HCOOH aqueous solution

Solvent B: MeOH

Run time: 8 min

Gradient: 20-95 % solvent B over 5 min

Detection: 254 nm and 214 nm

MS condition:

Ion source: ES+ (or ES-)   MS range: 50~900 m/z

Capillary: 3 kV   Cone: 3 V   Extractor: 3 V

Drying gas flow: 600 L/hr   cone: 50 L/hr

Desolvation temperature: 300 °C

Source temperature: 100 °C

Sample preparation:

The sample was dissolved in methanol, the concentration about 0.1-1.0 mg/mL, then filtered through the syringes filter with 0.22 μm.

Preparative RP-HPLC:

Agilent 1260 Infinity HPLC system

UV detection at 210 nm and 254 nm
Gradient or isocratic elution through a Phenomenex Luna C8 (2) column 100 Å Axia (250 × 21.2 mm; particle size 5 μm)
Flow rate: 10 mL/min
Gradients are as specified in the individual examples.

Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminium-backed plates which were visualised using fluorescence quenching under UV light or a basic $KMnO_4$ dip or Ninhydrin dip.

Preparative thin-layer chromatography (prep TLC) was performed using Tklst (China), grand grade: (HPTLC): 8±2 μm>80 %; (TLC): 10-40 μm. Type: GF254. Compounds were visualised by UV (254 nm).

Flash chromatography was performed using a Biotage Isolera purification system using either Grace or RediSep® silica cartridges.
Column chromatography was performed using Tklst (China), grand grade, 100-200 meshes silica gel.

Microwave irradiation was achieved using a CEM Explorer SP Microwave Reactor.

Where necessary, anhydrous solvents were purchased from Sigma-Aldrich or dried using conventional methods. Solutions of inorganic acids or bases where made up as aqueous solutions unless stated otherwise.

Additional Cartridges used are as follows:
Phase Separator:
Manufacturer: Biotage
Product: ISOLUTE ® Phase Separator (3 mL unless otherwise stated)

SCX and SCX-2 cartridges:
Manufacturer: Biotage
Product: ISOLUTE ® SCX 1 g, (6 mL SPE Column unless otherwise stated)

Manufacturer: Biotage
Product: ISOLUTE ® SCX-2 1 g (6 mL Column)

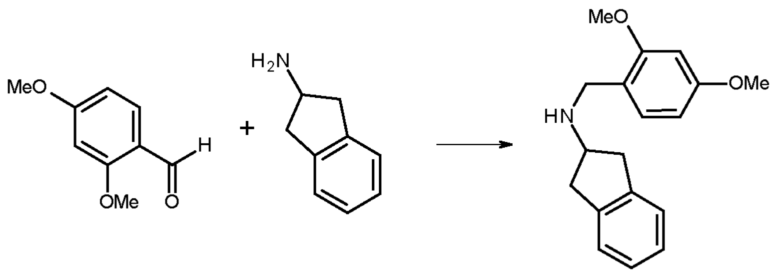
Manufacturer: Silicycle
Product: SCX-2 500mg or 5g

Manufacturer: Agilent
Product: Bond Elut® SCX 10g

Sample extraction cartridge:
Manufacturer: Waters
Product: Oasis ® HLB 35 cc (6 g) LP extraction cartridge

Intermediate Preparations

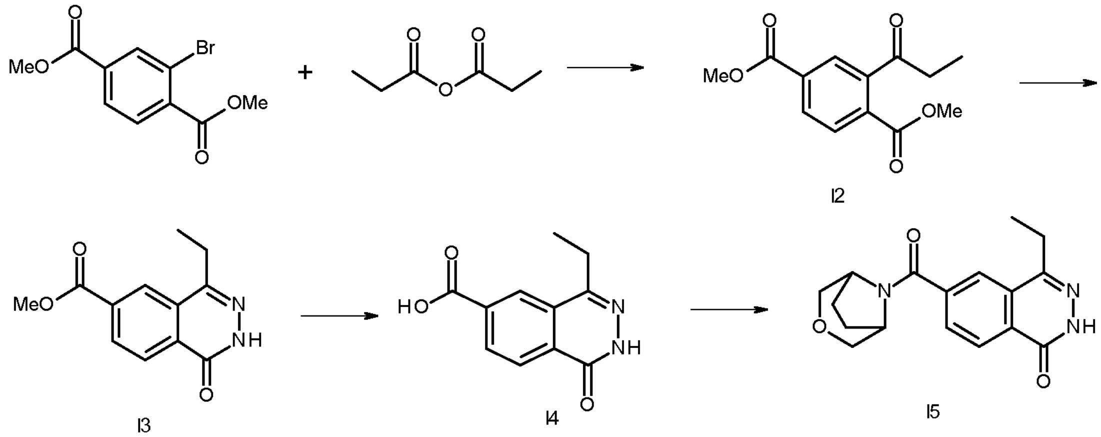
(i) N-(2,4-Dimethoxybenzyl)-2,3-dihydro-1H-inden-2-amine (I1)



I1

To a solution of 2,3-dihydro-1*H*-inden-2-amine (20.0 g, 0.150 mol) in ethanol (300 mL) was added 2,4-dimethoxybenzaldehyde (25.0 g, 0.150 mol). The reaction mixture was stirred at 70 °C for 2 hours, then cooled to 0 °C before $NaBH_4$ (11.4 g, 0.300 mol) was added. The resulting mixture was stirred at 0 °C for 30 minutes and poured into water (150 mL). Chloroform (150 mL) was added and the resulting mixture filtered. The filtrate was concentrated under reduced pressure and the aqueous mixture extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine (2 x 80 mL), dried (Na_2SO_4), filtered and concentrated to give the desired compound as a yellow oil (41 g, 96%). LCMS: RT 1.45 min; *m/z* 284.2 $[M+H]^+$.

(ii) 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethylphthalazin-1(2H)-one (I5)



(a) Dimethyl 2-propionylterephthalate (I2)

A mixture of zinc powder (0.720 g, 11.0 mmol), $CoBr_2$ (150 mg, 0.69 mmol), allyl bromide (60 uL, 0.7 mmol) and TFA (1 drop) was stirred under nitrogen in acetonitrile (7 mL) for 10 minutes at room temperature. Dimethyl 2-bromoterephthalate (2.0 g, 7.0 mmol) and propionic anhydride (1.05 g, 8.07 mmol) were then added and the mixture stirred for 5 hours. The mixture was quenched with aqueous sodium bicarbonate and water and the aqueous phase was then extracted with diethyl ether. The combined organic fractions were dried (Na_2SO_4), filtered and concentrated. The residue obtained was purified by column chromatography (5-10% EtOAc in hexanes) to give the desired product (1.1 g, 61%) as a yellow solid. LCMS RT 2.37 min; *m/z* 251.1 $[M+H]^+$.

(b) Methyl 4-ethyl-1-oxo-1,2-dihydrophthalazine-6-carboxylate (I3)

To a solution of dimethyl 2-propionylterephthalate I2 (1.0 g, 4.0 mmol) in DCM (10 mL) was added $N_2H_4.H_2O$ (80% aqueous solution, 250 mg, 4.0 mmol), and the resulting mixture was stirred at room temperature overnight. DCM (100 mL) and water (100 mL) were added. The organic layer was washed with 1 M aqueous HCl (5 x 50 mL), dried (Na_2SO_4), filtered and concentrated to give the desired product (300 mg, 32%) as an off-white solid. LCMS RT 2.23 min; *m/z* 233.1 $[M+H]^+$.

(c) 4-Ethyl-1-oxo-1,2-dihydrophthalazine-6-carboxylic acid (I4)

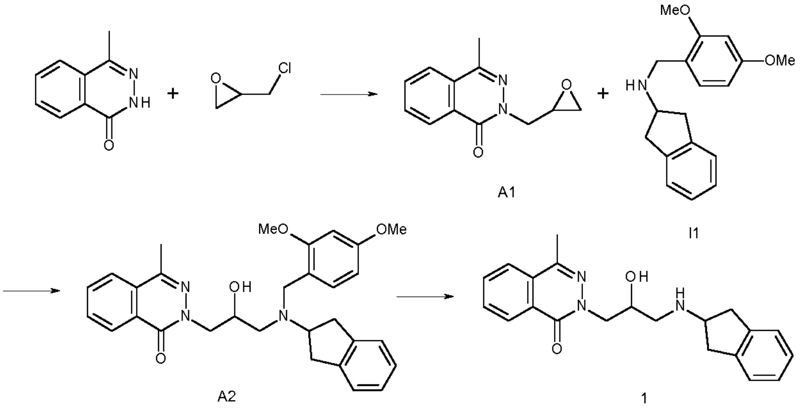
To a solution of methyl 4-ethyl-1-oxo-1,2-dihydrophthalazine-6-carboxylate I3 (0.300 g, 1.29 mmol) in THF (6 mL), MeOH (2 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (164 mg, 3.91 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated before the resultant residue was taken up in water (15 mL). The aqueous solution was acidified with 1M aqueous HCl to pH 4 and the aqueous phase extracted with DCM (3 x 30 mL). The pooled organic fractions were dried (Na_2SO_4), filtered and concentrated to give the desired product (260 mg, 92%) as an off-white solid. LCMS RT 1.18 min; *m/z* 219.1 $[M+H]^+$.

(d) 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethylphthalazin-1(2H)-one (I5)

To a solution of 4-ethyl-1-oxo-1,2-dihydrophthalazine-6-carboxylic acid I4 (120 mg, 0.56 mmol) and 3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (91 mg, 0.61 mmol) in DCM (10 mL) was added DIPEA (399 μL, 2.24 mmol), EDCI.HCl (215 mg, 1.12 mmol) and HOBt (8 mg, 0.06 mmol). The resulting mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (30 mL) was added and the aqueous extracted with DCM (3 x 50 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated to give the desired product (80 mg, 46%) as a grey solid. LCMS RT 1.35 min; *m/z* 314.1 $[M+H]^+$.

Examples

Example 1: 2-(3-((2,3-Dihydro-1*H*-inden-2-yl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (1)



(a) 4-Methyl-2-(oxiran-2-ylmethyl)phthalazin-1(2H)-one (A1)

To a suspension of Na_2SO_4 (0.400 g, 2.82 mmol) in DMF (2.5 mL) was added 4-methylphthalazin-1(2*H*)-one (0.200 g, 1.25 mmol) and NaH (60% in mineral oil, 0.070 g, 1.7 mmol). A solution of 2-(chloromethyl)oxirane (0.185 g, 2.00 mmol) in DMF (1.5 mL) was added dropwise and the mixture stirred at room temperature for 1 hour then at 60 °C for 4 hours. The mixture was filtered and the filtrate diluted with EtOAc (50 mL), washed with water (3 x 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (10% EtOAc in petroleum ether) to give the title compound as a white solid (0.100 g, 37%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.48-8.46 (m, 1H), 7.85-7.75 (m, 3H), 4.47-4.42 (m, 1H), 4.32-4.27 (m, 1H), 3.46-3.42 (m, 1H), 2.87-2.85 (m, 1H), 2.77-2.75 (m, 1H), 2.60 (s, 3H); LCMS: RT 1.64 min; *m/z* 217.1 $[M+H]^+$.

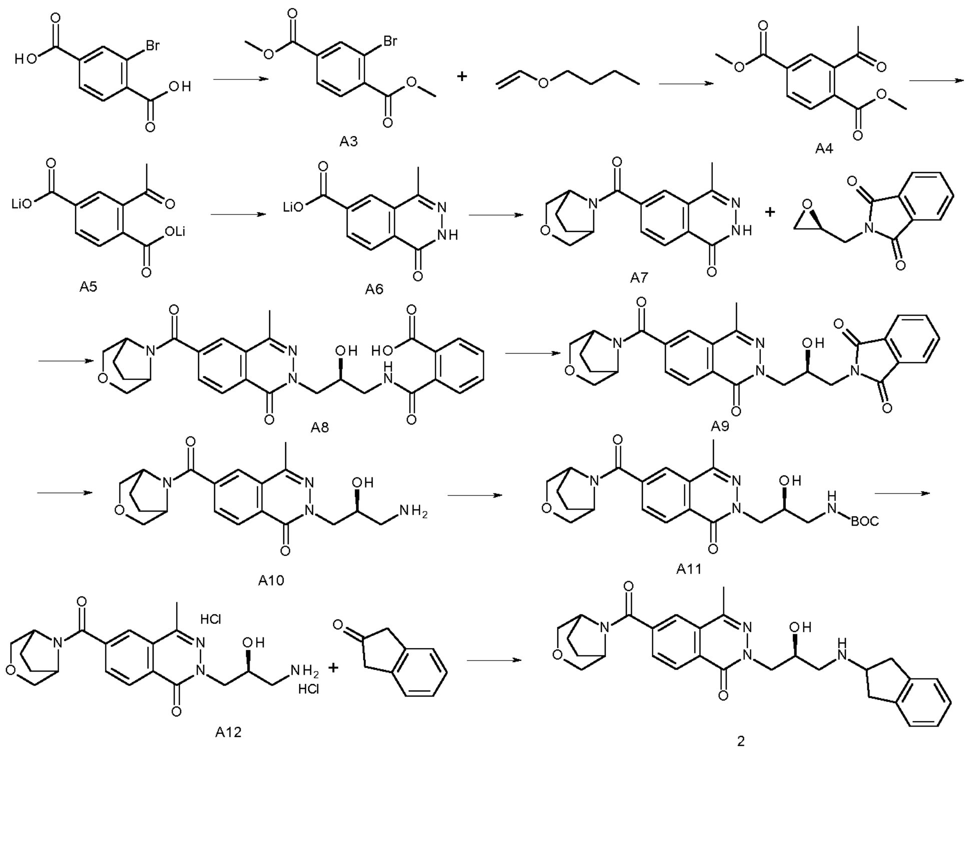
(b) 2-(3-((2,3-Dihydro-1H-inden-2-yl)(2,4-dimethoxybenzyl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (A2)

To a solution of 4-methyl-2-(oxiran-2-ylmethyl)phthalazin-1(2*H*)-one A1 (0.090 g, 0.42 mmol) in EtOH (5 mL) was added a solution of *N*-(2,4-dimethoxybenzyl)-2,3-dihydro-1*H*-inden-2-amine I1 (238 mg, 0.840 mmol) in EtOH (5 mL). The resulting mixture was heated at 80 °C overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography (33% EtOAc in petroleum ether) to give the title compound as yellow oil (170 mg, 81%). LCMS: RT 2.29 min; *m/z* 500.2$[M+H]^+$.

(c) 2-(3-((2,3-Dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (1)

A solution of 2-(3-((2,3-dihydro-1*H*-inden-2-yl)(2,4-dimethoxybenzyl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2*H*)-one A2 (170 mg, 0.34 mmol) in TFA (5 mL) was heated at reflux for 4 hours. The solvent was removed under reduced pressure and the residue obtained was suspended in saturated aqueous $NaHCO_3$ (20 mL). The aqueous was extracted with DCM (2 x 10 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated. The crude product was purified by *preparative* TLC 5% MeOH in DCM to give the title compound as a white solid (33 mg, 28%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (d, J= 8 Hz, 1H), 8.01-7.87 (m, 3H), 7.26-7.19 (m, 4H), 4.45-4.27 (m, 3H), 4.14-4.06 (m, 1H), 3.45 -3.37(m, 2H), 3.28-3.24 (m, 1H), 3.19-3.09 (m, 3H), 2.63 (s, 3H),; LCMS: RT 1.90 min; *m/z* 350.1[M+H]$^+$.

Example 2: 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-((S)-3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (2)



(a) Dimethyl 2-bromoterephthalate (A3)

To a solution of 2-bromoterephthalic acid (2.0 g, 8.2 mmol) in MeOH (20 mL) at 0 °C under N_2 was added thionyl chloride (5.8 g, 49 mmol) dropwise. The resulting mixture was stirred at room temperature overnight. The mixture was concentrated and the residue partitioned between DCM (20 mL) and saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with DCM (3 x 10 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), brine (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated to give the title compound (1.85 g, 83%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 1.6 Hz, 1H), 7.99 (dd, J = 8.0, 1.2 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H); LCMS RT 2.63 min; m/z 273,275 $[M+H]^+$.

(b) Dimethyl 2-acetylterephthalate (A4)

To a solution of dimethyl 2-bromoterephthalate A3 (2.65 g, 9.70 mmol) in CH_3CN (30 mL) was added PPh_3 (918 mg, 3.50 mmol), TEA (1.96 g, 19.4 mmol), 1-(vinyloxy)butane (4.9 g, 49 mmol) and $Pd(OAc)_2$ (392 mg, 1.75 mmol) at room temperature under N_2. The resulting mixture was heated at reflux overnight under N_2. The mixture was filtered, the filtrate was concentrated and the residue obtained was diluted with THF (30 mL) and 3 M HCl (30 mL). The mixture was stirred at room temperature for 1 hour. The organics were removed under reduced pressure and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ aqueous solution (3 x 10 mL), brine (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (EtOAc/PetroleumEther = 1/10) to give the title compound (1.1 g, 48%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J =8.0, 1.6 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.58 (s, 3H); LCMS RT 2.12 min; m/z 237.1 $[M+H]^+$

(c) Lithium 2-acetylterephthalate (A5)

To a solution of dimethyl 2-acetylterephthalate A4 (1.1 g, 4.7 mmol) in THF (10 mL), MeOH (6 mL) and H_2O (3 mL) was added $LiOH.H_2O$ (978 mg, 23.3 mmol). The resulting mixture was stirred at room temperature overnight, then concentrated *in vacuo* to dryness. The compound was dried by azeotroping with methanol to give the crude title compound (2.6 g, >95%) which was used in the next step without purification. LCMS RT 0.61 min; m/z 209 $[M-Li+H_2]^+$.

(d) Lithium 4-methyl-1-oxo-1,2-dihydrophthalazine-6-carboxylate (A6)

To a solution of lithium 2-acetylterephthalate A5 (2.6 g crude product, 4.7 mmol) in isopropanol (10 mL) was added 50% hydrazine hydrate (932 mg, 9.32 mmol). The resulting mixture was heated at reflux overnight. The mixture was concentrated to dryness and azeotroped with methanol to give the crude title compound (2.1 g, >95%) as a grey solid, which was used in the next step without purification. LCMS RT 2.59 min; m/z 205.1 $[M+H]^+$.

(e) 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2H)-one A7

A solution of lithium 4-methyl-1-oxo-1,2-dihydrophthalazine-6-carboxylate A6 (2.1 g crude product, 4.7 mmol) in thionyl chloride (10 mL) was heated at reflux for 2 hours. The mixture was concentrated to dryness to give the crude acid chloride. The residue was dissolved in DCM (20 mL), then TEA (2.35 g, 23.3 mmol) and 3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (1.05 g, 6.99 mmol) were added. The resulting mixture was stirred at room temperature overnight then diluted with water (10 mL) and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), brine (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated. The residue obtained was purified by column chromatography (MeOH/DCM = 1/50) to give the title compound (600 mg, 45% yield over three steps) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* =1.2 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.78 (s, 1H), 3.92-3.90 (m, 2H), 3.76-3.59 (m, 3H), 2.61 (s, 3H), 2.09-1.99 (m, 4H); LCMS RT 0.83 min; *m/z* 300.1 $[M+H]^+$.

(f) 2-(((2S)-3-(6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methyl-1-oxophthalazin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)benzoic acid (A8)

To a solution of 6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2*H*)-one A7 (0.300 g, 1.00 mmol) in DMF (10 mL) under N_2 was added (*S*)-2-(oxiran-2-ylmethyl) isoindoline-1,3-dione (0.610 g, 3.00 mmol) and K_2CO_3 (553 mg, 4.00 mmol). The resulting mixture was stirred at 85 °C overnight then the mixture filtered and the filtrate acidified to pH 3-4 with 4 M aqueous HCl. The aqueous was extracted with DCM (5 x 5 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a yellow oil (contains some DMF). LCMS RT 1.94 min; *m/z* 521.2 $[M+H]^+$.

(g) 2-((2S)-3-(6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methyl-1-oxophthalazin-2(1H)-yl)-2-hydroxypropyl)isoindoline-1,3-dione (A9)

A solution of 2-(((2*S*)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methyl-1-oxophthalazin-2(1*H*)-yl)-2-hydroxypropyl)carbamoyl)benzoic acid A8 (crude product from above step, 1.0 mmol) in EtOH (10 mL) was heated at reflux overnight. The mixture was concentrated and the residue diluted with EtOAc (10 mL) and water (10 mL). The separated aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (3 x 5 mL), brine (3x5 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by preparative TLC (MeOH/DCM = 1/20) to give the title compound (260 mg, 51% yield over two steps) as an off-white solid. ^{1}H NMR (400

MHz, MeOD) δ 8.40 (d, *J* = 8.4 Hz, 1H), 7.99-7.97 (m, 1H), 7.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.82-7.76 (m, 4H), 4.69 (s, 1H), 4.55-4.48 (m, 1H), 4.37-4.24 (m, 2H), 3.93-3.83 (m, 3H), 3.81-3.73 (m, 3H), 3.60-3.57 (m, 1H), 2.57 (s, 3H), 2.10-2.03 (m, 4H); LCMS RT 2.29 min; *m/z* 503.2 $[M+H]^+$.

(h) 2-((S)-3-Amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2H)-one (A10)

To a solution of 2-((2*S*)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methyl-1-oxophthalazin-2(1*H*)-yl)-2-hydroxypropyl)isoindoline-1,3-dione A9 (250 mg, 0.50 mmol) in EtOH (5 mL) was added 75% hydrazine hydrate (100 mg, 1.5 mmol). The resulting mixture was heated at reflux for 4 hours. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product (210 mg, >95%) as a yellow solid. LCMS RT 2.22 min; *m/z* 373.2 $[M+H]^+$.

(i) tert-Butyl ((2S)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methyl-1-oxophthalazin- 2(1H)-yl)-2-hydroxypropyl)carbamate (A11)

To a solution of 2-((*S*)-3-amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl) -4-methylphthalazin-1(2*H*)-one A10 (190 mg, 0.51 mmol) in DCM (6 mL) was added TEA (155 mg, 1.53 mmol) and Boc_2O (223 mg, 1.02 mmol). The mixture was stirred at room temperature for 2 hours then partitioned between water (5 mL) and DCM (10 mL). The aqueous phase was extracted with DCM (3 x 5 mL) and the combined organic fractions washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), brine (3 x 5 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (MeOH/DCM = 1/50) to give the title compound (150 mg, 62%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 1.2 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.70 (s, 1H), 4.33-4.27 (m, 1H), 4.21-4.15 (m, 2H), 3.93-3.86 (m, 2H), 3.77-3.75 (m, 2H), 3.60-3.57 (m, 1H), 3.28-3.24 (m, 1H), 3.16-3.11 (m, 1H), 2.64 (s, 3H), 2.11-2.04 (m, 4H), 1.42 (s, 9H); LCMS RT 2.39 min; *m/z* 473.2$[M+H]^+$, 495.2 $[M+Na]^+$.

(j) 2-((S)-3-Amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2H)-one dihydrochloride (A12)

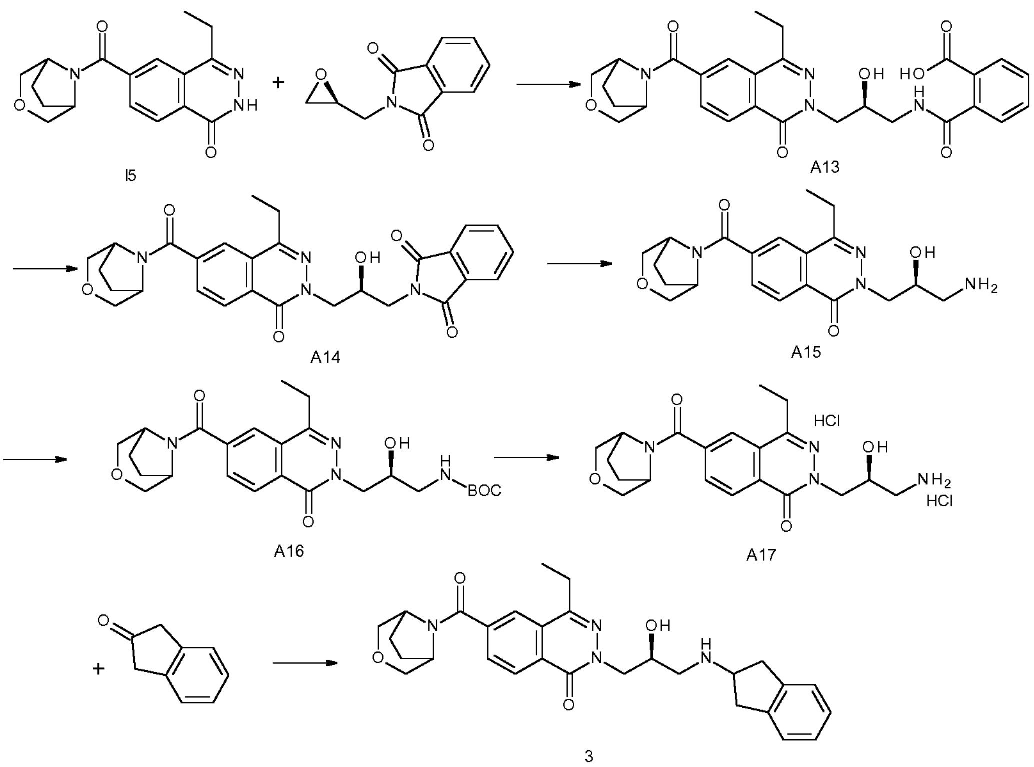
A solution of *tert*-butyl ((2*S*)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methyl-1-oxophthalazin-2(1*H*)-yl)-2-hydroxypropyl)carbamate A11 (150 mg, 0.32 mmol) in 2 M HCl in Et_2O (10 mL) was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* to give the title compound (118 mg, 84%) as a off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 0.8 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.71 (s, 1H), 4.36-4.24 (m, 3H), 3.92-3.86 (m, 2H), 3.77-3.74 (m, 2H), 3.60-3.57 (m, 1H), 3.15-3.12 (m, 1H), 2.98-2.93 (m, 1H), 2.65 (s, 3H), 2.11-2.04 (m, 4H); LCMS RT 2.45 min; *m/z* 373.2 $[M+H]^+$.

(k) 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-((S)-3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (2)

To a solution of 2-((*S*)-3-amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2*H*)-one dihydrochloride A12 (40 mg, 0.09 mmol) in 1,2-dichloroethane (5 mL) at room temperature under N_2 was added TEA (46 mg, 0.45 mmol), AcOH (36 mg), 1*H*-inden-2(3*H*)-one (24 mg, 0.18 mmol) and $NaBH(OAc)_3$ (58 mg, 0.27 mmol). The mixture was stirred at room temperature overnight under N_2, then concentrated and the residue diluted with water (10 mL) and DCM (10 mL). The aqueous phase was extracted with DCM (3 x 5 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (3 x 5 mL), brine (3 x 5 mL), dried (Na_2SO_4) filtered and concentrated. The residue was purified by preparative TLC (MeOH/DCM = 1/20) to give the crude product (15 mg) as a black solid.

The reaction was repeated twice more on the same scale and the three batches of crude products (batch 1 (16 mg), batch 2 (16 mg), batch 3 (15 mg)) combined and purified by preparative-HPLC to give the title compound (13 mg, 8%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 1.2 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.27-7.19 (m, 4H), 4.71 (s, 1H), 4.45-4.38 (m, 1H), 4.37-4.28 (m, 2H), 4.16-4.08 (m, 1H), 3.93-3.86 (m, 2H), 3.77-3.74 (m, 2H), 3.60-3.57 (m, 1H), 3.46-3.38 (m, 2H), 3.28-3.27 (m, 1H), 3.18-3.11 (m, 3H), 2.65 (s, 3H), 2.11-2.04 (m, 4H); LCMS RT 1.81 min; *m/z* 489.3 $[M+H]^+$.

Example 3: 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-((*S*)-3-((2,3-dihydro-1*H*-inden-2-yl)amino)-2-hydroxypropyl)-4-ethylphthalazin-1(2*H*)-one (3)



(a) 2-(((2S)-3-(6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethyl-1-oxophthalazin-2(1H)-yl)-2-hydroxypropyl)carbamoyl)benzoic acid (A13)

To a solution of 6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethylphthalazin-1(2*H*)-one I5 (0.200 g, 0.638 mmol) in DMF (10 mL) under N_2 was added (*S*)-2-(oxiran-2-ylmethyl) isoindoline-1,3-dione (130 mg, 0.64 mmol) and K_2CO_3 (133 mg, 0.962 mmol). The resulting mixture was heated at 85 °C overnight. The reaction was cooled and the solids removed by filtration. The filtrate was acidified to pH 3-4 with 4 M aqueous HCl then extracted with DCM (5 x 5 mL). The combined organic fractions were dried (Na_2SO_4) filtered and concentrated to give the crude product as yellow oil which was used in the next step without purification (contained some DMF). LCMS RT 2.13 min; *m/z* 535.2 $[M+H]^+$.

(b) 2-((2S)-3-(6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethyl-1-oxophthalazin-2(1H)-yl)-2-hydroxypropyl)isoindoline-1,3-dione (A14)

A solution of 2-(((2*S*)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethyl-1-oxophthalazin-2(1*H*)-yl)-2-hydroxypropyl)carbamoyl)benzoic acid A13 (crude product obtained above, 0.64 mmol) in EtOH (10 mL) was heated at reflux overnight. The mixture was concentrated and the residue partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (3 x 5 mL), brine (3 × 5 mL), dried (Na_2SO_4), filtered and concentrated to give the title compound (300 mg, 91% yield over two steps) as an off-white solid. LCMS RT 2.49 min; *m/z* 517.2 $[M+H]^+$.

(c) 2-((S)-3-Amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethylphthalazin-1(2H)-one (A15)

To a solution of 2-((2*S*)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethyl-1-oxophthalazin-2(1*H*)-yl)-2-hydroxypropyl)isoindoline-1,3-dione A14 (0.300 g, 0.581 mmol) in a mixture of EtOH (5 mL) and DCM (5 mL) was added 80% hydrazine hydrate (44 mg, 0.7 mmol). The resulting mixture was heated at reflux for 4 hours under N_2. The solids were removed by filtration and the filtrate concentrated to afford the crude product (280 mg, >95%) as yellow oil. LCMS RT 2.78 min; *m/z* 387.2 $[M+H]^+$.

(d) tert-Butyl ((2S)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethyl-1-oxophthalazin-2(1H)-yl)-2-hydroxypropyl)carbamate (A16)

To a solution of 2-((*S*)-3-amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethylphthalazin-1(2*H*)-one A15 (crude, 280 mg, 0.58 mmol@100%) in THF (6 mL) was added TEA (117 mg, 1.16 mmol) and Boc_2O (164 mg, 0.751 mmol). The mixture was stirred at room temperature overnight. The reaction was diluted with water (5 mL) and DCM (5 mL) and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 x 15 mL), brine (15 mL), dried (Na_2SO_4), filtered and concentrated. The residue obtained was purified by preparative TLC (MeOH/DCM = 1/10) to give the title compound (170 mg, 60%) as a yellow solid. LCMS RT 2.51 min; *m/z* 487.3 $[M+H]^+$.

(e) 2-((S)-3-Amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2H)-one dihydrochloride (A17)

A mixture of *tert*-butyl ((2*S*)-3-(6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-ethyl-1-oxophthalazin-2(1*H*)-yl)-2-hydroxypropyl)carbamate A16 (170 mg, 0.35 mmol) in 2 M HCl in Et_2O (15 mL) was stirred at room temperature for 2 hours. The mixture was concentrated to give the title compound (161 mg, 99%) as an off-white solid.

(f) 6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-((S)-3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-4-ethylphthalazin-1(2H)-one (3)

To a solution of 2-((*S*)-3-amino-2-hydroxypropyl)-6-(3-oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-4-methylphthalazin-1(2*H*)-one dihydrochloride A17 (0.080 g, 0.17 mmol) in DCM (5 mL) was added TEA (26 mg, 0.26 mmol), 1H-inden-2(3*H*)-one (28 mg, 0.21 mmol) and $NaBH_4$ (13 mg, 0.34 mmol). The mixture was stirred at room temperature overnight, concentrated and the residue was purified by preparative TLC (MeOH/DCM = 1/10) to give the product (15 mg) as a black solid.

The reaction was repeated on the same scale and the two batches of product combined and purified again by preparative TLC to give the title compound (15 mg, 9%) as a grey solid. ^1H NMR (400 MHz, CD_3OD) δ 8.48 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.96-7.94 (d, J = 8.0 Hz, 1H), 7.25-7.21 (m, 4H), 4.71 (br s, 1H), 4.50-4.30 (m, 3H), 4.15-4.11 (m, 1H), 3.92-3.75 (m, 5H), 3.64-3.58 (m, 1H), 3.48-3.39 (m, 2H), 3.18-3.06 (m, 5H), 2.14-1.98 (m, 4H), 1.38-1.35 (m, 3H); LCMS RT 2.10 min; *m/z* 503.3 $[M+H]^+$.

Assays

PRMT5 Biochemical Assay

Compounds of the invention may be tested for *in vitro* activity in the following assay:

A histone H4 derived peptide is used as substrate (amino acid sequence: Ser-Gly-Arg-Gly-Lys-Gly-Gly-Lys-Gly-Leu-Gly-Lys-Gly-Gly-Ala-Lys-Arg-His-Arg-Lys-Val-NH_2). Full-length PRMT5 enzyme (NCBI Reference sequence NP_006100.2) was co-expressed with His_6-MEP50 in insect cells and purified via Nickel immobilized metal affinity and gel filtration chromatography (“the enzyme”).

The 6 µL reactions are run in Greiner brand black 384-well low volume assay plates. All reactions contained assay buffer (phosphate buffered saline, 0.01 % (v/v) Tween-20, 0.01% (w/v) albumin from chicken egg white, 1 mM Dithiothreitol, 1 µM peptide substrate, 1 µM *S*-Adenosyl methionine, and 15 ng/reaction enzyme, with the enzyme being omitted from negative control reactions. Compounds were added in a volume of 100 nL from dilution series prepared in DMSO, positive and negative control reactions receiving the same volume DMSO without compound. The plates were sealed with adhesive seals and incubated for 4 hours at 37 degree Celsius. Reaction progress was measured using the Transcreener™ EPIGEN methyltransferase assay (BellBrook Labs, Madison, WI) as recommended by the manufacturer. To each reaction 2 µL detection mix were added, containing coupling enzymes, fluorescence polarisation tracer, and AMP antibody. Plates were incubated for

90 minutes before being read on a PerkinElmer EnVision™ plate reader in fluorescence polarisation mode. IC_{50} values were obtained from the raw readings by calculating percent inhibition (%I) for each reaction relative to controls on the same plate (%I=(I-CN)/(CP-CN) where CN/ CP are the averages of the negative/ positive reactions, respectively), then fitting the %I data *vs*. compound concentration [I] to %I=(A+((B-A)/(1+((C/[I])^D)))) where A is the lower asymptote, B is the upper asymptote, C is the IC_{50} value, and D is the slope.

Compound Number	**IC_{50} (μM)**
1	4.53
2	0.17
3	0.03

PRMT5 Biomarker Assay

Compounds of the invention may be tested for potency to inhibit symmetrical dimethylation of arginine in the following assay:

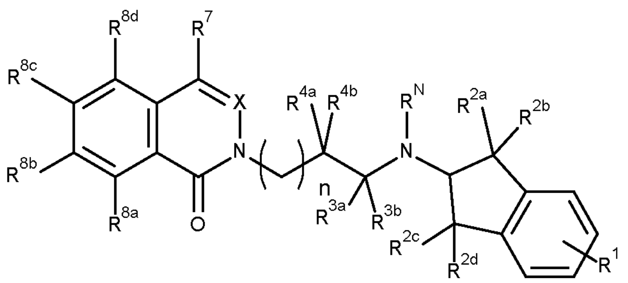
The cell line TE11 was seeded at a density of 6,000 cells per well in 96 well optical quality tissue culture plates in DME medium and 10% foetal bovine serum, and allowed to adhere for 5 hours under standard culture conditions (37 degree Celsius, 5% CO_2). Compound dilutions prepared in DMSO were added to the medium, with negative control wells reserved for treatment with DMSO only and maximum inhibition controls receiving a potent PRMT5 inhibitor compound at 1 µM concentration. After incubation for 72 hours, the cells were fixed with 3.7% formaldehyde in PBS for 30 minutes at room temperature, washed with phosphate buffer saline and blocked with Odyssey blocking buffer (LI-COR, Lincoln, NE). Rabbit anti-Di-Methyl Histone H4 Arginine 3 specific antibody (Epigentek) in Odyssey blocking buffer was added and incubated for 14 hours at 4 degree Celsius. After washing, anti-rabbit secondary antibody labelled with Alexa647 dye (LifeTechnologies) and Hoechst 33342 (1 µg/mL, SigmaAldrich) were added for 1 hour incubation. Plates were washed and read on a PerkinElmer Envision 2103 in fluorescence intensity scanning mode (24 scans across the well area). The plates were imaged on a PerkinElmer Phenix high content imaging platform. Using a Columbus image analysis pipeline, individual nuclei were located by Hoechst 33342 stain and the methylation level was calculated from the Alexa647-related intensity in the same area. IC_{50} values were obtained from the mean Alexa647-related intensity per cell by calculating percent inhibition (%I) for each well relative to controls on the same plate (%I=(I-CN)/(CP-CN) where CN/ CP are the averages of the negative/ maximum inhibition controls, respectively), then fitting the %I data *vs*. compound concentration [I] to %I=(A+((B-

A)/(1+((C/[I])^D)))) where A is the lower asymptote, B is the upper asymptote, C is the IC_{50} value, and D is the slope.

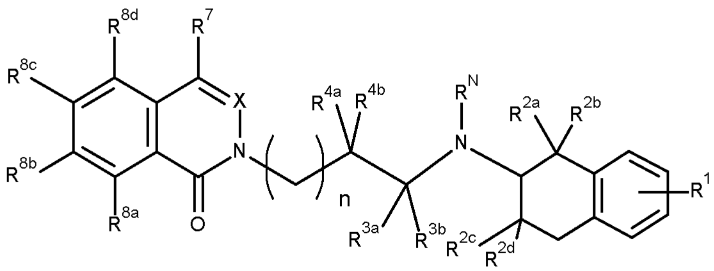
Compound Number	**IC_{50} (μM)**
2	0.0180
3	0.0019

Claims

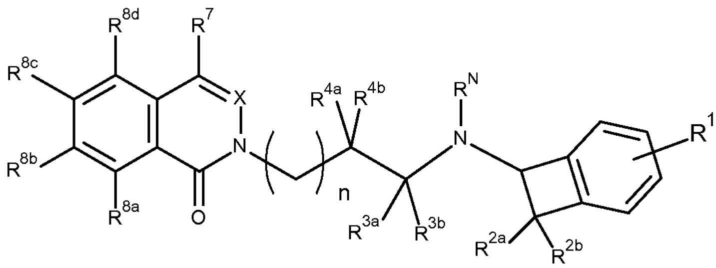
1. A compound of formula Ia, Ib or Ic:



(Ia)



(Ib)



(Ic)

wherein:

n is 1 or 2;

R^N is H or Me;

R^1 is optionally one or more halo or methyl groups;

R^{2a} and R^{2b} are independently selected from the group consisting of:

(i) F;

(ii) H;

(iii) Me; and

(iv) CH_2OH;

R^{2c} and R^{2d} (if present) are independently selected from the group consisting of:

(i) F;

(ii) H;

(iii) Me; and

(iv) CH_2OH;

R^{3a} and R^{3b} are independently selected from H and Me;

R^{4a} is selected from OH, $-NH_2$, $-C(=O)NH_2$, and $-CH_2OH$;

R^{4b} is either H or Me;

X is either N or CH;

R^7 is selected from H and C_{1-4} alkyl;

(a) one of R^{8a}, R^{8b}, R^{8c} and R^{8d} is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, NHC_{1-4} alkyl;

(b) another of R^{8a}, R^{8b}, R^{8c} and R^{8d} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, acylamidomethyl, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4} alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl;

(c) the others of R^{8a}, R^{8b}, R^{8c} and R^{8d} are H.

2. A compound according to claim 1, wherein n is 1.

3. A compound according to claim 1, wherein n is 2.

4. A compound according to any one of claims 1 to 3, wherein R^N is H.

5. A compound according to any one of claims 1 to 3, wherein R^N is Me.

6. A compound according to any one of claims 1 to 5, wherein there are no R^1 substituents.

7. A compound according to any one of claims 1 to 5, wherein R^1 represents one to four Me or halo groups.

8. A compound according to any one of claims 1 to 7, wherein R^{2a}, R^{2b}, R^{2c} and R^{2d} (if present) are all H.

9. A compound according to any one of claims 1 to 7 of formula Ia or Ib, wherein R^{2a}, R^{2b}, R^{2c} and R^{2d} are comprised of three H and one Me or CH_2OH group.

10. A compound according to claim 9 of formula Ia or Ib, wherein R^{2a} is Me and R^{2b}, R^{2c} and R^{2d} are H.

11. A compound according to claim 9, wherein R^{2c} is Me or CH_2OH and R^{2a}, R^{2b} and R^{2d} are H.

12. A compound according to any one of claims 1 to 7 of formula Ia or Ib, wherein R^{2a}, R^{2b}, R^{2c} and R^{2d} are comprised of two H and two Me groups.

13. A compound according to claim 12, wherein R^{2a} and R^{2c} are Me and R^{2b} and R^{2d} are H.

14. A compound according to claim 12, wherein R^{2a} and R^{2b} are Me and R^{2c} and R^{2d} are H.

15. A compound according to claim 12, wherein R^{2c} and R^{2d} are Me and R^{2a} and R^{2b} are H.

16. A compound according to any one of claims 1 to 7 of formula Ic, wherein R^{2a} is H and R^{2b} is a Me or CH_2OH group.

17. A compound according to any one of claims 1 to 7 of formula Ic, wherein R^{2a} and R^{2b} are each a Me or CH_2OH group.

18. A compound according to any one of claims 1 to 17, wherein R^{3a} is H and R^{3b} is Me.

19. A compound according to any one of claims 1 to 17, wherein R^{3a} and R^{3b} are both H.

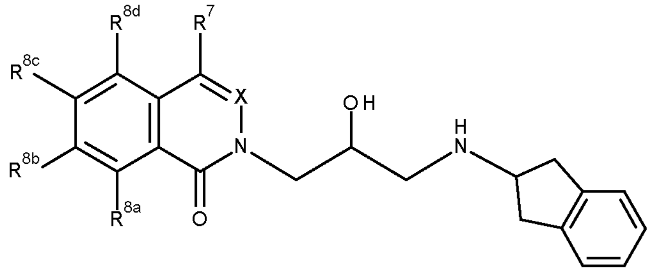
20. A compound according to any one of claims 1 to 17, wherein R^{3a} and R^{3b} are both Me.

21. A compound according to any one of claims 1 to 20, wherein R^{4a} is OH.

22. A compound according to any one of claims 1 to 21, wherein R^{4b} is H.

23. A compound according to any one of claims 1 to 21, wherein R^{4b} is Me.

24. A compound according to claim 1 which is of formula Ia1, Ib1 or Ic1:



(Ia1)

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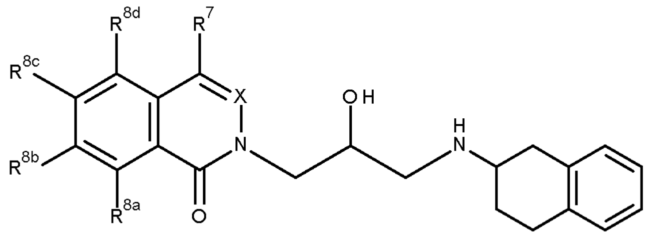

(Ib1)

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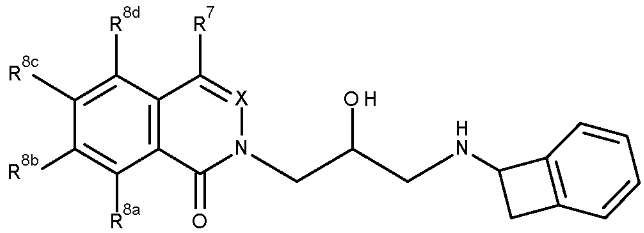

(Ic1)

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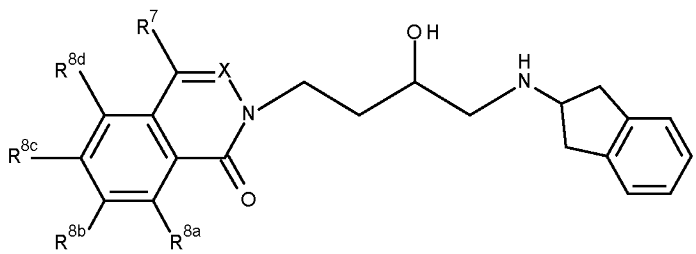
25. A compound according to claim 1 which is of formula Ia2, Ib2 or Ic2:



(Ia2)

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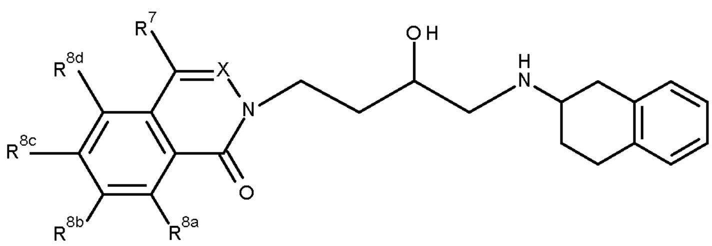

(Ib2)

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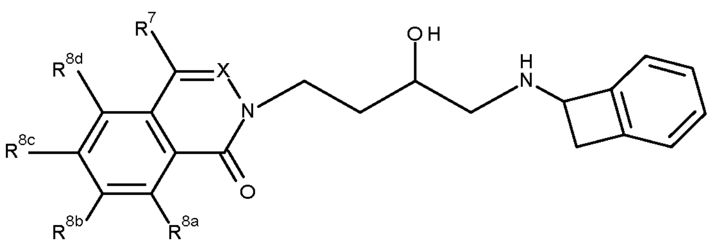

(Ic2)

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26. A compound according to any one of claims 1 to 25, wherein the compound is a racemate at the carbon atom to which R^{4b} and R^{4a} are attached.

27. A compound according to any one of claims 1 to 25, wherein the compound is a single enantiomer at the carbon atom to which R^{4b} and R^{4a} are attached.

28. A compound according to claim 27, wherein the compound is the *(R)*-enantiomer.

29. A compound according to claim 27, wherein the compound is the *(S)*-enantiomer.

30. A compound according to any one of claims 1 to 29 wherein X is N.

31. A compound according to any one of claims 1 to 29 wherein X is CH.

32. A compound according to any one of claims 1 to 31, wherein R^7 is H.

33. A compound according to any one of claims 1 to 31, wherein R^7 is methyl or ethyl.

34. A compound according to claim 33, wherein R^7 is ethyl.

35. A compound according to any one of claims 1 to 34, wherein the one of R^{8a}, R^{8b}, R^{8c} and R^{8d} that is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy and NHC_{1-4} alkyl is selected from halo, C_{1-4} alkyl, methoxy or ethoxy.

36. A compound according to claim 35, wherein the one of R^{8a}, R^{8b}, R^{8c} and R^{8d} that is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy and NHC_{1-4} alkyl is either chloro or ethoxy.

37. A compound according to any one of claims 1 to 36, wherein R^{8a} is selected from H, halo, C_{1-4} alkyl, C_{1-4} alkoxy and NHC_{1-4} alkyl.

38. A compound according to claim 37, wherein R^{8a} is selected from halo, C_{1-4} alkyl, methoxy or ethoxy.

39. A compound according to claim 38, wherein R^{8a} is either chloro or ethoxy.

40. A compound according to any one of claims 1 to 39, wherein the one of R^{8a}, R^{8b}, R^{8c} and R^{8d} that is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4} alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl is selected from C_{1-4} alkyl, fluoro, chloro, bromo, acetyl, methoxy, ethoxy, -C(=O)Me, -C(=O)Et, $-CH_2C(=O)Me$, phenyl, $-CF_3$, $-CF_2H$, -CN, $-CH_2CN$, -OBn, -OPh, $-OCF_3$,$-OCF_2H$, -O-(C_6H_4)-CN, -COOH, $-CH_2COOH$, -C(=O)OMe, $-C(=O)NH_2$, -C(=O)NMeH, $-C(=O)NMe_2$, -C(=O)N^{i}PrH, -C(=O)-piperidinyl, -C(=O)-pyrrolidinyl,-C(=O)-morpholino (which may be bridged or substituted with one or two methyl groups), -C(=O)-azetidinyl, $-CH_2C(=O)NH_2$, $-CH_2C(=O)$-azetidinyl, $-CH_2C(=O)NMeH$, $-CH_2C(=O)N^iPrH$, $-CH_2C(=O)$-pyrrolidinyl, $-CH_2C(=O)$-morpholino, $-CH_2$-morpholino, $-CH_2$-methylpiperazinyl, $-OCH_2$pyridinyl, $-OCH_2$-methyloxadiazolyl, $-CH_2$-imidazolyl, -O-tetrahydropyranyl, $-CH_2$-tetraydropyanyl,-NH-methylpyrazinyl, $-CH_2$-triazolyl, $-NHSO_2Ph$, $-NHSO_2Me$, $-SO_2NMePh$, $-SO_2NMe_2$, $-SO_2NHEt$, $-SO_2CF_3$,- γ-lactam, $-CH_2NHC(=O)Me$, $-CH_2NHC(=O)OMe$, $-CH_2NHC(=O)CF_3$, morpholino, $-CH_2NH_2$, -C(=O)Ph, $-OCH_2$-isoxazolyl, -NH-pyrimidinyl, pyridizinyl, pyrimidinyl, pyridinyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, pyrazinyl, pyridazinyl , methyloxadiazolyl, oxadiazolyl, dimethyloxadiazolyl, isoxazolyl, dimethyltriazolyl, imidazolyl, benzimidazolyl and thiadiazolyl.

41. A compound according to any one of claims 1 to 39, wherein one of R^{8b}, R^{8c} and R^{8d} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-6} cycloalkyl, C_{5-6} heteroaryl, C_{5-6} heteroaryl methyl, C_{4-6} heterocyclyl, C_{4-6} heterocyclyl methyl, phenyl, benzyl, halo, amido, amidomethyl, acylamido, C_{1-4} alkyl ester, C_{1-4} alkyl ester methyl, C_{1-4} alkyl carbamoyl, C_{1-4} alkyl carbamoyl methyl, C_{1-4} alkylacyl, C_{1-4} alkylacyl methyl, phenylcarbonyl, carboxy, carboxymethyl, ether, amino, amino methyl, sulfonamido, sulfonamino, sulfone, sulfoxide, nitrile and nitrilemethyl.

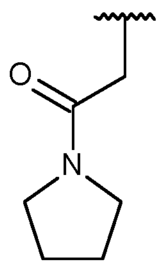
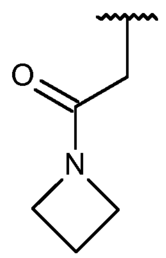
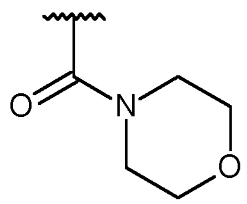
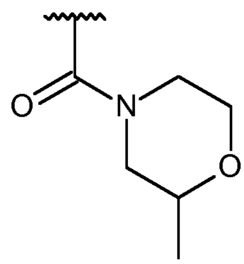
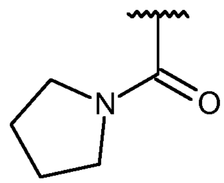
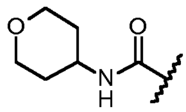
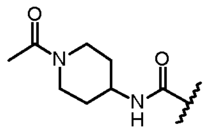
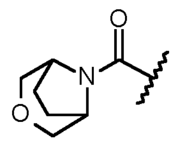
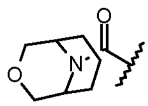
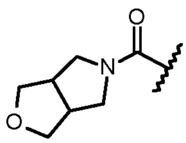
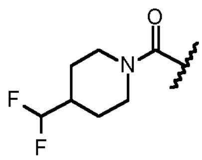
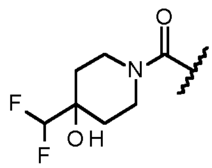
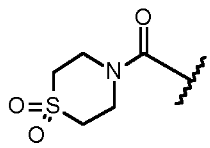
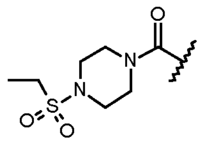
42. A compound according to claim 41, wherein one of R^{8b}, R^{8c} and R^{8d} is selected from C_{1-4} alkyl, fluoro, chloro, bromo, acetyl, methoxy, ethoxy, -C(=O)Me, -C(=O)Et, $-CH_2C(=O)Me$, phenyl, $-CF_3$, $-CF_2H$, -CN, $-CH_2CN$, -OBn, -OPh, $-OCF_3$,$-OCF_2H$, -O-(C_6H_4)-CN, -COOH, $-CH_2COOH$, -C(=O)OMe, $-C(=O)NH_2$, -C(=O)NMeH, $-C(=O)NMe_2$, -C(=O)N^{i}PrH, -C(=O)-piperidinyl, -C(=O)-pyrrolidinyl,-C(=O)-morpholino (which may be bridged or substituted with one or two methyl groups), -C(=O)-azetidinyl, $-CH_2C(=O)NH_2$, $-CH_2C(=O)$-azetidinyl, $-CH_2C(=O)NMeH$, $-CH_2C(=O)N^iPrH$, $-CH_2C(=O)$-pyrrolidinyl, -

$CH_2C(=O)$-morpholino, -CH_2-morpholino, -CH_2-methylpiperazinyl, -OCH_2pyridinyl, -OCH_2-methyloxadiazolyl, -CH_2-imidazolyl, -O-tetrahydropyranyl, -CH_2-tetraydropyanyl,-NH-methylpyrazinyl, -CH_2-triazolyl, -$NHSO_2Ph$, -$NHSO_2Me$, -SO_2NMePh, -SO_2NMe_2, -SO_2NHEt, -SO_2CF_3,- γ-lactam, -$CH_2NHC(=O)Me$, -$CH_2NHC(=O)OMe$, -$CH_2NHC(=O)CF_3$, morpholino, -CH_2NH_2, -C(=O)Ph, -OCH_2-isoxazolyl, -NH-pyrimidinyl, pyridizinyl, pyrimidinyl, pyridinyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, pyrazinyl, pyridazinyl , methyloxadiazolyl, oxadiazolyl, dimethyloxadiazolyl, isoxazolyl, dimethyltriazolyl, imidazolyl, benzimidazolyl and thiadiazolyl.

43. A compound according to claim 42, wherein one of R^{8b} and R^{8d} is selected from C_{1-4} alkyl, amino or C_{5-6} heteroaryl.

44. A compound according to claim 42, wherein R^{8c} is selected from amido or amidomethyl.

45. A compound according to claim 44, wherein R^{8c} is selected from:

46. A compound according to claim 1, which is selected from:

2-(3-((2,3-Dihydro-1*H*-inden-2-yl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (1);

6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-((S)-3-((2,3-dihydro-1H-inden-2-yl)amino)-2-hydroxypropyl)-4-methylphthalazin-1(2H)-one (2); and
6-(3-Oxa-8-azabicyclo[3.2.1]octane-8-carbonyl)-2-((*S*)-3-((2,3-dihydro-1*H*-inden-2-yl)amino)-2-hydroxypropyl)-4-ethylphthalazin-1(2*H*)-one (3).

47. A compound according to any one of claims 1 to 46 for use in a method of therapy.

48. A pharmaceutical composition comprising a compound according to any one of claims 1 to 46 and a pharmaceutically acceptable excipient.

49. A method of treatment of cancer, comprising administering to a patient in need of treatment, a compound according to any one of claims 1 to 46, or a composition according to claim 48.

50. Use of a compound according to any one of claims 1 to 46 in the manufacture of a medicament for treating cancer.

51. A compound according to any one of claims 1 to 46 or pharmaceutical composition according to claim 48, for use in the treatment of cancer.

52. A method of treatment of hemoglobinopathies, comprising administering to a patient in need of treatment, a compound according to any one of claims 1 to 46 or pharmaceutical composition according to claim 48.

53. Use of a compound according to any one of claims 1 to 46 in the manufacture of a medicament for treating hemoglobinopathies.

54. A compound according to any one of claims 1 to 46 or pharmaceutical composition according to claim 48 for use in the treatment of hemoglobinopathies.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/055535

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D237/32 C07D498/08 A61K31/502 A61P7/00 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 A61P

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

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

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ELAYNE CHAN-PENEBRE ET AL: "A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models", NATURE CHEMICAL BIOLOGY, vol. 11, no. 6, 27 April 2015 (2015-04-27), pages 432-437, XP055297240, ISSN: 1552-4450, DOI: 10.1038/nchembio.1810 the whole document in particular Figure 1 -----	1-54
A	WO 2014/100734 A1 (EPIZYME INC [US]) 26 June 2014 (2014-06-26) the whole document in particular Table 1B -----	1-54

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

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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	Date of mailing of the international search report
29 May 2017	07/06/2017

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

3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/055535

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 2014/100716 A1 (EPIZYME INC [US]) 26 June 2014 (2014-06-26) the whole document in particular Scheme 6 on page 78, compound 1 and claims 19-21 -----	1-54
A,P	WO 2016/034671 A1 (CTXT PTY LTD [AU]) 10 March 2016 (2016-03-10) the whole document in particular claim 1 -----	1-54

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/055535

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014100734 A1	26-06-2014	CA 2894157 A1	26-06-2014
		EP 2935247 A1	28-10-2015
		JP 2016505597 A	25-02-2016
		US 2014228360 A1	14-08-2014
		US 2015361042 A1	17-12-2015
		US 2016137631 A1	19-05-2016
		WO 2014100734 A1	26-06-2014
WO 2014100716 A1	26-06-2014	CA 2899363 A1	26-06-2014
		EP 2935241 A1	28-10-2015
		JP 2016505001 A	18-02-2016
		US 2014213582 A1	31-07-2014
		US 2015344463 A1	03-12-2015
		US 2017088541 A1	30-03-2017
		WO 2014100716 A1	26-06-2014
WO 2016034671 A1	10-03-2016	NONE	