The present invention relates to compounds of the formula (I): as inhibitors of peptidylarginine deiminases (PADs). It also concerns their use in therapy, particularly in the prophylaxis or treatment of neural injury, and other conditions including cancer, multiple sclerosis, glaucoma, arthritis, rheumatoid arthritis lupus, Alzheimer's disease, and ulcerative colitis.

**Title:** PEPTIDYL ARGENTINE DEIMINASES (PAD) INHIBITORS

**Abstract:**
PEPTIDYLARGININE DEIMINASES (PAD) INHIBITORS

The present invention relates to compounds and their uses. In particular, though not exclusively, it concerns compounds as inhibitors of peptidylarginine deiminases (PADs) and their use in therapy.

The family of calcium ion-dependent peptidylarginine deiminases, including the five known mammalian isoforms, PAD1-4 and PAD6, catalyse the formation of citrulline residues in proteins from arginine residues (Ferretti et al., Protein Deimination in Human Health and Disease, eds. A. P. Nicholas and S. Bhattacharya, 2013, in press, Ying et al., J. Dermatol. Set, 2009, 53, 2, and Gyorgy et al., Int. J. Biochem. Cell. Biol, 2006, 38, 1662.). Such deimination, also referred to as citrullination, results in a loss of positive charge that can induce conformational changes in PAD protein structure, and alter its interactions with other proteins.

The known PAD isoforms have different tissue distributions, which often overlap, and are believed to have distinct substrate specificity. PAD2, the ancestral and more widely expressed PAD, is the main PAD in the central nervous system (CNS), though expression of other PADs has been reported in various neural cell types. For example, PAD4 is expressed in myelin, and PAD3 expression has been reported in human cerebellum and sciatic nerve.

Although little is known about PAD3 expression in amniote CNS, with the exception of the chick spinal cord where it was found to be expressed in neural progenitors during development, it is now known that PAD3 is expressed in human neural stem cells (hNSCs) and that raising cytoplasmic calcium with thapsigargin to mimic changes occurring in traumatic injuries, increases PAD3 but not PAD2 transcript, and induces hNSC death. This effect is also increased by over-expressing PAD3, and reduced by treatment with a PAD inhibitor or PAD3, but not PAD2, siRNA. Conversely, in untreated hNSCs, PAD inhibition increases cell growth. In addition, PAD3 up-regulation following chick spinal cord injury has been linked to extensive tissue damage and loss of regenerative capability. Thus, PADs play an important role in balancing cell survival/death, and PAD3, in particular, is seen as an important early regulator of calcium-induced cell death in hNSCs.
Taken together with the inventors’ knowledge, there is suggested an increasing association of the citrullination of PADs with several diseases, including rheumatoid arthritis (mainly PAD4 involvement), in which antibodies to citrullinated proteins and anti-PAD autoantibody levels can act as important diagnostic aids (Kolfenbach et al., *Arthritis Rheum.* 2010, 62, 2633, and Wegner et al, *Immunol. Rev.*, 2010, 233, 34). Up-regulation of PAD2 has been implicated in the development of glaucoma (Cafaro et al., *Mol Vis.*, 2010, 16, 1654) and autoimmune diseases such as multiple sclerosis, for which PAD inhibition in an animal model prevented onset of the disease (Wood et al., *Lab. Invest.*, 2008, 88, 354, Moscarello et al., *Dis. Model Mech.* 19 Feb Epub, and Jang et al., *Biochem. J.*, 2012, 445, 183). Increased protein deimination has also been reported in patients with Alzheimer's disease (Ishigam et al., *J. Neurosci Res.*, 2005, 80, 120) and in other neurodegenerative diseases (Harauz et al., *Neurochem. Res.*, 2007, 32, 137).

A role for PADs has also been demonstrated in traumatic injury. Tissue loss following spinal cord injury is associated with up-regulation of PAD3, and has been ameliorated using a non-selective PAD inhibitor, Cl-amidine. Cl-amidine (Slack et al., *ACS Chem. Biol.*, 2011, 6, 466, and Luo et al, *J. Am. Chem. Soc.*, 2006, 128, 1092) decreases deimination, apoptosis and consequently tissue loss in injured chick spinal cords (Lange et al. *Dev. Biol.* 2011, 355, 205), and ameliorates tissue damage following perinatal ischaemia. Thus, the putative role of PAD3 in spinal cord tissue loss following injury makes novel compounds that can effectively inhibit the activity of this isozyme of particular interest for neuroprotection.

The prevention and treatment of cancer may also be associated with PAD, since it is known that historic citrullination by PAD4 regulates tumour suppressor gene expression. PAD4 acts as a co-repressor of p53 to regulate sestrin2 expression by histone citrullination in cancer cells (Wang et al, *J. Biol. Chem.* 2012, 287, 25941). It is also known that Cl-amidine inhibits cancer cell growth at 200 μM (Li et al, *Oncogene* 2010, 29, 3153), and a further PAD inhibitor (mainly PAD4) inhibits cancer growth in a mouse sarcoma xenograft model (Wang et al, *J. Biol. Chem.* 2012, 287, 25941). PAD4 is also up-regulated in oestrogen-dependent ovarian tumour tissue (Wang et al, *Int. J. Biol. Sci.* 2010, 6, 454).
A further known PAD inhibitor is benzoyl L-arginine amide (BAA; *Biochemistry*, 2006, 45, 1727; clogP = 3.8). This entity has an appreciable potency but is not active in the CNS.

In addition, both Cl-amidine and benzoyl L-arginine amide are known to function as alkylating agents. For example, with regard to Cl-amidine, a covalent bond is formed between the PAD protein and the CTI2-NIIR by displacement of chloride at the chloroamidine carbon atom. However, this alkylation mechanism is not generally desirable (i.e. it is irreversible) and, as a result, has only been used so far to probe PAD biology.

Interest in PADs and the need for elucidating their function(s) is rapidly rising, as their role in cell homeostasis is still poorly understood and the importance of citrullination in several pathologies that affect a large proportion of the aging population is becoming increasingly apparent. Furthermore, targeting these enzymes has the potential to provide an attractive therapeutic strategy for several chronic diseases and also for traumatic neural injury.

PAD inhibitors are limited in number and chemical structure, being mainly halogenated amidine derivatives (Luo et al., *J. Am. Chem. Soc.*, 2006, 128, 1092) and some guanidine derivatives (Bozdag et al., *Bioorg Med Chem Lett.*, 2013, 23, 715). Another general current limitation is that PAD isoform selectivity remains to be achieved; Cl-amidine is a representative example (IC50 = 6 µM for PAD3 and PAD4; Slack et al., *ACS Chem. Biol*, 2011, 6, 466, and Luo et al., *J Am. Chem. Soc.*, 2006, 128, 1092). It is an object of the present invention, therefore, to provide non-peptidic, potent PAD inhibitors with drug-like properties that cannot alkylate protein residues, and that preferably bind to PAD only through non-covalent interactions.

According to the invention, there is provided a compound according to the formula (I):

![Formula Image]

wherein

ring A is an optionally substituted 5- to 7-membered aryl, heteroaryl, or heterocyclyl ring;
ring B is an optionally substituted 4- to 7-membered heteroaryl, or heterocyclyl ring;
R\(^1\) is a group independently selected from hydrogen, halogen, hydroxyl, cyano optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group; 

R\(^2\) is a group independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group; or R\(^1\) and R\(^2\) may be joined together to form an optionally substituted 5- to 7-membered aryl, heteroaryl, or heterocyclyl ring; 

W is a bond or a group selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylenc, optionally substituted heteroarylene, optionally substituted heterocyclyl, optionally substituted acyl, O, S(0)\(^q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; and 

Y is a bond or a group selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heterocyclyl, optionally substituted acyl, O, S, S(0)\(^q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; or a pharmaceutically acceptable salt thereof.

In formula (I), it will be appreciated that in embodiments where R\(^1\) and R\(^2\) are joined together to form an optionally substituted 5- to 7-membered aryl, heteroaryl, or heterocyclyl ring. R\(^1\) and R\(^2\) are located on adjacent atoms of the 5- to 7-membered aryl, heteroaryl, or heterocyclyl ring.
The invention also encompasses structural tautomers of the claimed compounds, which may be produced by the formal migration of a hydrogen atom. As such, tautomers are a special case of structural isomers which may rapidly interconvert depending on physical conditions.

The compounds encompassed by formula (I) have been found to represent a new class of potent, non-peptidic, reversible inhibitors of peptidylarginine deiminase. In addition, they exhibit no toxicity towards human neural stem cells and appear to increase the percentage of live cells following induced cell death. As such, they have distinct utility in the prevention or treatment of diseases and conditions associated with PAD expression.

The term 'Cₓᵧ alkyl' as used herein refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. For example, C₁₆ alkyl refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of C₁-6 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, and isohexyl.

The term 'Cₓᵧ alkenyl' as used herein refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds and having from x to y carbon atoms. Examples of C₂-6 alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-niethyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, and 5-hexenyl.

The term 'Cₓᵧ alkenylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'Cₓᵧ alkenyl' above. Examples of C₂-6 alkenylene groups include ethenylene, propenylene, butenylene, 1,3-butadienylene, pentenylene, hexenylcnc. and 1,3,5-hexatrienylene.
The term 'C<sub>x-y</sub> alkynyl' as used herein refers to a divalent hydrocarbon group containing one or more carbon-carbon triple bonds and having from x to y carbon atoms. Examples of C<sub>2-6</sub> alkynyl groups include ethynyl, propynyl, butynyl and pentynyl.

The term 'C<sub>x-y</sub> alkynylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C<sub>x-y</sub> alkynyl' above. Examples of C<sub>2-6</sub> alkynylene groups include ethynylene, propynylene, 1,3-butadiynylene, pentylenylene, hexynylene, and 1,3,5-hexatriynylene.

The term 'C<sub>x-y</sub> alkoxy' as used herein refers to an -0-C<sub>x-y</sub> alkyl group wherein C<sub>x-y</sub> alkyl is as defined herein. Examples of C<sub>1-6</sub> alkoxy groups include methoxy, ethoxy, propoxy, iso-propanoxy, butoxy, tert-butoxy, pentoxy and hexoxy.

The term 'cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 6 carbon atoms. Examples of 3- to 6-membered cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term 'aryl' as used herein refers to a 5- to 6-membered monocyclic hydrocarbon ring containing x to y carbon atoms, wherein the ring is aromatic. An example of such an aryl group is phenyl. Alternatively, the term 'C<sub>x-y</sub> aryl' as used herein refers to a monocyclic or bicyclic ring containing from x to y carbon atoms, wherein at least one ring is aromatic. Examples of C<sub>6-14</sub> aryl groups include phenyl, naphthyl, tetrahydronaphthalenyl, anthryl, phenanthryl, acenaphthylcnyl, biphenyl, anthraenyl, phenanthrenyl, and phenalenyl.

The term 'arylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C<sub>x-y</sub> aryl' above. An example of such an arylene group is phenylene. Alternatively, the term 'C<sub>x-y</sub> arylene' as used herein refers to a monocyclic or bicyclic ring containing from x to y carbon atoms, wherein at least one ring is aromatic. Examples of C<sub>6-14</sub> arylene groups include phenylene, naphthylene, tetrahydronaphthalenylene, anthrylene, phenanthrylene, acenaphthylidencylene, biphenylene, anthracenylene, phenanthrenylene, and phenalenylene.
The term 'C_{x-y} aralkyl' as used herein refers to a linear or branched saturated hydrocarbon group linked to an aryl group containing from x to y carbon atoms in total. Examples of C_{7-12} aralkyl groups include benzyl, phenethyl, naphthylmethyl, and biphenylylmethyl. C_{7-12} aralkyl groups are preferred.

The term 'heteroaryl' as used herein refers to a 5- to 7-membered monocyclic aromatic ring in which the monocyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen, and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, tria/olyl, tetrazolyl,imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyridyl, triazinyl, and tetrazinyl. The term 'heteroarylene' as used herein refers to a divalent heteroaryl group obtained by removing one hydrogen atom from 'heteroaryl' above.

The term 'heterocyclyl' refers to a 5- to 7-membered monocyclic ring which may be saturated or partially unsaturated, in which the monocyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen, and sulphur. Examples of such monocyclic rings include aziridinyl, oxiranyl, pyrrolidinyl, azctidinyl, pyrazolidinyl, oxazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valcrolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl and azcpanyl. In cases where the heterocyclyl group is divalent, the group may be obtained by removing one hydrogen atom from 'heterocyclyl' above.

The term 'amino' as used herein refers to an organonitrogen compound with the connectivity -N(R')(R''), where R' and R'' are each independently a hydrogen or an optional substituent as defined below in relation to formula (I).

The term 'acyl' as used herein refers to a group selected from:

(1) formyl;
(2) optionally substituted C_{1-6} alkyl carbonyloxy;
(3) optionally substituted C_{1-6} alkyl carbonyl;
(4) optionally substituted C_{2-6} alkenyl carbonyl;
(5) optionally substituted C_{2-6} alkynyl carbonyl;
(6) optionally substituted C_{6-i-o} aryl carbonyl;
(7) carboxyl;
(8) optionally substituted Ci-6 alkyl carbamoyl;
(9) carbamoyl; and
(10) optionally substituted Ci-6 alkoxy carbonyl.

The term 'C_{x-y} alkyl carbonyloxy' as used herein refers to an alkyl group wherein C_{x-y} alkyl is as defined herein and at least one methylene group (i.e. -CH_2-) is replaced with an ester group (e.g. -CO_2-). Examples of C_{1-6} alkyl carbonyloxy groups include ethanoate, propanoate, butanoate, pentanoate and hexanoate. The term 'carbonyloxy' as used herein refers to a single carbonyloxy group of the formula: -CO_2-.

The term 'C_{x-y} alkyl carbonyl' as used herein refers to an alkenyl group wherein C_{x-y} alkyl is as defined herein and at least one methylene group (i.e. -CH_2-) is replaced with a carbonyl group (i.e. >C=0). Examples of C_{1-6} alkyl carbonyl groups include methylcarbonyl, ethyl-1-carbonyl, ethyl-2-carbonyl, propyl-1-carbonyl, propyl-2-carbonyl, propyl-3-carbonyl, isopropylcarbonyl, butyl-1-carbonyl, butyl-2-carbonyl, butyl-3-carbonyl, butyl-4-carbonyl, isobutylcarbonyl, tertiarybutyl carbonyl pentylcarbonyl, and hexylcarbonyl. The term 'carbonyl' as used herein refers to a single carbonyl group of the formula: >C=0.

The term 'C_{x-y} alkenyl carbonyl' as used herein refers to an alkenyl group wherein C_{x-y} alkenyl is as defined herein and at least one methylene group (i.e. -CH_2-) is replaced with a carbonyl group (i.e. >C=0). Examples of C_{2-6} alkenyl carbonyl groups include ethenylcarbonyl, propenylcarbonyl, butenylcarbonyl, pentenyl carbonyl, and hexenylcarbonyl.

The term 'C_{x-y} alkynyl carbonyl' as used herein refers to an alkynyl group wherein C_{x-y} alkynyl is as defined herein and at least one methylene group (i.e. -CH_2-) is replaced with a carbonyl group (i.e. >C=0). Examples of C_{2-6} alkynyl carbonyl groups include ethynylcarbonyl, propynylcarbonyl, butynylcarbonyl, pentynyl carbonyl, and hexynylcarbonyl.
The term 'C<sub>x-y</sub> aryl carbonyl' as used herein refers to an aryl group wherein C<sub>x-y</sub> aryl is as defined herein covalently linked to at least one carbonyl group (i.e. >C=O). Examples of C<sub>6-10</sub> aryl carbonyl groups benzoyl, 1-naphthoyl, and 2-naphthoyl.

The term 'C<sub>x-y</sub> alkyl carbamoyl' as used herein refers to an alkyl group wherein C<sub>x-y</sub> alkyl is as defined herein and at least one methylene group (i.e. -CH<sub>2</sub>-) is replaced with an amide group (e.g. -C(0)NR-, where R is a hydrogen atom, a 5- or 6-membered heterocyclyl group, a 5- or 6-membered heteroaryl group, a 3- to 6-membered cycloalkyl group, a C<sub>i-6</sub> alkyl group, or a C<sub>6-i4</sub> aryl group, preferably a hydrogen atom). Examples of C<sub>i-6</sub> alkyl carbamoyl groups include ethyl carbamoyl, propyl carbamoyl, butyl carbamoyl, pentyl carbamoyl, and hexyl carbamoyl. The term 'carbamoyl' as used herein refers to a single carbamoyl group of the formula: -C(0)NR-, where R is as defined above.

The term 'C<sub>x-y</sub> alkoxy carbonyl' as used herein refers to an alkyl group wherein C<sub>x-y</sub> alkyl is as defined herein and at least one methylene group (i.e. -CH<sub>2</sub>-) is replaced with an ester group (e.g. -OC(O)-). Examples of C<sub>i-6</sub> alkyl carbonyl groups include ethyl oxycarbonyl, propyl oxycarbonyl, butyl oxycarbonyl, pentyl oxycarbonyl, and hexyl oxycarbonyl. The term 'oxycarbonyl' as used herein refers to a single oxycarbonyl group of the formula: -OC(O)-.

Any of the acyl groups (1) to (10) noted above may be converted into a divalent species by removal of a hydrogen atom (e.g. when used in accordance with the groups represented by W and Y). For example, a 'C<sub>x-y</sub> alkyl carbonyl' group may be converted into a 'C<sub>x-y</sub> alkylene carbonyl' group by removal of a hydrogen atom. Thus, the term 'C<sub>x-y</sub> alkylene carbonyl' as used herein refers to a divalent group as defined above for the group C<sub>x-y</sub> alkylene and wherein at least one methylene group (i.e. -CH<sub>2</sub>-) is replaced with at least one carbonyl group (i.e. >C=O). Examples of C<sub>1-6</sub> alkylene carbonyl groups include -CH<sub>2</sub>CO-, -COCH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CO-, -COCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>COCH<sub>2</sub>-, and -Cl<sub>1</sub>Cl<sub>1</sub>COCl<sub>1</sub>Cl<sub>1</sub>-. 

The term 'hydroxy l' as used herein refers to a group of the formula -OH. If such a group is substituted, the resulting group is an ether of the formula -O-.
The term 'thiol' as used herein refers to a group of the formula -SH. If such a group is substituted, the resulting group is a thioether of the formula -S-.

The term 'oxo' as used herein refers to a group of the formula =O.

The term 'thioxo' as used herein refers to a group of the formula =S.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom, and any radioactive isotope thereof, including fluorine-18, iodine-123, iodine-124, iodine-125, and iodine-131, unless otherwise specified.

The term 'haloC\textsubscript{i-6} alkyl' as used herein refers to a C\textsubscript{i-6} alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl and trifluoroethyl.

Each symbol in formula (I) is described in detail in the following.

In a preferred aspect, ring A is an optionally substituted 5- or 6-membered heteroaryl or heterocyclyl ring containing from 1 to 4 heteroatoms selected from O, N and S. More preferably, ring A is an optionally substituted 5- or 6-membered (preferably 5-membered) heteroaryl ring containing from 1 to 3 heteroatoms (preferably 1 or 2) selected from O, N and S.

In particular, ring A may be represented by a ring selected from:
each of which rings may be optionally further substituted. The additional structural features of formula (I) may be joined and substituted at any substitutable position of the above ring systems. The optional further substituents on each of the above rings may be the same as those listed below in relation formula (I), and may be joined and substituted at any substitutable position of the above ring systems.

Ring B may be an optionally substituted 5- or 6-membered heteroaryl or heterocyclyl ring containing from 1 to 4 heteroatoms selected from O, N and S. Preferably, ring B is an optionally substituted 5- or 6-membered (preferably 5-membered) heteroaryl or heterocyclyl ring (preferably heterocyclyl) containing from 1 to 3 heteroatoms (preferably 1 or 2) selected from O, N and S.

In particular, ring B is represented by a ring selected from:
each of which rings may be optionally further substituted. The additional structural features of formula (I) may be joined and substituted at any substitutable position of the above ring systems. The optional further substituents on each of the above rings may be the same as those listed below in relation formula (I), and may be joined and substituted at any substitutable position of the above ring systems.

R¹ may be a group independently selected from hydrogen, halogen, hydroxy!, cyano optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted acyl, optionally substituted amino, and optionally substituted thiol;

R² may be a group independently selected from hydrogen, halogen, hydroxyl, cyano optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy,
optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted acyl, optionally substituted amino, and optionally substituted thiol;
or R\(^1\) and R\(^2\) may be joined together to form an optionally substituted 5- to 6-membered aryl, heteroaryl, or heterocyclyl ring.

Preferably, R\(^1\) and R\(^2\) are joined together to form an optionally substituted 5- or 6-membered (preferably 6-membered) aryl or heteroaryl (preferably containing 1 or 2 nitrogen atoms) ring. In a particularly preferred embodiment, R\(^1\) and R\(^2\) are joined together to form an optionally substituted 6-membered aryl ring.

In cases where R\(^1\) and R\(^2\) are joined together to form an optionally substituted ring, the optional substituents on the resulting ring may be the same as those listed below in relation formula (I).

W may be a bond or a group selected from optionally substituted alkylene, optionally substituted alkynylene, optionally substituted arylcycloalkenyl, optionally substituted alkenylene, optionally substituted arylcycloalkene, optionally substituted heteroarylene, optionally substituted heterocyclyl, and optionally substituted acyl. Preferably, W is an optionally substituted alkylene group, optionally substituted alkenylene group, an optionally substituted arylene group, an optionally substituted heterocyclyl group, or an optionally substituted acyl group.

Y may be a bond or a group selected from optionally substituted alkylene, O, S, S(0)\(_q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) in thus context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted aryl, optionally substituted alkenyl, and optionally substituted acyl. Preferably, Y is a bond or a group selected from optionally substituted alkylene, O, S, S(0)\(_q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heterocyclyl, and optionally substituted acyl. More preferably, Y is an optionally substituted alkylene group or NR\(^4\), wherein R\(^4\) in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl,
optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

Each of the optionally substituted heterocyclyl, optionally substituted heteroaryl, and optionally substituted aryl rings, the optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted thiol, optionally substituted acyl, optionally substituted alkyl carbonyl, optionally substituted alkoxy carbonyl, optionally substituted alkyl carboxyloxy, optionally substituted alkenyl carbonyl, optionally substituted alkynyl carbonyl, optionally substituted aryl carbonyl, optionally substituted aryl carbamoyl, optionally substituted alkoxy carbamoyl, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroarylene, optionally substituted aralkyl, and optionally substituted amino groups, and the optionally further substituted ring A and ring B structures, mentioned in relation to formula (I), may be substituted by:
(1) one or two groups selected from -J-aryl, -J-heteroaryl, -J-heterocyclyl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₆ alkylene, and said aryl is selected from phenyl, said heteroaryl is selected from triazolyl, thiazolyl, thienyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, and pyridyl, said heterocyclyl is selected from pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, and thiazolidinyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and/or
(2) one to three substituents selected from
(a) C₁₋₆ alkyl (preferably methyl, ethyl or isopropyl),
(b) Ci-6 alkenyl (preferably propenyl),
(c) Ci-6 alkynyl (preferably ethynyl or propynyl),
(d) halogen (preferably Cl or Br),
(e) haloCi-6 alkyl (preferably trifluoromethyl),
(f) cyano,
(g) amino, optionally mono-or di-substituted with Ci₋₆ alkyl, /e/V-butoxycarbonyl or benzyl,
(h) Ci-6 alkoxy (preferably methoxy).
(i) Ci-6 alkyl carbonyl, including ketones and derivatives thereof such as ketals and hemiketals, and aldehydes (e.g. formyl) and derivatives thereof such as acetals and hemiacetals (preferably acetyl),

(j) Ci-6 alkoxy carbonyl,

(k) Ci-6 alkyl carboxyloxy, including carboxyl,

(l) Ci-6 alkyl carbamoyl, including carbamoyl,

(m) Ci-6 alkyl thioether,

(n) nitro, and

(o) hydroxyl.

In particular, each of the optionally substituted heterocyclyl, optionally substituted heteroaryl, and optionally substituted aryl rings, and each of the optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl groups, optionally substituted arylene, optionally substituted heteroarylene, and optionally substituted aralkyl groups, are preferably substituted by:

(1) one group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or Cl-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl; and/or

(2) one to three substituents selected from

(a) Ci-3 alkyl (preferably methyl, ethyl or isopropyl),

(b) halogen (preferably Cl or Br),

(c) haloCi-3 alkyl (preferably trifluoromethyl),

(d) cyano,

(e) amino, optionally mono- or di-substituted with Ci-6 alkyl, tert-butoxycarbonyl or benzyl,

(f) Ci-3 alkoxy (preferably methoxy),

(g) Ci-3 alkyl carbonyl (preferably acetyl),

(h) Ci-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester),

(i) Ci-3 alkyl carbamoyl, including carbamoyl,

(j) nitro, and

(k) hydroxyl.

Each of the optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted thiol, optionally
substituted acyl, optionally substituted alkyl carbonyl, optionally substituted alkoxy carbonyl, optionally substituted alkyl carboxyloxy, optionally substituted alkenyl carbonyl, optionally substituted alkynyl carbonyl, optionally substituted aryl carbonyl, optionally substituted alkyl carbamoyl, optionally substituted alkoxy carbamoyl, optionally substituted alkylene, optionally substituted alkenylene, and optionally substituted alkynylene groups are preferably substituted by:

one to three substituents selected from

(a) C1-3 alkyl (preferably methyl, ethyl or isopropyl),
(b) halogen (preferably Cl or Br),
(c) haloC1,3 alkyl (preferably trifluoromethyl),
(d) amino, optionally mono-or di-substituted with C1-3 alkyl, tert-butoxycarbonyl or benzyl,
(e) C1-3 alkoxy (preferably methoxy),
(f) C1-3 alkyl carbonyl (preferably acetyl),
(g) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester),
(h) C1-3 alkyl carbamoyl, including carbamoyl, and
(i) hydroxyl.

The optionally substituted amino groups are preferably substituted by:

(1) one group selected from -J-aryl and -J-C3,6 cycloalkyl, wherein J represents a bond or C1-3 alkyene, said aryl is phenyl, and said C3,6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl; and/or
(2) one to three substituents selected from
(a) C1-3 alkyl (preferably methyl, ethyl or isopropyl),
(c) haloC1,3 alkyl (preferably trifluoromethyl),
(g) C1-3 alkyl carbonyl (preferably acetyl),
(h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester).

The optionally further substituted ring A and ring B structures are preferably substituted by at least one oxo group. Preferably, ring B is substituted by one or two oxo groups (preferably one). In particular, the oxo group may be located on a carbon atom adjacent to a nitrogen atom, thereby forming a cyclic amide functionality.

In a preferred aspect of the invention, there is provided a compound of the formula (II):
wherein

R\(^1\) is a group independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group; R\(^2\) is a group independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group; or R\(^1\) and R\(^2\) may be joined together to form an optionally substituted 5- or 6-membered aryl or heteroaryl ring;

W is joined to a substitutable position at either X\(_1\), X\(_2\) or X\(_3\), and is a bond or a group selected from optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted aralkylene, optionally substituted aryleylene, optionally substituted heteroarylene, optionally substituted heterocyclyl, and optionally substituted acyl;

Y is a group selected from optionally substituted alkenylene, O, S, S(0)\(_q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl

X\(_i\) is a group selected from O, S, NR\(^5\), and CR\(^6\)R\(^7\), wherein R\(^5\), R\(^6\), and R\(^7\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\(^6\) and R\(^7\) are taken together to form an oxo group or thioxo group; and

X\(_2\) is a group selected from O, S, N, NR\(^5\), CR\(^6\)R\(^7\), and CR\(^8\), wherein R\(^5\), R\(^6\), R\(^7\), and R\(^8\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\(^6\) and R\(^7\) are taken together to form an oxo group or thioxo group.
substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroary1, optionally substituted heterocyclyl, and optionally substituted acyl, or R6 and R7 are taken together to form an oxo group or thioxo group;

X₃ is a group selected from O, S, N, NR₅, CR₆R₇, and CR₈, wherein R₅, R₆, R₇, and R₈ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R₆ and R₇ are taken together to form an oxo group or thioxo group:

X₄ is a group selected from O, S, N, NR₅, CR₆R₇, and CR₈, wherein R₅, R₆, R₇, and R₈ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R₆ and R₇ are taken together to form an oxo group or thioxo group;

X₅ is a group selected from O, S, N, NR₅, CR₆R₇, and CR₈, wherein R₅, R₆, R₇, and R₈ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R₆ and R₇ are taken together to form an oxo group or thioxo group;

U—V is a group which may be saturated or unsaturated, and U and V may be independently selected from O, N, NR₅, CR₆R₇, CR₈, S(0)₉, wherein q is 0, 1, or 2, and either U or V, but not both, may be a combination of two atoms selected from R₉R₇C-CR₆R₇, R₉C=CR₈, R₉R₇C-S, R₉R₇C-NR₅, R₉C=N, S-NR₅, S=N, O-NR₅, R₅N-NR₅, and N=N, wherein R₅, R₆, R₇, R₈, and R₉ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R₆ and R₇ are taken together to form an oxo group or thioxo group.
In another preferred aspect of the invention, there is provided a compound of the formula (III):

wherein

D, E, G, and H are each independently selected from N and CR³, wherein each R⁹ in this context is independently selected from hydrogen, halogen, hydroxyl cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

W is joined to a substitutable position at either Xi, X₂ or X₃, and is a bond or a group selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heterocyclyl, and optionally substituted acyl;

Y is a group selected from optionally substituted alkylene, O, S, S(0)ᵢ q, wherein q is 0, 1, or 2, and NR⁴, wherein R⁴ in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

Xi is a group selected from O, S, NR⁵, and CR⁶R⁷, wherein R⁵, R⁶, and R⁷ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R⁶ and R⁷ are taken together to form an oxo group or thioxo group;

X₂ is a group selected from O, S, N, NR⁵, CR⁶R⁷, and CR⁸, wherein R⁵, R⁶, R⁷, and R⁸ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R⁶ and R⁷ are taken together to form an oxo group or thioxo group:
$X_4$ is a group selected from $0$, $S$, $N$, $NR^5$, $CR^6R^7$, and $CR^8$, wherein $R^5$, $R^6$, $R^7$, and $R^8$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ are taken together to form an oxo group or thioxo group;

$X_5$ is a group selected from $O$, $S$, $NR^5$, and $CR^6R^7$, wherein $R^5$, $R^6$, and $R^7$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ are taken together to form an oxo group or thioxo group;

$U—V$ is a group which may be saturated or unsaturated, and $U$ and $V$ may be independently selected from $O$, $N$, $NR^5$, $CR^6R^7$, $CR^8$, $S(0)_q$, wherein $q$ is $0$, $1$, or $2$, and either $U$ or $V$, but not both, may be a combination of two atoms selected from $R^6R^7C-CR^6R^7$, $R^6C=CR^8$, $R^6R^7C=S$, $R^6R^7C-NR^5$, $R^8C=N$, $S-NR^5$, $S=N$, $O-NR^5$, $R^6N-NR^5$, and $N=N$, wherein $R^5$, $R^6$, $R^6$, $R^7$, $R^7$, and $R^8$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ or $R^6$ and $R^7$ are taken together to form an oxo group or thioxo group.

Such compounds exhibit 10 to 100 times more potency than the known, benchmark PAD inhibitor Cl-amidine.

In a further preferred aspect of the invention, there is provided a compound of the formula (IV):
wherein
D, E, G, and H are each independently selected from N and CR₉, wherein each Rᵉ in this
context is independently selected from hydrogen, halogen, hydroxyl, cyano, optionally
substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally
substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally
substituted heterocyclyl, and optionally substituted acyl;
W is joined to a substitutable position at either Xi, X₂ or X₃, and is a bond or a group
selected from optionally substituted alkenylene, optionally substituted alkenylene, optionally
substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene,
optionally substituted heterocyclyl, and optionally substituted acyl;
Y is a group selected from optionally substituted alkenylene, O, S, S(0)₉, wherein q is 0, 1, or
2, and NR₄, wherein R₄ in this context is a group selected from hydrogen, optionally
substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl,
and optionally substituted acyl;
Xi is a group selected from O, S, NR₅, and CR₆R₇, wherein R₅, R₆, and R₇ in this context
are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted
alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted
aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally
substituted acyl, or R₆ and R₇ are taken together to form an oxo group or thioxo group;
X₂ is a group selected from N and CR₈, wherein R₈ in this context is selected from
hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl,
optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl,
optically substituted heterocyclyl, and optionally substituted acyl;
X₃ is a group selected from N and CR₈, wherein R₈ in this context is selected from
hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl,
optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl,
optically substituted heterocyclyl, and optionally substituted acyl;
X₄ is a group selected from N and CR⁸, wherein R⁸ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroeyelyl, and optionally substituted acyl.

X₅ is a group selected from O, S, NR⁵, and CR⁶R⁷, wherein R⁵, R⁶, and R⁷ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroeyelyl, and optionally substituted acyl. or R⁶ and R⁷ arc taken together to form an oxo group or thioxo group; and

U—V is a group which may be saturated or unsaturated, and U and V may be independently selected from O, N, NR⁵, CR⁶R⁷, CR⁸, S(0)q, wherein q is 0, 1, or 2, and either U or V, but not both, may be a combination of two atoms selected from R⁶R⁷C-CR⁶R⁷, R⁸C=CR⁸, R⁶R⁷C-S, R⁶R⁷C-NR⁵, R⁸C=N, S-NR⁵, S=N, O-NR⁵, R⁵N-NR⁵, and N=N, wherein R⁵, R⁶, R⁷, R⁸ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroeyelyl, and optionally substituted acyl, or R⁶ and R⁷ or R⁶ and R⁷ are taken together to form an oxo group or thioxo group.

Such compounds show no toxicity to human neural stem cells and, indeed, show an encouraging propensity to increase the percentage of live cells in a system of induced cell death compared to controls and other compounds.

With regard to formulae (II) to (IV), W is preferably joined to a substitutable position at either X₂ or X₃, and X is NR⁵, wherein R⁵ in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroeyelyl, and optionally substituted acyl.

Preferably, X₅ is NR⁵ and R⁵ in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroeyelyl, and optionally substituted acyl.
In another preferred embodiment, one or two (preferably one) of D, E, G, and H are N and the remaining groups are CR⁹, wherein each R⁹ in this context is selected from hydrogen, halogen, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

In addition, it is preferable where U and V are each independently selected from 0, NR⁵, CR⁶R⁷, and S(0)ₚ, wherein q is 0, 1, or 2, and wherein R⁵, R⁶, and R⁷ in this context are each independently selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R⁶ and R⁷ are taken together to form an oxo group or thioxo group.

It is also preferable where Y is NR⁴, wherein R⁴ in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

In an especially preferred aspect of the invention, there is provided a compound of the formula (V):

```
D, E, G, and H are each CR⁹, and each R⁹ in this context is independently selected from hydrogen, halogen, hydroxy, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl:
```
W is a group selected from optionally substituted alkylene, optionally substituted alkenylene, and optionally substituted acyl;
Y is a group selected from optionally substituted alkylene. O, S, and NR$_4$, wherein R$_4$ in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;
X$_1$ is NH;
X$_2$ is CR$_8$, wherein R$_8$ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;
X$_4$ is N;
X$_5$ is NR$_5$, wherein R$_5$ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl:
and
V is CR$_6$R$_7$, wherein R$_6$ and R$_7$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

It is believed that there may be favourable interactions between certain groups in the structure of compounds of the invention and certain amino acid residues in the PAD enzyme substrate binding site. The presence or absence of such favourable interactions in the enzyme substrate binding site may not, however, necessarily be a prerequisite property of compounds of the invention. Without wishing to be bound to a particular theory, it is believed that the carbonyl group of the imidazolin-4-one ring forms a hydrogen bond with Asp$^{473}$; the nitrogen corresponding to X$_4$ forms a hydrogen bond with Asp$^{350}$; and the hydrogen of the NH corresponding to X$_1$ forms a hydrogen bond with Arg$^{369}$. It is plausible that binding modes of this type lead to the potent efficacy associated with these compounds.
In formula (V), preferably one or two of D, E, G, and H are CR\(^9\), wherein R\(^9\) in this context is independently selected from halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, and each of the remaining groups are CH\(_3\). Even more preferably, only one of D, E, G, and H is CR\(^9\), wherein R\(^9\) as defined above, and the remaining groups are CH\(_3\).

In each of formulae (II) to (V), the optional substituents on each of the groups mentioned may be the same as those mentioned above in relation to formula (I). In addition, any of the preferred aspects mentioned above in relation to formula (I) may also represent preferred features of formulae (II) to (V).

In another highly preferred embodiment of the invention, there is provided a compound of the formula (VI):

![Compound Diagram](image)

wherein

R\(^9\) is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) cyano;

(v) Ci-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloCi\(_3\) alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with Ci\(_3\) alkyl, /t/V-butoxycarbonyl or benzyl, (d) Ci\(_3\) alkoxy (preferably methoxy).
(e) C_{1-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy.
including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxy i;

(vi) C_{1-6} alkoxy optionally substituted with one to three substituents selected
from (a) halogen (preferably Cl or Br), (b) haloC_{3-6} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{1-3}
alkyl, tert-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy),
(e) C_3 alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl

carbamoyl, including carbamoyl, and (g) hydroxy i.

(vii) C_{6-14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-
c_{3-6} cycloalkyi, wherein J represents a bond or C_{1-3} alkylene, said aryl is
phenyl, and said C_{3-6} cycloalkyi is selected from cyclopropyl, cyclopentyl
and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3}
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or
Br), (c) haloC_{3-6} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono-or di-substituted with C_{1-6} alkyl, ferf-butoxycarbonyl or
benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl
(preferably acetyl), (h) C_{1-3} alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including

carbamoyl, (j) nitro, and (k) hydroxy i.

(viii) C_{7-16} aralkyl optionally substituted with (1) a group selected from -J-aryl and
-J-C_{3-6} cycloalkyi, wherein J represents a bond or C_{1-3} alkylene, said aryl is
phenyl, and said C_{3-6} cycloalkyi is selected from cyclopropyl, cyclopentyl
and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3}
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or
Br), (c) haloC_{3-6} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono-or di-substituted with C_{1-6} alkyl, ferf-butoxycarbonyl or
benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl
(preferably acetyl), (h) C_{1-3} alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including

carbamoyl, (j) nitro, and (k) hydroxy i, and
(ix) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C₃-6 cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloCᵢ₋₃ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Cᵢ₋₆ alkyl, tert-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl.

R⁸ is a group selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxyl;
(iv) Cᵢ₋₆ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCᵢ₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy).
(v) C₂₋₆ alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCᵢ₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy).
(e) Cᵢ₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(vi) C₆₋₁₄ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyloxy (preferably methoxy), (b) C₁₋₃ alkyl carbonyl (preferably acetyl), (c) C₁₋₃ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; 

(vii) C7-16 aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; and 

(viii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; 

W is a group selected from:

(i) C1-6 alkyne optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC1-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3
alkyl, /m-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy),
(e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl
carbamoyl, including carbamoyl, and (g) hydroxy i:

(ii) C2-6 alkenylene optionally substituted with one to three substituents selected
from (a) halogen (preferably CI or Br), (b) haloC1-3 alkyl (preferably trifluoromethyl),
(c) amino, optionally mono-or di-substituted with C1-3
alkyl, tert-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy),
(e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl
carbamoyl, including carbamoyl, and (g) hydroxy i; and

(iii) an acyl group optionally substituted with (1) a group selected from -J-aryl
and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkyene. said aryl
is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl
and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or
Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or
benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl
(preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including
carbamoyl, (j) nitro, and (k) hydroxyl;

Y is NR4, wherein R4 in this context is a group selected from:

(i) hydrogen,

(ii) C1-6 alkyl optionally substituted with one to three substituents selected from
(a) halogen (preferably CI or Br), (b) haloC3 alkyl (preferably trifluoromethyl),
(c) amino, optionally mono-or di-substituted with C1-3
alkyl, tert-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy),
(e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl
carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C2-6 alkenyl optionally substituted with one to three substituents selected
from (a) halogen (preferably CI or Br), (b) haloC1-3 alkyl (preferably
trifluoromethyl), (c) amino, optionally mono-or di-substituted with C\textsubscript{1-3} alkyl, tert-butoxycarbonyl or benzyl, (d) C\textsubscript{1-3} alkoxy (preferably methoxy), (e) C\textsubscript{1-3} alkyl carbonyl (preferably acetyl), (f) C\textsubscript{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl.

(iv) C\textsubscript{6-14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkyne, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopentyl, cyclohexyl, and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl). (d) cyano, (e) amino, optionally mono-or di-substituted with Ci\textsubscript{6} alkyl, tert-butoxycarbonyl or benzyl, (f) Ci\textsubscript{1-3} alkoxy (preferably methoxy). (g) C\textsubscript{1-3} alkyl carbonyl (preferably acetyl), (h) Ci\textsubscript{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl.

(v) C\textsubscript{7-16} aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkyne, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopentyl, cyclohexyl, and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl). (d) cyano. (e) amino, optionally mono-or di-substituted with Ci\textsubscript{6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{1-3} alkoxy (preferably methoxy), (g) C\textsubscript{1-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkyne, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopentyl, cyclohexyl, and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono-or di-substituted with C_{1-6} alkyl, ier/-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{i-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

X 5 is NR^5, wherein R^5 in this context is a group selected from:

(i) hydrogen,

(ii) C_{i-6} alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC_{i-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{i-3} alkyl, ter/t-butoxycarbonyl or benzyl, (d) C_{i-3} alkoxy (preferably methoxy), (e) C_{i-3} alkyl carbonyl (preferably acetyl), (f) C_{i-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C_{2-6} alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC_{i-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{i-3} alkyl, tert-butoxycarbonyl or benzyl, (d) C_{i-3} alkoxy (preferably methoxy), (e) C_{i-3} alkyl carbonyl (preferably acetyl), (f) C_{i-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl

(iv) C_{a-14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-, C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkyne, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{i-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC_{i-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C_{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C_{i-3} alkoxy (preferably methoxy), (g) C_{i-3} alkyl carbonyl (preferably acetyl), (h) C_{i-3} alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C7-16 aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyloptionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; and

V is CR6R7, wherein R6 and R7 in this context are each independently selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) C1-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC1-3 alkyl (preferably...
trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{i-3} alkyl, tert-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{i-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(v) C_{i-6} alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC_{i-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{i-3} alkyl, tert-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{i-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) C_{6-i4} aryl optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkenylene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC_{i-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C_{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{i-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(vii) C_{7-i6} aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkenylene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC_{i-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C_{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carbonyloxy, including carboxyl.
(preferably carboxyl or methyl ester), (i) C₁-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(viii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C₃-6 cycloalkyl, wherein J represents a bond or C₁-3 alkylene, said aryl is phenyl, and said C₃-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC₁-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C₆ alky. tert-butoxycarbonyl or benzyl, (f) C₁-3 alkoxy (preferably methoxy), (g) C₁-3 alkyl carbonyl (preferably acetyl), (h) C₁-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl.

In a preferred aspect of formula (VI), W is preferably a group selected from:

(i) Ci-6 alkyne optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁-3 alkyl. tert-butoxycarbonyl or benzyl, (d) C₁-3 alkoxy (preferably methoxy), (e) C₁-3 alkyl carbonyl (preferably acetyl), (f) C₁-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl, and

(ii) C₂-6 alkenylene optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloO-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁-3 alkyl, ieri-butoxycarbonyl or benzyl, (d) C₁-3 alkoxy (preferably methoxy), (e) C₁-3 alkyl carbonyl (preferably acetyl), (f) C₁-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

Y is preferably NR⁴, wherein R⁴ in this context is a group selected from:

(i) hydrogen, and

(ii) Ci-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁-3 alkyl, tert-butoxycarbonyl or benzyl, (d) C₁-3 alkoxy (preferably methoxy), (e) C₁-3 alkyl carbonyl (preferably acetyl), (f) C₁-3 alkyl carboxyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C₃₋₅ alkyl carbamoyl, including carbamoyl, and (g) hydroxy; and

X⁵ is NR⁵, wherein R⁵ in this context is a group selected from:

(i) hydrogen, and

(ii) C₆₋₅ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC₃₋₅ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₅ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₃₋₅ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₅ alkyl carbamoyl, including carbamoyl, and (g) hydroxy and/or

V is CR⁶R⁷, wherein R⁶ and R⁷ in this context are each independently selected from:

(i) hydrogen;

(ii) halogen;

(iii) C₆₋₅ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC₃₋₅ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₅ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₃₋₅ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₅ alkyl carbamoyl, including carbamoyl, and (g) hydroxy; and

(iv) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₅ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₅ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC₃₋₅ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C₆₋₅ alkyl, tert-butoxycarbonyl or benzyl, (f) C₃₋₅ alkoxy (preferably methoxy), (g) C₁₋₅ alkyl carbonyl (preferably acetyl), (h) C₁₋₅ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₅ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy

In a further highly preferred embodiment of the invention, there is provided a compound of the formula (VII):
wherein

R⁹ is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxy I;

(iv) cyano;

(v) Ci-6 alkyl optionally substituted with one to three substituents selected from
   (a) halogen (preferably Cl or Br), (b) haloCi-3 alkyl (preferably tritluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, teri-butoxycarbonyl or benzyl, (d) Ci-3 alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) Ci-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) Ci-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxy I;

(vi) Ci-6 alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC³-6 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, tri-butoxycarbonyl or benzyl, (d) Ci-3 alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) Ci-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C³-3 alkyl carbamoyle, including carbamoyl, and (g) hydroxy I;

(vii) C⁶-14 aryl optionally substituted with (1) a group selected from -J-aryl and -J-C³-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C³-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) Cl-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono-or di-substituted with $\textit{Ci}_{6}$ alkyl, tert-butoxycarbonyl or benzyl, (f) $\textit{Ci}_{3}$ alkoxy (preferably methoxy), (g) $\textit{c} \_3$ alkyl carbonyl (preferably acetyl), (h) $\textit{c} \_3$ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) $\textit{Ci}_{3}$ alkyl carbamoyl, including carboxamoyl, (j) nitro, and (k) hydroxyl; and

(viii) $\textit{c} \_7$-$\textit{c} \_1$ aralkyl optionally substituted with (1) a group selected from -$\textit{J}$-aryl and -$\textit{J}$-$\textit{C} \_3$-$\textit{C} \_6$ cycloalkyl, wherein $\textit{J}$ represents a bond or $\textit{c} \_1$-$\textit{c} \_3$ alkylene, said aryl is phenyl, and said $\textit{c} \_3$-$\textit{c} \_6$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl. and/or (2) one to three substituents selected from (a) $\textit{c} \_1$-$\textit{c} \_3$ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) halo$\textit{Ci}_{3}$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with $\textit{Ci}_{6}$ alkyl, tert-butoxycarbonyl or benzyl, (f) $\textit{c} \_1$-$\textit{c} \_3$ alkoxy (preferably methoxy), (g) $\textit{c} \_1$-$\textit{c} \_3$ alkyl carbonyl (preferably acetyl), (h) $\textit{c} \_1$-$\textit{c} \_3$ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) $\textit{c} \_1$-$\textit{c} \_3$ alkyl carbamoyl, including carboxamoyl, (j) nitro, and (k) hydroxyl; and

(ix) an acyl group optionally substituted with (1) a group selected from -$\textit{J}$-aryl and -$\textit{J}$-$\textit{C} \_3$-$\textit{C} \_6$ cycloalkyl, wherein $\textit{J}$ represents a bond or $\textit{c} \_1$-$\textit{c} \_3$ alkylene, said aryl is phenyl, and said $\textit{c} \_3$-$\textit{c} \_6$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl. and/or (2) one to three substituents selected from (a) $\textit{c} \_1$-$\textit{c} \_3$ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) halo$\textit{Ci}_{3}$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with $\textit{c} \_1$-$\textit{c} \_3$ alkyl, tert-butoxycarbonyl or benzyl, (f) $\textit{c} \_1$-$\textit{c} \_3$ alkoxy (preferably methoxy), (g) $\textit{c} \_1$-$\textit{c} \_3$ alkyl carbonyl (preferably acetyl), (h) $\textit{c} \_1$-$\textit{c} \_3$ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) $\textit{c} \_1$-$\textit{c} \_3$ alkyl carbamoyl, including carboxamoyl, (j) nitro, and (k) hydroxyl;

$R^8$ is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) $\textit{c} \_1$-$\textit{c} \_6$ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) halo$\textit{Ci}_{3}$ alkyl (preferably...
trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, /tert-/-butoxycarbonyl or benzyl, (d) Ci-3 alkoxy (preferably methoxy),
(e) Ci-3 alkyl carbonyl (preferably acetyl), (f) Ci-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) Ci-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(v) C₂-₆ alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) halo-Ci-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with Ci-3 alkyl, /tert-/-butoxycarbonyl or benzyl, (d) Ci-3 alkoxy (preferably methoxy),
(e) Ci-3 alkyl carbonyl (preferably acetyl), (f) Ci-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) Ci-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) C₆₋₁₄ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C₃-₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃-₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) Ci-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) halo-Ci-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci₋₆ alkyl, /tert-butoxycarbonyl or benzyl, (f) Ci-3 alkoxy (preferably methoxy), (g) Ci-3 alkyl carbonyl (preferably acetyl), (h) Ci-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) Ci₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(vii) C₇₋₁₆ aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C₃-₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) Ci-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) halo-Ci-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci₋₆ alkyl, /tert-butoxycarbonyl or benzyl, (f) Ci-3 alkoxy (preferably methoxy), (g) Ci₋₃ alkyl carbonyl (preferably acetyl), (h) Ci-3 alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) Ci,3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; and

(viii) an acyl group optionally substituted with (1) a group selected from J-aryl and J-C3-6 cycloalkyl, wherein J represents a bond or C 1-3 alkylene. said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci-6 alkyl, /tv/-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy;

R10 is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) cyano;

(v) Ci-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with Ci-3 alkyl, /tv/-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) Ci,3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) Ci-6 alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, /tv/-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C1,3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(vii) C_{6-14} aryl optionally substituted with (1) a group selected from -J-aryl and -1-
C_3-6 cycloalkyl, wherein J represents a bond or C1-3 alkyrene, said aryl is
phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl
and cyclohexyl. and/or (2) one to three substituents selected from (a) C_1-3
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or
Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono- or di-substituted with C_{i-6} alkyl. tert-butoxycarbonyl or
benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl
(preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including
carbamoyl, (j) nitro, and (k) hydroxyl.;

(viii) C_{7-16} aralkyl optionally substituted with (1) a group selected from -J-aryl and
-J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkyrene, said aryl is
phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl
and cyclohexyl, and/or (2) one to three substituents selected from (a) C_1-3
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or
Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono- or di-substituted with C_{i-6} alkyl, fert-butoxycarbonyl or
benzyl, (f) C_{i-3} alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl
(preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including
carbamoyl, (j) nitro, and (k) hydroxyl; and

(ix) an acyl group optionally substituted with (1) a group selected from -J-aryl
and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkyrene, said aryl
is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl
and cyclohexyl, and/or (2) one to three substituents selected from (a) C_1-3
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or
Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono- or di-substituted with C_{i-6} alkyl, fert-butoxycarbonyl or
benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl
(preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including
carbamoyl, (j) nitro, and (k) hydroxyl;
R⁴ is a group selected from:

(i) hydrogen,

(ii) C1-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C₂-₆ alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl.

(iv) C₆₋₁₆ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylenc, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl, and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C₁₋₆ alkyl, tert-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C₇₋₁₆ aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylenc, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl, and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifluoromethyl), (d) cyano. (e) amino.
optionally mono-or di-substituted with Cl-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

R5 is a group selected from:

(i) hydrogen,

(ii) Cl-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC1-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, tert-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy), (e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C2-6 alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC1-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, tert-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy), (e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C$_1$-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl

(iv) C$_{3-14}$ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C$_{3-6}$ cycloalkyl, wherein J represents a bond or C$_1$-3 alkyne, said aryl is phenyl, and said C$_{3-6}$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C$_1$-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC$_3$ alkyl (preferably trifluoromethyl), (d) cyano. (e) amino, optionally mono-or di-substituted with C$_{1-6}$ alkyl, /e/7-butoxycarbonyl or benzyl, (f) C$_1$-3 alkoxy (preferably methoxy), (g) C$_1$-3 alkyl carbonyl (preferably acetyl), (h) C$_{1-3}$ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C$_1$-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C$_{7-16}$ aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C$_{3-6}$ cycloalkyl, wherein J represents a bond or C$_1$-3 alkyne, said aryl is phenyl, and said C$_{3-6}$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C$_1$-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC$_3$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C$_{1-6}$ alkyl, tert-butoxycarbonyl or bcn/yl. (f) C$_1$-3 alkoxy (preferably methoxy), (g) C$_1$-3 alkyl carbonyl (preferably acetyl), (h) C$_{1-3}$ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C$_1$-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C$_{3-6}$ cycloalkyl, wherein J represents a bond or C$_1$-3 alkyne, said aryl is phenyl, and said C$_{3-6}$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C$_1$-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC$_3$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C$_{1-6}$ alkyl, /e/7-butoxycarbonyl or benzyl, (f) C$_1$-3 alkoxy (preferably methoxy), (g) C$_1$-3 alkyl carbonyl (preferably acetyl), (h) C$_{1-3}$ alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C₃₋₅ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyoptionally substituted alkyl. optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; and

R⁶ and R⁷ are each independently selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxy;
(iv) C₆₋₁₄ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC₃₋₅ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₃₋₅ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(v) C₆₋₁₄ alkoxyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(vi) C₆₋₁₄ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC₁₋₃ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C₁₋₆ alkyl, tert-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carboxyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(vii) C7-16 aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylec, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(viii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

n is 0, 1, 2, or 3 (preferably 1).

Most specifically, there is provided a compound according to the formula (VIII):
wherein

\(R^9\) is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) cyano;

(v) \(C_{1-6}\) alkyl optionally substituted with one to three substituents selected from

(a) halogen (preferably \(\text{Cl}\) or \(\text{Br}\)),
(b) halo\(C_{1-3}\) alkyl (preferably trifluoromethyl),
(c) amino, optionally mono- or di-substituted with \(C_{1-3}\) alkyl, /eri-butoxycarbonyl or benzyl,
(d) \(C_{1-3}\) alkoxy (preferably methoxy),
(e) \(C_{1-3}\) alkyl carbonyl (preferably acetyl),
(f) \(C_{1-3}\) alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester),
(h) \(C_{1-3}\) alkyl carbamoyl, including carboxyl, and (g) hydroxyl;

(vi) \(C_{1-6}\) alkoxy optionally substituted with one to three substituents selected from

(a) halogen (preferably \(\text{Cl}\) or \(\text{Br}\)),
(b) halo\(C_{1-3}\) alkyl (preferably trifluoromethyl),
(c) amino, optionally mono- or di-substituted with \(C_{1-3}\) alkyl, /trZ-butoxycarbonyl or benzyl,
(d) \(C_{1-3}\) alkoxy (preferably methoxy),
(e) \(C_{1-3}\) alkyl carbonyl (preferably acetyl),
(f) \(C_{1-3}\) alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester),
(h) \(C_{1-3}\) alkyl carbamoyl, including carboxyl, and (g) hydroxyl;

(vii) \(C_{1-14}\) aryl optionally substituted with (1) a group selected from -J-aryl and -J-
\(C_{3-6}\) cycloalkyl, wherein J represents a bond or \(C_{1-3}\) alkylene, said aryl is phenyl, and said \(C_{3-6}\) cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl and/or (2) one to three substituents selected from (a) \(C_{1-3}\) alkyl (preferably methyl, ethyl or isopropyl),
(b) halogen (preferably \(\text{Cl}\) or \(\text{Br}\)),
(c) halo\(C_{1-3}\) alkyl (preferably trifluoromethyl),
(d) cyano, (e) amino.
optionally mono-or di-substituted with C\textsubscript{i}-6 alkyl, teri-butoxycarbonyl or benzyl, (f) C\textsubscript{i-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(viii) C\textsubscript{7-16} aralkyl optionally substituted with (1) a group selected from \(-J\)-aryl and \(-J\)-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkylene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{i-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{i-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{i-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{1-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(ix) an acyl group optionally substituted with (1) a group selected from \(-J\)-aryl and \(-J\)-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkylene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{i-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{i-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{1-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{1-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl.

In particular, the compound of the invention may be 2-[2-(1H-indol-3-yl)-ethylamino]-3,5-
dihydroimidazol-4-one.
In another preferred embodiment of the invention, there is provided a compound according to formula (IX):

\[
\text{3-Acetyl-2-[2-(5-hydroxy-1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one:}
\]

or 2-[2-(1H-indol-3-yl)-ethanolamino]-5,5-dimethyloxazol-4-one:

\[
\text{In another preferred embodiment of the invention, there is provided a compound according to formula (IX):}
\]

\[
\text{wherein}
\]
ring A is an optionally substituted aryl ring (preferably C₆H₄ aryl, more preferably phenyl);
W is an optionally substituted alkylene group (preferably C₁₋₆ alkylcnc, more preferably C₁₋₃ alkylcnc);
Y is a group selected from O, S, S(0)ₘ, wherein m is 0, 1, or 2, and NR₄; wherein R₄ is a group selected from hydrogen, optionally substituted alkyl, optionally substituted aryl.
and optionally substituted aralkyl (preferably NR₅, wherein R₅ is a group selected from hydrogen and optionally substituted alkyl);
X₄ is a group selected from N and CR₈, wherein R₈ in this context is selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl (preferably N);
X₅ is a group selected from 0, S, NR₅, and CR₆R₇, wherein R₆, R₇, and R₇ in this context are each independently selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl. or R₆ and R₇ are taken together to form an oxo group or thioxo group (preferably O or NR₅, wherein R₅ in this context is selected from hydrogen, optionally substituted alkyl, and optionally substituted acyl); and
U—V is a group which may be saturated or unsaturated, and U and V may be independently selected from O, N, NR₅, CR₆R₇, CR₈, S(0)ₘ, wherein m is 0, 1, or 2, and either U or V, but not both, may be a combination of two atoms selected from R₉R₇C-CR₆R₇, R₈C=CR₈, R₈R₇C-S, R₆R₇C-NR₅, R₆C=N, S-NR₅, S=N, O-NR₅, R₅N-NR₄, and N=N, wherein R₅, R₆, R₇, R₇, and R₆ in this context are each independently selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl, or R₆ and R₇ or R₆ and R₇ are taken together to form an oxo group or thioxo group (preferably U and V may be independently selected from O, NR₅, and CR₆R₇, wherein R₅, R₆, and R₇ in this context are each independently selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, and optionally substituted aralkyl, or R₆ and R₇ are taken together to form an oxo group, and/or at least one of U or V is CR₆R₇, wherein R₆ and R₇ are taken together to form an oxo group).

In formula (IX), the optional substituents on each of the groups mentioned may be the same as those mentioned above in relation to formula (I).
More preferably, there is provided a compound of formula (IX), wherein

ring A is a C\textsubscript{6-14} aryl (preferably phenyl) optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C\textsubscript{1-6} alkoxyl;

W is a Ci-6 alkylene (preferably C\textsubscript{1-3} alkylene) optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C\textsubscript{1-6} alkoxyl;

Y is a group selected from 0 and NR\textsubscript{4}, wherein R\textsubscript{4} is a group selected from hydrogen, C\textsubscript{1-6} alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C\textsubscript{1-6} alkoxy, C\textsubscript{6-14} aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, and C\textsubscript{7-12} aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy (preferably NR\textsubscript{4}, wherein R\textsubscript{4} is a group selected from hydrogen and C\textsubscript{1-6} alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C\textsubscript{1-6} alkoxy);

X\textsubscript{4} is a group selected from N and CR\textsubscript{8}, wherein R\textsubscript{8} in this context is selected from hydrogen, halogen, hydroxyl, C\textsubscript{1-6} alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C\textsubscript{1-6} alkoxy, C\textsubscript{6-14} aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, and C\textsubscript{7-12} aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy (preferably N);

X\textsubscript{5} is a group selected from O, S, NR\textsubscript{5}, and CR\textsubscript{6}R\textsubscript{7}, wherein R\textsubscript{5}, R\textsubscript{6}, and R\textsubscript{7} in this context are each independently selected from hydrogen, halogen, hydroxyl, C\textsubscript{1-6} alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, C\textsubscript{6-14} aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, and C\textsubscript{7-12} aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, or R\textsubscript{5} and R\textsubscript{7} are taken together to form an oxo group or thioxo group (preferably O or NR\textsubscript{5}), wherein R\textsubscript{5} in this context is selected from hydrogen, C\textsubscript{1-6} alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, C\textsubscript{6-14} aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, and C\textsubscript{7-12} aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci\textsubscript{6} alkoxy, or R\textsubscript{5} and R\textsubscript{7} are taken together to form an oxo group or thioxo group (preferably O or NR\textsubscript{5}), wherein R\textsubscript{5} in this context is selected from hydrogen, C\textsubscript{1-6} alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, C\textsubscript{6-14} aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, and C\textsubscript{7-12} aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci\textsubscript{6} alkoxy, and C\textsubscript{7-12} aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci\textsubscript{6} alkoxy, and

U—V are independently selected from O, NR\textsubscript{5}, and CR\textsubscript{6}R\textsubscript{7}, wherein R\textsubscript{5}, R\textsubscript{6}, and R\textsubscript{7} in this context are each independently selected from hydrogen, halogen, hydroxyl, Ci-6 alkyl
optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy, \( \text{CVu} \) aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy, and \( \text{C}_{7-12} \) aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy, or \( \text{R}^6 \) and \( \text{R}^7 \) are taken together to form an oxo group (preferably one of \( \text{U} \) and \( \text{V} \) is \( \text{CR}^6\text{R}^7 \), wherein \( \text{R}^6 \) and \( \text{R}^7 \) are taken together to form an oxo group, and the other group is \( \text{CR}^6\text{R}^7 \), wherein \( \text{R}^6 \) and \( \text{R}^7 \) in this context are each independently selected from hydrogen, halogen, hydroxyl, \( \text{C}_{1-6} \) alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy, \( \text{CVu} \) aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy, and \( \text{C}_{7-12} \) aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy).

In a particularly preferred embodiment, the compound of formula (IX) has the structure:

![Structure](image)

wherein

ring \( \Lambda \) is a \( \text{C}_{6-14} \) aryl (preferably phenyl) optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and \( \text{C}_{1-6} \) alkoxy.

In particular, the compound of the invention may be 2-(phenethylamino)-1,5-dihydro-4//-imidazol-4-one:

![Structure](image)

In another preferred embodiment of the invention, there is provided a compound according to formula (X):
wherein

ring B is an optionally substituted 6-membered heterocyclyl or heteroaryl ring (preferably 6-membered heterocyclyl);

D, E, G, and H are each independently selected from N and CR$^3$, wherein each R$^9$ in this context is independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, and optionally substituted aralkyl (preferably one of D, E, G, and H is N); wherein each R$^9$ in this context is independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, and optionally substituted aralkyl; W is joined to a substitutable position at either $X_2$ or $X_3$, and is an optionally substituted alkylene group (preferably W is joined to $X_3$);

Y is a group selected from O, S, S(0)$_q$, wherein q is 0, 1, or 2, and NR$^4$, wherein R$^4$ is a group selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl (preferably NR$^4$, wherein R$^4$ is a group selected from hydrogen and optionally substituted aralkyl);

Xi is a group selected from O, S, and NR$^5$, wherein R$^5$ in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl (preferably NR$^5$, wherein R$^5$ in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl);

$X_2$ is a group selected from N and CR$^8$, wherein R$^8$ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl (preferably CR$^8$, wherein R$^8$ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl); and

$X_3$ is a group selected from N and CR$^8$, wherein R$^8$ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl (preferably $X_3$ is C and is covalently attached to W).
In formula (X), the optional substituents on each of the groups mentioned may be the same as those mentioned above in relation to formula (I).

More preferably, there is provided a compound of formula (X), wherein

ring B is a 6-membered heterocyclyl or heteroaryl ring (preferably 6-membered heterocyclyl) containing at least two heteroatoms independently selected from O and N (preferably containing two nitrogen atoms) optionally substituted by 1 to 3 substituents selected from halogen, hydroxy, Ci-6 alkyl, C_i,6 alkoxy, and an oxo group;

D, E, G, and H are each independently selected from N and CR^9, wherein each R^9 in this context is independently selected from hydrogen, halogen, hydroxyl, cyano. Ci-6 alkyl, Ci-6 alkoxy, C_i,4 aryl, and C_7-12 aralkyl (preferably H is N, or each of D, E, G, and H is CR^9, wherein each R^9 in this context is independently selected from hydrogen, halogen, hydroxyl, cyano, Ci,6 alkyl, Ci,6 alkoxy);

W is joined to X3, and is a Ci,6 alkylene group (preferably C1-3 alkylene) optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci,6 alkoxy;

Y is a group selected from O and NR^4, wherein R^4 is a group selected from hydrogen, Ci,6 alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci,6 alkoxy, C_i,4 aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C_i,6 alkoxy, and C_7,12 aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy (preferably NR^4, wherein R^4 is a group selected from hydrogen and Ci,6 alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci,6 alkoxy);

X_i is NR^5, wherein R^5 in this context is selected from hydrogen, C_i,6 alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, C_i,4 aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci,6 alkoxy, and C_7,12 aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and C_i,6 alkoxy (preferably hydrogen);

X_2 is CR^8, wherein R^8 in this context is selected from hydrogen, C_i,6 alkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci-6 alkoxy, C_i,4 aryl optionally substituted by 1 to 3 substituents selected from halogen, hydroxyl, and Ci,6
alkoxyl, and C7-12 aralkyl optionally substituted by 1 to 3 substituents selected from halogen, hydroxy, and C1-6 alkoxyl (preferably hydrogen); and X₃ is C and is covalently attached to W.

In a particularly preferred embodiment, the compound of formula (X) has the structure:

![Structure Image]

wherein ring B is a 6-membered heterocyclyl or heteroaryl ring (preferably 6-membered heterocyclyl) containing at least two heteroatoms independently selected from O and N (preferably containing two nitrogen atoms) optionally substituted by 1 to 3 substituents selected from halogen, hydroxy, C1-6 alkyl, C1-6 alkoxyl, and an oxo group.

In particular, the compound of the invention may be 6-hydroxy-4-[1 H-indol-3-yl]-ethylamino]-1H-pyrimidin-2-one:

![Compound Image]

In another aspect of the invention, there is provided a composition comprising a compound according to the invention, and one or more pharmaceutically acceptable excipients. Furthermore, any of the preferred structural variants mentioned above in relation to formulae (I)-(X) also represent preferred aspects of this composition.

The one or more pharmaceutically acceptable excipients in the composition may include pharmaceutically acceptable diluents and carriers. Pharmaceutically acceptable diluents,
Excipients and carriers that may be used in the compositions include, but are not limited to, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, coenzyme A, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

In another embodiment, the compound or composition according to the invention is for use in therapy.

In particular, dysregulation of intracellular Ca\(^{2+}\) homeostasis is one of the key causes of neural cell death following central nervous system traumatic injury, cerebral stroke and also in some neurodegenerative diseases. PADs are Ca\(^{2+}\)-dependent enzymes that have been proposed to be involved in these pathologies. In addition, members of the PAD family have been implicated in glaucoma, autoimmune diseases including rheumatoid arthritis and multiple sclerosis, and in chronic inflammatory conditions (e.g. ulcerative colitis). A PAD role in some forms of cancer and skin diseases has also been suggested.

Thus, inhibition of PADs has significant implications in the prophylaxis or treatment of neural injury, and/or the prophylaxis or treatment of cancer, multiple sclerosis, glaucoma, arthritis, rheumatoid arthritis, lupus, Alzheimer's disease and ulcerative colitis.

Given the evident involvement of PAD4 in the regulation of tumour suppressor gene expression, the present compounds therefore have potential in the prevention or treatment of various cancers, particularly ovarian cancer (oestrogen-dependent), and prostate cancer.

A composition according to the invention may also contain one or more additional active pharmaceutical ingredients.
The composition of the invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. Preferably, the compositions are administered orally or parenterally, more specifically by injection. The composition may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes intraperitoneal, subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intra-arterial, intrathecal, intraorbital, and intraleisonal injection or infusion techniques. Preferably, the route of administration of the composition is intra-articular, intravenous or intramuscular administration (most preferably intravenous).

The composition may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

The invention also relates to a method of preventing or treating neural injury, cancer, multiple sclerosis, arthritis, rheumatoid arthritis, lupus, Alzheimer's disease, and/or ulcerative colitis in a subject comprising administering a prophylactically or therapeutically effective amount of a compound or composition according to the invention.

The invention will now be described in more detail by way of example only, and with reference to the following figures.
Description of the Figures

Figure 1
The effect of 2-[2-(1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one (referred to herein as la, 3 or CM1) on human neural cells (methylene blue assay) showed that compound 3 did not decrease the percentage of viable cells but rather increased it, indicating as little toxicity towards those cells as that of Cl-amidine. In particular, figure 1 shows the percentage of human neural stem cells surviving (detected by methylene blue assay) after treatment with either imidazolin-4-one 3 or Cl-amidine (CT-am). No reduction in the percentage of live cells after 24 h treatment was observed at any of the concentrations tested.

Figure 2
The effect of imidazolin-4-one 3 on PAD activity in protein extracts from HEK293T cells over-expressing human recombinant PAD3 using the BAEE assay. In an in vitro assay, imidazolin-4-one 3 showed comparable potency to Cl-amidine up to 1 mM, and markedly superior potency at 100 µM. This shows that imidazolin-4-one 3 is a PAD inhibitor, can reduce human PAD3 activity, and appears to be more potent than Cl-amidine in the BAEE assay. Both compounds inhibit potently inhibit PAD activity in vitro (** = p<0.01)

Figure 3
The effect of imidazolin-4-one 3 on human neural stem cells in culture in order to establish potency compared to Cl-amidine in live cells. Cell death was induced in human neural cells by treatment with 5 µM thapsigargin, and their pre-treatment with different concentrations of imidazolin-4-one 3 and Cl-amidine was examined for their ability to antagonise cell death. Thapsigargin-induced cell death was not altered by Cl-amidine at or below concentrations of 1 µM, and a significant, though partial, increase in cell survival was observed only at concentrations above 10 µM. In marked contrast, imidazolin-4-one 3 maximally restored cell survival at 100 nM, and was highly effective at all the concentrations tested (up to 1 mM). The greater difference in potency between imidazolin-4-one 3 and Cl-amidine in the cell assay as compared to the enzymatic assay in protein extracts may be at least in part due to more effective accumulation of the imidazolin-4-one 3 within the cell given its greater lipophilicity. Controls and thapsigargin (5 µM) alone (no inhibitor) contain either ethanol (controls for Cl-amidine, grey bar) or both ethanol and
DMSO (controls for imidazolin-4-one 3, striped bar). Imidazolin-4-one 3 is more powerful than Cl-amidine in rescuing cells from thapsigargin-induced cell death as assessed by the methylene blue assay. * = p<0.05 , ** = p<0.01 (as compared to thapsigargin treated cells), w = p<0.01 (as compared to corresponding control) and ^ = p<0.01 (as compared to Cl-amidine at the same concentration).

Figure 4
The extent to which imidazolin-4-one 3 inhibited cell death in the HEK293T cells over-expressing the human recombinant PAD3. In PAD3-expressing HEK293T cells 1µM thapsigargin was sufficient to induce cell death. A significant increase in cell survival, as assessed by the methylene blue assay, was achieved by treatment with both imidazolin-4-one 3 and Cl-amidine. However, whereas imidazolin-4-one 3 was effective at 10 µM, the same extent of inhibition required Cl-amidine at a concentration of 100 µM. This further supports the view that imidazolin-4-one 3 is more potent than Cl-amidine in human cell-based assays and can inhibit human PAD3 activity in live cells. This is of particular interest since PAD3 has been found to be up-regulated following spinal cord injury in which extensive neural tissue loss has occurred, and such loss was significantly reduced by Cl-amidine treatment. Imidazolin-4-one 3 is effective at a 10 fold lower concentration (* = p<0.51; ** = p<0.01). All samples including control and 1 µM thapsigargin alone (striped bars) contain both ethanol and DMSO.

Figure 5
Kinetics of inhibition. Over-expressing PAD3 in a non-neural human cell line increases the sensitivity of these cells to Ca\(^{2+}\)-induced cell death. This is reduced by CM1 treatment, consistent with its PAD inhibitory activity. Thus, experimental evidence suggests that CM1 is a competitive, reversible inhibitor.

Figure 6
The extent to which compounds Ila, 19 and 17 inhibit cell death, as assessed by the methylene blue assay and employing 5 µM thapsigargin to induce cell death. Treatment 1 is a control; treatment 2 is 100 µM compound Ila; treatment 3 is 100 µM compound 19; treatment 4 is 100 µM compound 17; treatment 5 is thapsigargin; treatment 6 is 10 µM compound Ila and thapsigargin; treatment 7 is 100 µM compound Ila and thapsigargin;
treatment 8 is 10 µM compound 19 and thapsigargin; treatment 9 is 100 µM compound 19 and thapsigargin; treatment 10 is 10 µM compound 17 and thapsigargin; and treatment 11 is 100 µM compound 17 and thapsigargin.

Figure 7
The extent to which compounds lib and Va inhibit cell death, as assessed by the methylene blue assay and employing 5 µM thapsigargin to induce cell death. Treatment 1 is a control; treatment 2 is 10 µM compound 11b; treatment 3 is 100 µM compound lib; treatment 4 is 10 µM compound Va; treatment 5 is 100 µM compound Va; treatment 6 is thapsigargin; treatment 7 is 10 µM compound 11b and thapsigargin; treatment 8 is 100 µM compound 11b and thapsigargin; treatment 9 is 10 µM compound Va and thapsigargin; and treatment 10 is 100 µM compound Va and thapsigargin.

Examples

**General Synthesis**

*Preparation of 2-thiohydantoin derivatives*

2-thiohydantoin derivatives 12 (R^6=H) may be prepared by reacting an *alpha*-amino acid with ammonium thiocyanate in the presence of acetic anhydride (Burgess *et al.*, *J. Org. Chem.* 2006, 71, 2507). For example, l-acetyl-2-methyl-2-thiohydantoin was obtained from glycine and ammonium thiocyanate. An alternative route consists of heating an *alpha*-amino acid with thiourea (Wang *et al.*, *Molecules* 2006, 11, 739).
Where $R^6$ is not $I$, thiohydantoins (12) can usually be prepared by the action of thiocarbonyldipyridone on an ester of an alpha-ammo acid, followed by reaction with an amine [3]. Thiohydantoins (12) can then be converted into the corresponding 2-methylthiohydantoins (13) by heating with methyl iodide (Zhu et al., *J. Med. Chem.* 2010, 53, 951). It should be noted that where $R^6$ is $I$, the $3H$-tautomer depicted above may be in equilibrium with the $1H$-tautomer, especially in solution.

1-Acetyl-2-thiohydantoin (12a)
Glycine (3.0 g, 39.9 mmol) and ammonium thiocyanate (3.15 g, 41.4 mmol) were ground together in a pestle and mortar. The intimate mixture was transferred to a 50 mL round-bottom flask, then acetic anhydride (22.5 mL, 238 mmol) was added, and the mixture heated in an oil bath at 100 °C for 30 min. After allowing to cool, the pale orange solution was poured into a mixture of ice and water (60 mL), and the mixture kept at 4 °C overnight. The orange precipitate was filtered, washed with cold water and dried under vacuum to give 1-acetyl-2-thiohydantoin as pale orange microprisms (2.45 g, 39%), m.p. 173-174 °C (lit. m.p. 175-176 °C). A larger scale using glycine (10.0 g), ammonium thiocyanate (10.4 g), and acetic anhydride (75 mL) afforded 1-acetyl-2-thiohydantoin in 53%.

2-Thiohydantoin (12b)
1-Acetyl-2-thiohydantoin (0.148 g, 0.94 mmol) was heated with hydrochloric acid (5 mL, 3 M) under reflux for 1 h. After allowing to cool, the resulting clear yellow solution was extracted with ethyl acetate (4 x 5 mL). The combined organic extracts were dried over MgSO₄ to give 2-thiohydantoin as pale orange microprisms (71 mg, 65%), m.p. 226 °C (decomp).

1-tert-Butyloxy carbonyl-2-thiohydantoin (12c)
A mixture of 2-thiohydantoin (0.499 g, 4.30 mmol) di-tert-butyl dicarbonate (1.20 g, 5.48 mmol) and 4-dimethylammonopyridine (53 mg, 0.43 mmol) and acetonitrile (5 mL) was for was vigorously stirred at 20 °C under nitrogen for 48 h, then evaporated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL), the organic layer dried over MgSO₄, filtered and the filtrate was evaporated under reduced pressure. The residue was dried under vacuum overnight to give 1-iWY-butyloxy carbonyl-2-thiohydantoin as a pink solid (0.70 g, 75%), m.p. 122 °C.
1-Acetyl-2-methyl-2-thiohydantoin (13a)
To a solution of methyl iodide (0.50 mL, 7.74 mmol) in acetonitrile (70 ml) was added 1-acetyl-2-thiohydantoin (0.818 g, 5.18 mmol) and potassium carbonate (0.876 g, 6.34 mmol). The mixture was stirred at 20 °C under nitrogen for 3 h, then the solvent removed under reduced pressure and the residue dried under vacuum overnight. The solid was dissolved in dichloromethane (70 mL) and filtered under suction. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (2% methanol in ethyl acetate) to give 1-acetyl-2-methyl-2-thiohydantoin as a pale yellow solid (0.48 g, 54%), m.p. 195 °C (decomp.), (lit. m.p. 197 °C).

2-Methyl-2-thiohydantoin (13b)
To a solution of methyl iodide (0.80 mL, 12.4 mmol) in acetonitrile (15 ml.) was added 2-thiohydantoin (0.30 g, 2.59 mmol) and potassium carbonate (0.429 g, 3.10 mmol). The mixture was vigorously stirred at 40 °C under nitrogen for 26 h, then the solution was filtered, and the filtrate evaporated under reduced pressure. The residue was dried under vacuum overnight. The solid was recrystallised from ethanol to give 2-methyl-2-thiohydantoin as a solid (0.193 g, 57%), m.p. 157-158 °C.

Synthesis of Tryptamine Derivatives

Method A: One-pot Japp-Klingemann and Fischer indole synthesis
The following sequence involves a Japp-Klingemann reaction of the anion of 2 with the diazonium salt of an arylamine 3 to give an azo intermediate that undergoes decarboxylase rearrangement that includes a Fischer indole synthesis, to give tryptamine 1 (Szantay et al., Synthesis, 1974, 354). The malonate derivative 2 can be prepared by alkylation of diethyl malonate with 3-chloro-1-bromopropane. This method has been used to prepare 1a (R1= H).
Diethyl 3-chloropropyl malonate (2) - (adapted from Fischer et al., Liebigs Ann. 1913, 398, 118.).

Dry ethanol (50 mL) is placed in a dry, 250 mL round-bottom flask containing a stirring bar and flushed out with nitrogen. Over about 20 minutes, sodium metal (2.92 g CAUTION: avoid all moisture) is added in about ten portions. Only if the reaction becomes extremely vigorous should be cooled by immersing the flask in a bath of cold water for a few seconds.

While the solution of sodium ethoxide is cooling, the reactants solution is prepared as follows. Diethyl malonate (40.0 g, 19.2 mL) is added to dry diethyl ether (30 mL, CAUTION: highly inflammable) followed by 1-bromo-3-chloropropane (20.0 g, 12.6 mL; CAUTION: avoid contact or inhalation), taking care to exclude moisture from the system at all times.

When the solution of sodium ethoxide has cooled (if necessary by surrounding the flask in an ice-water-bath) to about 30 °C, with constant stirring the above malonate-halide solution is added. The solution turns yellowish, and after a short time a heavy, white precipitate of sodium bromide appears. The mixture is stirred at room temperature under a blanket of nitrogen with balloon attachment for 2 days, after which time the mixture should be neutral to indicator paper. The solvent is removed on the rotary evaporator. To the cool residue is added water (50 mL); the mixture is then shaken to dissolve the sodium bromide. An oily layer of crude product separates. The mixture is then extracted with dichloromethane (2 x 30 mL), and the combined organic layers dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue is distilled under reduced pressure. A small initial run passes
over (up to 100 °C at 12 mmHg) which is discarded. With the vacuum reinstated, the main fraction then distils at around 146-147 °C/12 mm Hg.

Method B: Acylation of a tryptamine followed by hydrolysis

Tryptamine derivatives unsubstituted at the 2-position can be carboxylated at the 2-position by acylative cyclisation with di-trif-butyl dicarbonate to give the tricyclic lactam 4 (Ma et al., Eur. J. Med. Chem. 2010, 45, 5513) which is then hydrolysed (with acid, or preferably with alkali) to give the carboxylic acid 5 after acidification, if necessary.

\[
\begin{align*}
\text{NH}_2 & \quad (\text{Cl}_3\text{CO})_2\text{CO} \\
\text{NH} & \quad \text{COOH}
\end{align*}
\]

The above route can yield a wide range of tryptamine derivatives, especially by using variously substituted tryptamine derivatives, or by functional group modification of the 2-carboxy group, or both.

Method C: Pyruvate-arylamine indole synthesis then aminomethylation at the 3-position

The cyclisation of N-aryl imines by the method of Glorius, (Wiirtz et al., Angew. Chem. Int. Ed. 2008, 47, 7230) using copper(II) acetate and palladium(II) acetate, has been shown to apply in a one-pot synthesis of an indole by reaction of an arylamine with a ketonic carbonyl compounds, including simple ketones and also ethyl pyruvate (Wei et al., J. Am. Chem. Soc. 2012, 134, 9098). Prepared in that way, the ester 6 can be converted into the corresponding amide, either by reaction with ammonia (aqueous solution or as a solution in an organic solvent), or by hydrolysis to the corresponding carboxylic acid, and subsequent activation or conversion into the acid chloride, and then reaction with ammonia. Ester 6 may also be reduced with LiAlH₄ (Tsotinis et al., J. Med. Chem. 2006, 50, 6436) to give the alcohol 7 which by reductive alkylation with an amido acetal (either the acetamide or the trifluoracetamide) in the presence of Et₃SiH and trifluoroacetic acid (Righi et al., J. Org. Chem. 2012, 77, 6351) affords tryptamine 8, and hence by hydrolysis, tryptamine derivatives of type 9. If necessary, the hydroxy group of 7 is protected (e.g. as the acetate or trifluoroacetate) prior to the reductive alkylation step, and subsequently deprotected.
The above route can yield a wide range of tryptamine derivatives, especially other 2-substituents than those described above, either by using an appropriately substituted ketonic carbonyl compound, or by functional group modification at a stage after the formation of the indole, or both. A wide range of arylamines may be used.

**General methods for preparing 2-substituted derivatives of tryptamine**

**Preparation of 2-substituted derivatives of tryptamine**

Previous work has described the introduction of a 2-substituent into protected derivatives of tryptamine such as tert-butyl 2-(1-(4-methoxybenzyl)-1H-indol-3-yl)ethylcarbamate (10), or corresponding derivatives that are protected on both nitrogen atoms, for example both nitrogen atoms bearing tert-butylxoycarbonyl groups, or the indole nitrogen atom being protected as the tert-methoxybenzyl group.

Suitably protected derivatives of tryptamine can then be reacted with a variety of electrophilcs as follows, to give the following 2-substituent (shown in brackets): metalation with π-butyllithium followed by addition of N,N-dimethylformamide (CHO) (Jones *et ah*, *J. Am. Chem. Soc.* **2009, 131**, 13606); metalation with 2,2,6,6-tetramethylpiperidinylithium followed by addition of methoxycarbonyl cyanide (COOEt) (Rowley *et al.*, *J. Med. Chem.* **2001, 44**, 1603); metal-catalysed addition of an electrophilic alkene, e.g. of ethyl acrylate in the presence of di-(tert-butyl) peroxide and Pd(OAc)$_2$ (CH=CHC$_2$Et) (Zi *et al.*, *J. Am. Chem. Soc.* **2012, 134**, 9126); addition of lithium dimethyl malonate to a chloroindole...
imine in the presence of zinc chloride (CH$_2$COOEt) (Kuehne et al., J. Org. Chem. 1997, 62, 7950); (ruthenium-catalysed addition of a bromomalonate ester (CH(COOEt)$_2$) (Furst et al., Org. Lett. 2012, 14, 3104); metal-catalysed addition of an allyl halide, vinyl halide, or especially an aryl halide or a heteroaromatic halide, or any of the corresponding trifluoromethanesulphonates, e.g. using 4-bromopyridine in the presence of Pd(OAc)$_2$ (4-pyridyl) (Jones et al., J. Org. Chem. 2007, 72, 1476), or using 3-bromofuran or 3-bromothiophene in the presence of Pd(PPh$_3$)$_4$ (3-furyl or 3-thienyl, respectively; Rowley et al., J. Med. Chem. 2001, 44, 1603); a trifluoromethyl-iodine(III) reagent (trifluoromethyl) (Shimizu et al., Tetrahedron Lett. 2010, 51, 5947). A 2-alkyl substituent may be introduced using tert-butyl hypochlorite and an alkyl or allyl borane (German et al., J. Med. Chem. 2011, 54, 7259). An allylstannane may also be used to introduce a 2-allyl substituent. Dithiocarbonates in the presence of dialkanyl peroxide (alkoxycarbonylmethyl) (Reyes-Guttierez et al., Org. Biomol. Chem. 2009, 7, 1388). The CH=CHCO$_2$Et added above may also be hydrogenated over palladium on carbon to give the saturated ester (CH=CHCO$_2$Et) which may then be reduced to the saturated alcohol ((CH$_2$)$_2$CH$_2$OH) [4]. A 2-aryl group may also be introduced by reaction of the tryptamine derivative with a diazonium salt (Sawada et al., Tetrahedron Lett. 2003, 44, 4919).

Bromination at the 2-position

Tryptamine derivatives in which the chain nitrogen atom is protected, e.g. as its phthalimidino derivative, undergo bromination at the 2-position with bromine, N-bromosuccinimide or pyridinium tribromide (Feng et al., Org. Lett. 2011, 13, 5827). Such derivatives of 2-bromotryptamine may be converted into other 2-substituents by standard methods including palladium-catalysed carbon-carbon bond-forming reactions (Heck, Stille, Suzuki and Sonogashira reactions).

Iodination at the 5-position

Tryptamine derivatives [in which the chain nitrogen atom is protected, e.g. as an O-methyl carbamate,] undergo iodination at the 5-position upon treatment with N-iodosuccinimide and trifluoroacetic acid, usually in the range -40 °C to 0°C (Goto et al., Med. Chem. Lett. 2011, 2, 948, and D. L. Boger, WO2011/103007 (p 52-3)). In the usual case, a 2-substituent is required.
Hydroxylation at the 5-position

Tryptamine derivatives in which the chain nitrogen atom is protected, e.g. as an 0-methyl carbamate, undergo hydroxylation at the 5-position upon treatment with lead tetracacetate and trifluoroacetic acid, followed by zinc (Sun et al, Org. Lett. 2011, 13, 5302).

Hydroxylation of 5-iodotryptamine derivatives can be achieved by palladium-catalysed reactions involving hydrogen peroxide (D. L. Boger, WO2011/103007 (pp 52-3)).

5-Cyanotryptamine derivatives


6-Fluorotryptamine derivatives

6-Fluoroindoles have prepared from 2-iodo-5-fluoroaniline (Rowley et al, J. Med. Chem. 2001, 44, 1603). Therefore, 6-fluorotryptamine derivatives can be prepared from the corresponding 6-fluoroindoles using one of the methods for the synthesis of tryptamine derivatives outlined above, preferably method C.

Preparation of 2-[2-(1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one (1) and derivatives

The route of 3 to 4 to 2 is as found in J. Med. Chem. 2010, 53, 951. For substituted indole syntheses: (a) 6-fluoroindoles, prepared from 2-ido-5-fluoroaniline as described in J Med. Chem. 2001, 44, 1603; (b) 2-alkylation as described in J. Med. Chem. 2000, 43, 101 1 or 2-arylation as described in Chem. Eur. J. 2010, 16, 1124.

For a general route to indoles, the sequence 9 to 10 to 1 is preferred, which is described in Szantay et al, Synthesis, 1974, 354.
Possible routes to type 1 with $R^3=\text{Me}$ are described in Dubash et al., *J. Med. Chem.* 1994, 37, 4307 from indole-3-carboxaldehydes by condensation with nitroalkanes and subsequent reduction with lithium aluminium hydride.

Further possible routes to type 1 with $R^3=\text{Me}$ alone, or $R^1=7-\text{OR} \ (\text{R}=\text{H}, \text{CH}_2\text{R}; \text{etc.})$, or both of those are generally described in Dubash et al., *Synth. Commun.* 2004, 34, 1791.

2-[2-(1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one derivatives (1) were prepared by the reaction of substituted tryptamine derivatives with 1-acetyl-2-methyl-2-thiohydantoins (13), or analogs, as shown below. The reaction of tryptophan (in racemic or enantiomeric forms), or a suitably protected carboxy analog, with 13 would afford tryptamine derivatives 1 ($R^3=\text{COOH} \ or \ \text{COOR}').

A mixture of 1-acetyl-2-methylthiohydantoin (0.469 g, 2.73 mmol) and tryptamine (0.438 g, 2.74 mmol) in ethanol (4 mL) was heated at reflux until t.l.c. showed that the initially formed 5-acetyl-2-[2-(1 H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one (about 4
days) had been consumed. After allowing to cool, the precipitate was filtered and washed with cold ethanol to give 2-[2-[(H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one (0.36 g, 55%) as a yellow solid, mp 222-223 °C; IR (νmax) (thin film) 3292, 1693, 1633, 1564 cm⁻¹; ¹H NMR (DMSO-de, 293 K, 300 MHz) δH 10.85 (1H, s, indole NH), 8.00 (1H, br. s, imidazolin-4-one ring NH), 7.55 (1H, d, J 6.9 Hz, 4-indolyl), 7.36 (1H, d, J 6.9 Hz, 7-indolyl), 7.32 (1H, br. s, CI2N/Y), 7.16 (1H, s, 2-indolyl). 7.08 (1H, t, J 6.9 Hz, 6-indolyl). 6.98 (1H, t, J 6.9 Hz, 5-indolyl), 3.65 (2H, br. m, CH₂CH₂NH), 2.93 (2H, t, J 7.0 Hz, CH₂CH₂NH): ¹³C NMR (DMSO-de, 293 K, 75 MHz) δC 187.4, 172.4, 136.2, 127.1, 122.8, 121.0, 118.3, 111.4, 49.7, 42.5, 25.5; LRMS m/z (EI⁺,%) 242 (M⁺, 5), 143 (100), 130 (46), calcd for C₁₃H₁₄N₄O 242.1 162; found: 242.1 157.

3-Acetyl-2-[(5-hydroxy-1H-indol-3-yl)-ethylaminol]-3,5-dihydroimidazol-4-one (1b)

A mixture of 1-acetyl-2-methylthiohydantoin (0.25 g, 1.46 mmol) and 5-hydroxytryptamine (0.257 g, 1.46 mmol) in ethanol (4 mL) was heated at reflux until t.l.c. showed that starting materials had been largely consumed (about 4 days). After allowing to cool, the precipitate was filtered and washed with cold ethanol to give 3-acetyl-2-[(5-hydroxy-1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one (0.26 g, 60%) as a solid.

Further Synthetic Procedures and Compounds

Thiohydantoin synthesis; General procedure A:

To a solution of N-protected amino acid (1 eq) in acetonitrile (10 mL) was added ethoxycarbonyl isothiocyanate (53 µL, 0.45 mmol, 1.2 eq) followed by pyridine (37 µL, 0.45 mmol, 1.2 eq) and the resulting solution stirred for 20 h at 20 °C. The solvent was evaporated and the crude residue dried for three days in the vacuum oven at 40 °C to remove excess pyridine. The yield was determined by weight.

ff-Methylation of thiohydantoin; General procedure B:

To a stirring mixture of crude thiohydantoin (1 eq) and anhydrous potassium carbonate (0.141 g, 1.03 mmol, 1.2 eq) in acetonitrile (10 mL) was added iodomethane (80 µL, 1.28 mmol, 1.5 eq) dropwise and the resulting mixture stirred for 4 h at 20 °C. The solvent was evaporated and the residue suspended in ethyl acetate (20 mL), filtered and the filtrate concentrated in vacuo to give a crude product. The yield was determined by weight.
Benzyl 4-oxo-2-thioxoimidazolidine-1-carboxylate 4.7

Cbz-glycine (0.200 g, 0.956 mmol) was used to prepare this material, which followed the General procedure A. Crude benzyl 4-oxo-2-thioxoimidazolidine-1-carboxylate was obtained as a yellow solid (0.229 g, 98%); mp 181-183 °C (mp 183- 184 °C34) IR (vmax) 3301, 3252 (NH), 2968 (CH), 2928 (CH), 1758 (C=0), 1729 (C=0), 1421 (Ar) cm-1; 1H NMR (500 MHz, chloroform-δ) δ 8.66 (1H, br. s, NH), 7.36-7.44 (5H, m, ArH), 5.33 (2H, s, PhCH2), 4.45 (11H, s, CH2CO); 13C NMR (126 MHz, chloroform-δ) δ 178.2 (C02Bn), 167.7 (C=0), 149.8 (C=S), 134.4 (4 aryl), 129.0 (3, 5 aryl), 128.8 (2, 6 aryl), 128.7 (1 aryl). 69.5 (PhCH2), 52.7 (CH2CO).

Benzyl 2-(methylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate

Crude benzyl 4-oxo-2-thioxoimidazolidine-1-carboxylate (0.283 g, 0.96 mmol) was used to prepare this material, which followed the General procedure B. Benzyl 2-(methylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate was obtained as a brown oil that solidified overnight (0.270 g, >100%); Rf 0.52 (50% hexane/EtOAc); IR (vmax) 3055 (CH), 2982 (CH), 2929 (CH), 1723 (C=0), 1467 (Ar) cm-1; 1H NMR (500 MHz, chloroform-δ) δ 7.30-7.38 5H, m, ArH), 5.32 (21H, s, PhCH2), 4.27 (2H, s, CH2CO), 2.59 (3H, s, SCH3); 13C NMR (126 MHz, chloroform-δ) δ 186.2 (C=0), 181.6 (C02Bn), 149.5 (N=CS), 134.2 (4 aryl), 129.2 (3, 5 aryl), 128.7 (2, 6 aryl). 128.7 (1 aryl). 69.5 (PhCH2), 52.5 (CH2CO), 16.3 (SC113); m/z (Cl+) 265 (74%, M+), 221 (57%), 91 (100%); HRMS C12H13N203S requires: 265.0647, found: 265.0641.

tert-Butyl 4-oxo-2-thioxoimidazolidine-1-carboxylate 3.6

N-Boe-glycine (2.00 g, 11.4 mmol) was used to prepare this material, which followed the General procedure A. tert-Butyl 4-oxo-2-thioxoimidazolidine-1-carboxylate was obtained as a pale yellow solid (2.42 g, 98%); mp 142-144 °C (mp 145-146 °C33); Rf 0.43 (33% EtOAc/hexane); IR (vmax) 3060 (NH), 2974 (CH), 2943 (CH), 1748 (C=0), 1719 (C=0) cm-1; 1H NMR (600 MHz, chloroform-δ) δ 8.94 (1H, br. s, NH), 4.41 (2H, s, CH2CO), 1.56 (9H, s, (CH3)3); 13C NMR (151 MHz, chloroform-δ) δ 178.6 (C02Bn), 168.3 (C=0), 148.4 (OS), 85.7 (C(CH3)3), 52.8 (CH2CO), 27.9 (CH3)3; m/z (El+) 216 (10%, M+), 160 (100%, M++/Bu), (19%, M+Boc); HRMS C8H12N203S requires: 216.0569, found: 216.0564.
**tert-Butyl 2-(methylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate**

Crude tert-butyl 4-oxo-2-thioxoimidazolidine-1-carboxylate (2.30 g, 10.6 mmol) was used to prepare this material, which followed the General procedure B. Purification by flash column chromatography (33% EtOAc/hexane to 10% MeOH/EtOAc) yielded **tert-butyl 2-(raethylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate** as a light beige solid (1.80 g, 73%); mp 121-123 °C; Rf0.25 (33% EtOAc/hexane); IR (vmax) 2982 (CH). 2932 (CI-I), 1738 (C=O), 1712 (C=0) cm⁻¹; 1H NMR (500 MHz, chloroform-J) δ 4.21 (2H, s, CH₂CO). 2.55 (3H, s, Sc/3), 1.52 (9H, s, (CH₃)₃); 13C NMR (126 MHz, chloroform-J) δ 186.1 (C=0), 181.9 (C02 βBu), 148.3 (N=CS), 85.6 (C(CH₃)₃), 52.9 (CHCO), 28.1 (CI-13), 16.3 (SCH₃); m/z (EI+) 230 (14%, M+), 174 (33%, M+/Bu), 130 (100%, M+Boc); FIRMS C9H14N2O3S requires: 230.0725, found: 230.0720.

**A^/c/V-ButoxycarbonyL-phenylalanine**

To L-phenylalanine (1.62 g, 9.81 mmol) in THF/vwater mixture (1:1, 40 mL) was added di-tert-butyl dicarbonate (2.32 g, 10.6 mmol), followed by sodium hydroxide (0.855 g, 21.4 mmol) and the reaction stirred for 24 h at 20 °C, under argon. Most of the THF was evaporated, the residue dissolved in DCM (60 mL) and layers separated. The aqueous layer was slowly acidified with HCl (2 M) until the precipitate ceased forming. The layers were separated again and the organic layer was dried (MgSO₄), filtered and the solvent evaporated to yield *iV-(tert-Butoxycarbonyl)-L-phenylalanine* as a clear gel (2.47 g, 95% (98%)b)); IR (vmax) 3450-2800 (NH and OH), 2978 (CH), 1713 (C=0), 1700 (C=0). 1497 (Ar) cm⁻¹; 1H NMR (1:2 mixture of carbamate rotamers) (500 MHz, chloroform-i) δ 9.50 (1H, br. s, C02/7). 7.19-7.29 (5H, m, ArH), 6.39 (br. s) and 5.00 (d, J = 7.5) (1H, NH), 4.62 (m) and 4.40 (m) (1H, CHBn), 3.08-3.18 (1H, m, PhCHH'). 3.01-3.08 (dd, J = 13.7, 6.2) and 2.83-2.91 (m) (1H, PhCH H'), 1.42 (611. s, (CH₃)₃), 1.30 (3H, s, C(CH₃)₃); 13C NMR (126 MHz, chloroform-J) δ 176.4 and 176.1 (COOH), 156.4 and 155.5 (CO₂H), 136.0 (4 aryl), 129.5 (3, 5 aryl). 128.6 (2, 6 aryl), 127.1 (1 aryl). 81.6 and 80.3 (CBn), 54.4 and 53.5 (C(CH₃)₃), 39.2 and 37.9 (PhCH2), 28.4 and 28.1 (CH3). NMR data are in accordance with the literature.

**tert-Butyl (S)-5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate**

Crude N-(tert-butoxycarbonyl)-L-phenylalanine (2.40 g, 9.05 mmol) was used to prepare this material, which followed the General procedure A. Crude tert-butyl (S)-5-**benzyl-4-**
**oxo-2-thioxoimidazolidine-1-carboxylate** was obtained as a dark orange oil (2.67 g, 96%); IR (vmax) 3531 (NH), 2979 (CH), 2915 (CH), 1753 (C=O), 1722 (CO), 1545 (Ar) cm⁻¹; 1H NMR (500 MHz, chloroform-CDCl₃) δ 8.66 (1H, br, s, NH), 7.26-7.30 (3H, m, 3, 4, 5 aryl), 7.08 (2H, dd, J = 6.5, 2.7, 2, 6 aryl), 4.81 (1H, dd, J = 5.6, 2.8, CH₂), 3.94 (1H, dd, J = 14.0, 5.7, PhCH₃), 3.29 (1H, dd, J = 14.1, 2.5, PhCH₂H), 1.63 (9H, s, (CH₃)₃); 13C NMR (126 MHz, chloroform-CDCl₃) δ 178.3 (C₂tBu), 170.8 (C=O), 148.6 (OS), 133.1 (4 aryl), 129.6 (3, 5 aryl), 128.9 (6, 6 aryl), 127.9 (1 aryl), 85.5 (C(CH₃)₃), 64.5 (CH₂), 36.0 (PhCH₂), 28.2 (CH₃). NMR data are in accordance with the literature.

**tert-Butyl (y)-5-benzyl-2-(methylthio)-4-oxo-4,5-dihydro-l/-imidazole-1-carboxylate**

Crude tert-butyl (5)-5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3.80 g, 9.05 mmol) was used to prepare this material, which followed the General procedure B. Purification by flash column chromatography (33% hexane/EtOAc) gave **tert-butyl (S)-5-benzyl-2-(methylthio)-4-oxo-4,5-dihydro-l/-imidazole-1-carboxylate** as an off-white solid (1.98 g, 68% (63%c)); mp 104-106 °C (mp 105-107 °C); Rf0.29 (33% hexane/EtOAc to 10% MeOH/EtOAc); IR (vmax) 2979 (CH), 2938 (CH), 1717 (C=O), 1458 (Ar) cm⁻¹; 1H NMR (500 MHz, chloroform-CDCl₃) δ 7.21-7.26 (3H, m, 3, 4, 5 aryl), 7.07 (2H, m, 2.6 aryl), 4.53 (1H, dd, CH₂), 3.40-3.44 (1H, dd, J = 14.0, 6.0, PhCH₂H), 3.31-3.34 (1H, dd, J = 14.0, 2.8, PhCH₂H), 2.39 (311, s, SCH₃), 1.62 (9H, s, (CH₃)₃); 13C NMR (126 MHz, chloroform-CDCl₃) δ 186.0 (C=O), 184.7 (CC)₂tBu), 148.4 (N=CS), 133.8 (4 aryl), 129.5 (3, 5 aryl), 128.6 (2, 6 aryl), 127.4 (1 aryl), 85.7 (C(CH₃)₃), 64.5 (CH₂), 36.1 (PhCH₂), 28.2 (CH₃); m/z (Cl⁺) 321 (100%, M⁺), 265 (59%); HRMS C₁₆H₂₁N₂O₃S requires: 321.1273, (found: 321.1275). NMR data are in accordance with the literature.

**tert-Butyl (ffl-2-((1//H-indol-3-yl)ethyl)amino)-5-benzyl-4-oxo-4,5-dihydro-l/-imidazole-1-carboxylate**

To a solution of tert-butyl (S)-5-benzyl-2-((methylthio)4-oxo-4,5-dihydro-l/-imidazole-1-carboxylate (0.312 g, 1.01 mmol) in ethanol (10 mL) was added tryptamine (0.162 g, 1.01 mmol) and the resulting mixture, which turned milky after a couple of minutes, was stirred for 15 h at 20 °C, under argon. The solvent was evaporated and the residue dissolved in ethyl acetate (50 mL), which was subsequently washed with water (50 mL) then brine (20 mL), dried (MgSO₄), filtered and the filtrate evaporated to dryness to afford crude tert-butyl (5)-2-((2//-indol-3-yl)ethyl)amino)-5-benzyl-4-oxo-4,5-dihydro-lH-imidazole-
1-carboxylate as voluminous, off-white crystals (0.390g, 89%); mp 136-138 °C; Rf 0.43 (33% hexane/EtOAc); IR (vmax) 3350-3100 (NH), 2976 (CH), 2933 (CHj. 1697 (C=O) 1595 (Ni-l bend), 1516 (Ar); 1H NMR (600 MHz, DMSO-d6) δ 10.82 (IH, s, 1/-indole), 8.42 (1H, br. s, NHCH2), 7.51 (1H, d, J = 7.9, C(13)H), 7.32 (1H, d, J = 8.1, C(16)H), 7.25 (2H, t, J = 7.5, C(9)// and 4 aryl), 7.21 (1H, t, J = 7.2, C(14)//), 7.01-7.07 (4H, m, 2, 4, 5, 6 aryl), 6.96 (1H, t, J = 7.4, C(15)H), 4.45 (1H, dd, J = 5.9, 2.3, C(5)H), 3.43-3.49 (111, m, C(7)//), 3.22-3.25 (1H, dd, J = 13.8, 6.0, C(6)H), 3.13-3.15 (111, dd, J = 13.8, 2.0, C(6)H'). 2.72 (2H, t, J = 7.5, C(8)//), 1.54 (9H, s, (CH3)3); 13C NMR (151 MHz, DMSO-d6) δ 183.4 (C02iBu), 166.5 (C=O), 150.1 (N=CN), 136.8 (Cl 2), 135.1 (4 aryl), 129.3 (3, 5 aryl), 128.2 (2, 6 aryl), 127.1 (Cl 7), 126.9 (1 aryl). 122.7 (CIO), 121.0 (Cl 4), 118.4 (Cl 3), 118.3 (Cl 5), 111.4 (C9), 110.9 (Cl 6), 84.0 (C(CH3)3), 62.5 (C5), 43.2 (C7), 35.2 (C6), 27.6 (CH3)3, 24.6 (C8); m/z (Cl+) 433 ([1 1%, M+), 377 (100%, M+-rBu), 333 (20%, M+-Boc); HRMS C25H29N4O3 requires: 433.2240, found: 433.2234.

To a solution of tert-butyl (S)-2-((2-(1H-indol-3-yl)ethyl)amino)-5-benzyl-1,5-dihydro-4//-imidazol-4-one (Vllb)

To a solution of tert-butyl (S)-2-((2-(1H-indol-3-yl)ethyl)amino)-5-benzyl-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate (0.250 g, 0.58 mmol) in DCM (1.5 mL) in a nitrogen-flushed flask was added TFA (0.26 mL) and the resulting solution stirred at 20 °C, under nitrogen. The reaction mixture, which was regularly checked by TLC (10% MeOH/EtOAc), reached completion after approx. 9 h. The solvent was evaporated and the resulting oil co-evaporated with toluene (3 x 5 mL) to give a brown solid, which was partitioned between sat. aq. sodium hydrogen carbonate (50 mL) and ethyl acetate (50 mL). The organic layer was washed with brine (20 mL), dried (MgSO4), filtered and the filtrate concentrated in vacuo to give the crude product. Purification by flash column chromatography (10%> MeOH/EtOAc; dry load onto silica) afforded (S)-2-((2-(1H-indol-3-yl)ethyl)amino)-5-
**benzyl-1,5-dihydro-4H-imidazol-4-one** as a yellow solid (0.143 g, 74%); mp 207-209 °C; Rf 0.54 (10% MeOH/EtOAc); IR (vmax) 3300-3000 (NH), 3055 (CH), 2950 (CH), 2923 (CM), 1642-1611 (C=O), 1447 (Ar) cm⁻¹; ¹H NMR (600 MHz, DMSO-d₆) (mixture of tautomers) δ 10.86 (1H, s, 1H-indole), 8.09 (s) and 7.38 (s) (0.66H, 1H-imidazole, tautomers); 7.93 (0.33H, s, NHCH₂, tautomer) 7.72 (1H, d, J= 7.2, 1H-imidazole and N/CH₂, tautomers), 7.49-7.54 (1H, dd, J= 19.8, 7.7, C(13)H), 7.33-7.35 (1H, d, d, J= 8.0, C(16)//), 7.18-7.24 (5H, m, ArH), 7.09 (1H, s, C(IO)H), 7.05-7.10 (2H, t, J= 7.7, C(14)//), 6.97-7.00 (1H, t, J= 6.8, C(15)H), 4.01 (1H, t, J= 4.2, C(5)H), 3.44 (q, J= 6.5) and 3.37 (br. s) (2H, C(7)H), 3.03 (dd, J= 13.6, 2.7) and 2.99 (dd, J= 14.2, 2.7) (1H, C(6)//H), 2.74-2.77 (dd, J= 13.7, 5.8) and 2.65-2.69 (dd, J= 13.6, 8.0) (1H, C(6)H³), 2.82 (2H, br. s, C(8)H); 13C NMR (151 MHz, DMSO-d₆) (tautomers) δ 188.2 and 187.5 (C=0), 171.2 and 170.5 (N=CN), 137.8 (Cl 2), 136.3 (4 aryl), 129.6 and 129.3 (3, 5 aryl), 128.2 and 127.9 (2, 6 aryl), 127.2 (Cl 7), 126.3 (1 aryl), 122.9 (CIO), 121.0 (Cl 4), 118.4 (Cl 3), 118.3 (Cl 5), 111.4 (C9), 111.3 (C16), 61.0 (C5), 42.3 and 41.6 (C7), 37.6 and 37.4 (C6), 25.5 and 24.7 (C8); m/z (Cl⁺) 333 (100%, M+); HRMS C₂₀H₂₁N₄O requires: 333.1715, found: 333.1712.

**/erf-Butyl 2-((2-(1H-imidazole-1-carboxylate)-4-oxo-4H-imidazol-4-one)**

To a solution of tert-butyl 2-(methylthio)-4-oxo-4H-imidazole-1-carboxylate (0.225 g, 0.98 mmol) in ethanol (10 mL) was added tryptamine (0.186 g, 1.17 mmol) and the resulting mixture, which immediately turned milky, was stirred for 15 h at 20 °C, under nitrogen. The precipitate was collected and washed with cold ethanol to afford crude tert-butyl 2-((2-(1H-imidazole-1-carboxylate)amino)-4-oxo-4H-imidazol-4-one as TLC-pure white solid (0.288g, 86%); mp 212-214 °C; Rf 0.32 (50% hexane/EtOAc); IR (vmax) 3330-3170 (NH), 3058 (Cl₃), 2974 (CH), 2934 (CH), 1709 (C=0), 1618 (NH bend). 1522 (Ar) 1459 (Ar) cm⁻¹; ¹H NMR (600 MHz, DMSO-d₆) δ 10.87 (1H, s, 1H-indole), 8.58 (1H, br. s, NHCH₂), 7.62 (1H, d, J= 7.9, C(13)H), 7.33 (1H, d, J= 8.1, C(16)H), 7.20 (3H, s, C(10)H), 7.07 (1H, t, J= 7.6, C(14)H), 6.98 (1H, t, J= 7.6, C(15)H), 4.04 (2H, s, C(5)H), 3.63-3.66 (2H, dd, J= 13.8, 6.9, C(7)H), 2.98 (2H, t, J= 7.6, C(8)H), 1.46 (9H, s, (CH₃)₃); 13C NMR (151 MHz, DMSO-d₆) δ 181.5 (CO2/Bu), 166.8 (C=0), 150.1 (N=CN), 136.3 (Cl 2), 127.2 (Cl 7), 122.8 (CIO), 121.1 (Cl 4), 118.5 (Cl 5), 111.4 (C9), 111.0 (C16), 83.5 (CH₃)₃, 51.5 (C5), 43.4 (C7), 27.6 (CH₃)₃, 24.9 (C8); m/z
To 2-(2-((1H-indol-3-yl)ethyl)amino)-4-oxo-4,5-dihydro-1//-imidazole-1-carboxylate (0.208 g, 0.611 mmol) in a nitrogen-flushed flask was slowly added 1:4 TFA:DCM mixture (1.5 mL) and the reaction stirred for 10 h at 20 °C, under nitrogen. The solvent was evaporated and the resulting oil co-evaporated with toluene (4 x 8 mL). The cream residue was washed with cold DCM (20 mL) to afford **2-((2-((1H-indol-3-yl)ethyl)amino)-1,5-dihydro-4//-imidazol-4-one** 2,2,2-trifluoroacetate as a white solid (0.199 g, 94%); mp 229- 233 °C; Rf= 0.25 (9% MeOH, 1% NH3/ DCM); IR (vmax) 3330- 3100 (NH), 2987 (CH), 2908 (CH), 1698- 1653 (C=O) cm-1; 1H NMR (600 MHz, DMSO-d6) (2:1 mixture of rotamers) δ 10.96 (IH, s, 1//-indole). 9.96 (s, major rotamer) and 9.45 (s, minor rotamer) (IH, 1//-imidazole). 9.83 (s, major rotamer) and 9.61 (s, minor rotamer) (HI. NHC2H), 7.56 (IH, d, J = 7.8, C(13)H), 7.35 (IH, d, J = 8.1, C(16)H), 7.21 (IH, s, C(10)H); 7.16 (IH, t, J = 7.5, C(14)H). 7.09 (IH, t, J = 7.5, C(15)H). 4.17 (s, major rotamer) and 4.10 (s, minor rotamer) (2H, C(5)H), 3.56 (211. t, J = 5.8, C(7)/I), 3.00 (t, J = 7.3, major rotamer) and 2.95 (t, J = 7.3, minor rotamer) (2H, C(8)H); 13C NMR (151 MHz, DMSO-d6) (rotamers) δ ppm 173.9 and 172.8 (CO), 158.9 (q, 2/C=F= 31.0, CF3COO), 158.6 and 157.5 (N=CN), 136.3 (C(2)), 126.9 (C(7)), 123.4 (C(10)), 121.1 (C(4)), 117.0 (q, 1/CF = 298.2, CF3COO), 118.4 (C(5)), 118.3 (C(3)), 111.5 (C(9)), 110.3 (C(16)), 48.2 and 48.1 (C(5)), 43.4 and 42.4 (C(7)), 24.9 and 24.0 (C(8)); m/z (Cl+) 243 (100%, M+); HRMS C13H15N4O requires: 243.1246, found: 243.1242.

**tert-Butyl 4-oxo-2-(phenethylamino)-4,5-dihydro-1//-imidazole-1-carboxylate**

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-1//-imidazole-1-carboxylate (0.250 g, 1.09 mmol) in ethanol (10 mL) was added 2-phenylethylamine (0.132 g, 1.09 mmol) and the resulting mixture stirred at 40 °C for 2 days. The solvent was evaporated and the residue dissolved in DCM (50 mL). The organic layer was washed with water (50 mL) then brine (20 mL), dried (MgS04), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (33% hexane/EtOAc) to afford **tert-butyl 4-oxo-2-(phenethylamino)-4,5-dihydro-1//-imidazole-1-carboxylate** as an off-
white solid (0.238 g, 72%); mp 130-131 °C; Rf 0.38 (33% hexane/EtOAc); IR (vmax) 3309 (NH), 2977 (CM), 2931 (CH), 1696 (C=O), 1580 (Nil bend), 1517 (Ar) cm-1; 1H NMR (600 MHz, chloroform -J) δ 8.24 (1H, br. s, NH). 7.31 (2H, t, J = 7.3, 2, 6 aryl), 7.22 (3H, t, J = 6.9, 3, 4, 5 aryl). 4.07 (2H, s, CH2CO), 3.74-3.78 (2H, dd, J = 13.4, 6.8, NHC H2). 2.87 (2H, t, J = 7.3, NHCH2CH2). 1.51 (9H, s, (CH3)3); 13C NMR (151 MHz, chloroform -J) δ 181.8 (C02 tBu), 167.6 (C=O), 150.9 (N=C-N), 138.0 (1 aryl), 129.0 (3, 5 aryl), 128.8 (4 aryl), 126.9 (2, 6 aryl), 85.1 (C(CH3)3), 51.5 (CH2CO), 44.7 (NHCH2), 35.6 (NHCH2CH2), 28.1 (C113); m/z (Cl+) 304 (96%, M+), 248 (100%, M+-iBu), 204 (12%, M+-Boc); FIRMS C16H122N303 requires: 304.1661, found: 304.1685.

2-(Phenethylamino)-1,5-dihydro-4 H-imidazol-4-one 2,2,2-trifluoroacetate (IIa.TFA)

To a solution of tert-butyl 4-oxo-2-(phenethylamino)-4,5-dihydro-l H-imidazole-1-carboxylate (0.250 g, 0.82 mmol) in DCM (1.2 mL) was added TFA (0.60 mL) and the resulting solution stirred at 20 °C until TLC (10% MeOH/EtOAc) indicated consumption of the starting material (~4 h). The solvent was evaporated and the resulting oil azeotroped with toluene (3 x 5 mL) to give 2-(phenethylamino)-1,5-dihydro-4 H-imidazol-4-one 2,2,2-trifluoroacetate as a TLC pure, light beige solid (0.258 g, 96%); mp 189-191 °C; Rf 0.38 (10% MeOIm/DCM); IR (vmax) 3200-3100 (NH), 2920 (CH), 2871 (CH), 1703 (C=O), 1615 (NH bend), 1427 (Ar) cm-1; 1H NMR (600 MHz, chloroform -J) (2:1 mixture of rotamers) δ 10.09 (br. s, major rotamer) and 9.68 (br. s, minor rotamer) (1H, 1/-imidazole), 9.99 (s, major rotamer) and 9.78 (s, minor rotamer) (1H, N/CII2), 7.27-7.33 (411. m, 2, 3, 5, 6 aryl), 7.23 (1H, t, J = 6.9, 4 aryl). 4.17 (s, major rotamer) and 4.12 (s, minor rotamer) (2H, CH2CO), 3.52 (2H, t, J = 6.8, NHC H2), 2.87 (t, J = 7.4, major rotamer) and 2.83 (t, J = 7.4, minor rotamer) (2H, NHCH2CH2); 13C NMR (151 MHz, chloroform-d) (rotamers) δ 173.8 and 172.8 (C=O), 159.4 (q, JCF= 32.6, CF3COO), 158.7 and 157.7 (N=C-N), 137.9 (1 aryl), 128.9 (3, 5 aryl). 128.4 (2, 6 aryl), 126.6 (4 aryl), 116.8 (q, JCF
= 295.7, CF3COO) 48.2 (CH2CO), 43.9 and 42.9 (NHCH2), 34.9 and 34.0 (NHCH2Cl I2); m/z (Cl+) 204 (100%, M+); HRMS C11H14N3O3F3 requires: 204.1137, found: 204.1132. Anal. Calcd for C13H14N3O3F3: C, 49.21; H, 4.45; N, 13.24. Found C, 49.02; H, 4.33; N, 12.71%.

2-(Phenethylamino)-1,5-dihydro-4H-imidazol-4-one hydrochloride (Ila.HCl)

To a solution of 1/c-butyl 4-oxo-2-(phenethylamino)-4,5-dihydro-l H-imidazole-1-carboxylate (0.150 g, 0.49 mmol) in DCM (1.2 mL) was added TFA (0.7 mL) and the resulting solution stirred at 20 °C for an hour. Cone, hydrochloric acid was added (0.5 mL) and the mixture stirred for a further 2 hours, after which the solvent was evaporated and the resulting oil azeotroped with toluene (3 x 5 mL) to give 2-(Phenethylamino)-1,5-dihydro-4H-imidazol-4-one hydrochloride as a TLC pure, light beige crystalline solid (0.116 g, 99%); mp °C; Rf 0.28 (10% MeOH/DCM); IR (vmax) 3217-3025 (NH), 2965 (CH), 2867 (CH), 1703 (C=O), 1615 (NH bend). 1597 (Ar), 1432 (Ar) cm-1; 1H NMR (600 MHz, chloroform-d) δ 10.49 (br. s, major rotamer) and 9.75 (br. s, minor rotamer) (1H, ring imidazolin-4-one N/7), 9.43 (s, major rotamer) and 9.35 (s, minor rotamer) (1H, N/=Cl:12), 7.34-7.30 (4H, m, 2, 3, 5, 6 aryl), 7.23 (1H, t, J = 6.9, 4 aryl). 4.16 (s, major rotamer) and 4.09 (s, minor rotamer) (2H, CH2CO). 3.57 (2H, t, J= 6.8, N=C7/2), 2.87 (t, J= 7.4, major rotamer) and 2.83 (t, J= 7.4, minor rotamer) (2H, NHCH2C H2); 13C NMR (151 MHz, chloroform-d) δ 173.6 and 172.5 (C=0), 158.4 and 157.2 (N=C-N), 137.9 (1 aryl), 129.0 (3, 5 aryl), 128.4 (2, 6 aryl), 126.5 (4 aryl), 48.2 (Cl2=CO), 44.0 and 43.1 (NHCH2), 35.0 and 34.1 (NHCH2CH2). m/z (Cl+) 204 (100%, M+); HRMS C11H14N3O3F3 requires: 204.1137, found: 204.1132. Anal. Calcd for C11H14N3O3C1: C, 55.12; H, 5.89; N, 17.53. Found C, 54.84; H, 5.83; N, 17.33%.
**tert-Butyl 2-([(4-hydroxyphenethyl)amino]-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate**

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate (0.218 g, 0.946 mmol) in ethanol (10 mL) was added tyramine (0.130 g, 0.946 mmol) and the resulting mixture stirred at 45 °C for 2 days. The solvent was evaporated and the residue dissolved in DCM (50 mL). The organic layer was washed with water (50 mL) then brine (20 mL), dried (MgSO4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (10% MeOH/EtOAc) to afford **tert-butyl 2-([(4-hydroxyphenethyl)amino]-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate** as an off-white solid (0.222 g, 73%); mp 130-131°C; Rf 0.59 (10% MeOH/EtOAc); IR (vmax) 3318 (OH), 3241 (NH), 2977 (CH), 1689 (C=O), 1588 (NH bend), 1513 (Ar), 1446 (Ar) cm⁻¹; 1H NMR (600 MHz, DMSO-d6) δ 9.23 (1H, s, OH), 8.46 (1H, br. s, N/CH2), 7.01 (2H, d, J = 8.4, 2, 6 aryl), 6.68 (3H, d, J = 8.4, 3, 5 aryl), 4.02 (2H, s, CH2CO), 3.49-3.53 (2H, dd, J = 15.1, 6.2, NHC/2), 2.74 (2H, t, J = 7.6, NHC/2CO), 1.47 (9H, s, (CH3)3); 13C NMR (151 MHz, DMSO-δ6) δ 264 (100%, M+/Bu), 220 (40%, M+/Boc). HRMS C16H22N3O4 requires: 320.1661; found: 320.1609.

2-((4-Hydroxyphenethyl)amino)-1,5-dihydro-4//-imidazol-4-one 2,2,2-trifluoroacetate (IIb)

To a solution of tert-butyl 2-((4-hydroxyphenethyl)amino)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate (0.153 g, 0.478 mmol) in DCM (1.5 mL) was added TFA (0.6 mL) and the resulting solution stirred at 20 °C until TLC (10% MeOH/EtOAc) indicated consumption of the starting material (~6 h). The solvent was evaporated and the resulting oil azeotroped with diethyl ether (3 x 5 mL) to give 16 as a TLC pure off-white solid (0.152 g, 95%); mp 208-210 °C; Rf 0.35 (15% MeOH/DCM); IR (vmax) 3300-3200 (OH) 3100-
2980 (NH), 2915 (CH), 2878 (CH), 1699-1663 (C=O), 1610 (Ar), 1516 (Ar) cm⁻¹; 1H NMR (600 MHz, DMSO-d6) (2:1 mixture of rotamers) δ 10.00 (br. s, major rotamer) and 9.57 (br. s, minor rotamer) (1H, 1//-imidazole) 9.87 (br. s, major rotamer) and 9.68 (br. s, minor rotamer) (1H, N//CH2). 9.35 (1H, br. s, OH), 7.04-7.08 (21H, d, J = 8.4, 2, 6 aryl), 6.69 (3H, d, J = 8.5, 3, 5 aryl), 4.17 (s, major rotamer) and 4.12 (s, minor rotamer) (21H, CH2CO). 3.43 (2H, t, J = 6.5, NHC7/2), 2.75 (t, J = 7.4, major rotamer) and 2.70 (t, J = 7.4, minor rotamer) (2H, NHCH2C H2); 13C NMR (151 MHz, DMSO-d6) (rotamers) δ 173.8 and 172.8 (C=O). 159.2 (q, 2JCF = 32.6, CF3COO), 158.6 (4 aryl), 157.5 and 156.1 (N=CN), 129.8 (1 aryl), 127.8 (2.6 aryl), 116.9 (q, 1JCF = 295.8, CF3COO), 115.2 (3, 5 aryl), 48.2 (CH2CO), 44.2 and 43.3 (NHCH2), 34.1 and 33.2 (NHCH2CH2); m/z (CI+) 220 (100%, M+); FIRMS C11H14N3O2 requires: 220.1086; found: 220.1081. Anal. Calcd for C13H14N3O4: C, 46.85; H, 4.23; N, 12.61. Found C, 45.90; H, 4.10; N, 12.20%.

tert-Butyl 2-((2-hydroxy-2-phenylethyl)amino)-4-oxo-4,5-dihydro-l//-imidazole-1-carboxylate

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-l//-imidazole-1-carboxylate (0.237 g, 1.03 mmol) in ethanol (10 ml) was added (±)-2-amino-1-phenylethanol (0.128 g, 0.94 mmol) and the resulting mixture stirred at 20 °C for 3 days, under nitrogen. Solvent was evaporated and the residue dissolved in DCM (30 mL), which was washed with water (30 mL) then brine (30 mL), dried (MgSO4), filtered and the filtrate evaporated. Crude product was purified by column chromatography (25% hexane/EtOAc to 10% MeOH/1/EtOAc ) to afford tert-butyl 2-((2-hydroxy-2-phenylethyl)amino)-4-oxo-4,5-dihydro-l H-imidazole-1-carboxylate (0.215 g, 72%) as a light yellow solid; mp 109-111 °C; Rf 0.59 (10% MeOH/EtOAc); IR (vmax) 3320 (OH), 3295 (NH), 2982 (CH), 2930 (CH), 1696 (C=O), 1596 (NH bend). 1506 (Ar). 1448 (Ar) cm⁻¹; 1H NMR (500 MHz, chloroform-d) δ 8.56 (HI, br. s, NHCH2), 7.32-7.38 (5H, m, ArH), 4.96 (1H, t, C//0 H), 4.00 (2H, s, CH2CO), 3.86 (IH, br. s, NHCH H), 3.58 (1H. br. s, NCH /F), 1.51 (9H, s, CH3); 13C NMR (126 MHz, chloroform-d) δ 181.7 (C0 2fBu), 168.1 (C=O), 150.7 (N=C-N), 141.3 (1 aryl), 128.6 (2, 6 aryl). 125.9 (3, 5 aryl), 85.2 (C(CH3)3), 72.6 (CHOH), 51.6 (CH2CO). 50.6 (NHCH2). 28.1 (CH3); m/z (CI+) 320 (17%, M+), 264 (93%, M+-rBu). 220 (81%, M+-Boc); hRMS C16H22N3O4 requires: 320.1610, found: 320.1609.
**tert-Butyl 2-((4-methoxybenzyl)amino)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate**

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate (0.249 g, 1.08 mmol) in ethanol (10 mL) was added 4-nitrobenzylamine (0.170 g, 1.30 mmol) and the resulting mixture, which turned milky after a couple of minutes, was stirred at 40 °C for three days. The precipitate was collected and washed with cold ethanol to afford tert-butyl 2-((4-nitrobenzyl)amino)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate as a TLC pure white solid (0.198 g, 57%); mp 187-190 °C; Rf 0.40 (17% hexane/EtOAc) IR (vmax) 3302 (NH), 2983 (CH), 2929 (CH), 1699 (C=0), 1611 (N=CN) cm⁻¹; 1H NMR (600 MHz, DMSO-d₆) δ 8.85 (IH, br. s, NHCH₂), 7.30 (2H, d, J = 8.7, 2, 6 aryl), 6.89 (211, d, J = 8.7, 3, 5 aryl), 4.48 (211, s, NiC/2), 4.04 (211, s, CH₂CO), 3.73 (311, s, OC7/3), 1.47 (911, s, (C/73)3); 13C NMR (151 MHz, OMSO-d₆) δ 181.5 (C02 tBu), 167.0 (C=0), 158.6 (4 aryl), 150.1 (N=C=N), 130.1 (1 aryl), 129.3 (2, 6 aryl), 113.8 (3, 5 aryl), 83.5 (C(CH3)3), 55.1 (0013), 51.7 (CH2CO), 45.5 (NHCH₂), 27.6 (CH₃); m/z (CI+) 320 (100%, M+), 264 HRMS C₁₆H₂₂N₃O₃ requires: 320.1610, found: 320.1608.

Analyzed for C₁₃H₁₄N₃O₃F₃: C, 46.85; H, 4.23; N, 12.61. Found C, 46.94; H, 4.22; N, 12.29%.

**tert-Butyl 2-((2-methoxybenzyl)amino)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate**

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate (0.204 g, 0.886 mmol) in ethanol (10 mL) was added 2-methoxybenzylamine (0.150 mL, 1.15 mmol) and the resulting mixture was stirred at 50 °C for four days. The solvent was evaporated and the residue purified by flash column chromatography (50% hexane/EtOAc; dry load onto Celite) to afford tert-butyl 2-((2-methoxybenzyl)amino)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate as a pale yellow solid (0.159 g, 56%); mp 194-197 jC; Rf 0.41 (50% hexane/EtOAc); IR (vmax) 3344 (NH), 3070 (CH), 2970 (CH), 2939 (CH), 1698 (C=0), 1608 (NH bend), 1521 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆) δ 8.75 (IH, br. s, NHCH₂), 7.35 (IH, d, J = 7.3, 6 aryl), 7.29 (111, t, J = 7.8, 5 aryl), 6.86-6.94 (2H, m, 3, 4 aryl), 4.69 (2H, s, NHCH₂), 4.06 (211, s, C7/2CO), 3.90 (3H, s, OCH₃), 2.51 (9H, s, (CH₃)3); 13C NMR (126 MHz, DMSO-t/6) δ 181.4 (C02fifiu), 167.1 (C=0), 156.7 (2 aryl), 150.2 (N=C=N), 128.7 (1 aryl), 128.0 (6 aryl), 125.2 (4 aryl), 120.3 (5 aryl), 110.7 (3 aryl), 83.6 (C(CH₃)3), 55.4 (OCH₃), 51.6 (CH₂CO), 42.0 (NHCl-12), 27.6 (CH₃)₃; m/z (CI+) 320 (51%, M+). 264 (100%, M+?Bu); HRMS C₁₆H₂₂N₃O₃ requires: 320.1610, found: 320.1608. M+/Bu, 220 (27%, M+Boc); HRMS C₁₆H₂₂N₃O₃ requires: 320.1610.

2-((4-Methoxybenzyl )amino)-1,5-dihydro-4H-imidazol-4-one 2,2,2-trifluoroacetate (lie)

To a solution of tert-butyl 2-((4-methoxybenzyl)amino)-4-oxo-4,5-dihydro-1/-imidazole-1-carboxylate (0.120 g, 0.382 mmol) in DCM (2 mL) was added TFA (1 mL) and the resulting solution stirred at 20 °C until TLC (10% MeOH/EtOAc) indicated consumption of the starting material (~4 h). The solvent was evaporated and the resulting oil azeotroped with toluene (3 x 5 mL) to give 2-((4-methoxybenzyl)amino)-1,5-dihydro-4Z/-imidazol-4-one 2,2,2-trifluoroacetate as a TLC pure white solid (0.125 g, 98%); mp 169-170 °C; Rf 0.36 (10% MeOH/DCM); IR (vmax) 3212 (NH), 2979 (CH), 2896 (CH), 1689–1638 (C=0), 1589 (Ar), 1515 (Ar) cm⁻¹; 1H NMR (600 MHz, DMSO- d6) (2:1 mixture of rotamers) δ 10.26 (br. s, major rotamer) and 10.1 (br. s, minor rotamer) (1H, 1H-imidazole), 10.02 (br. s, major rotamer) and 9.65 (br. s, minor rotamer) (1H, NHCH2), 7.31 (2H, d, J= 8.5, 2, 6 aryl), 6.95 (2H, d, J= 8.5, 3, 5 aryl), 4.44 (21, s, NHCH2/2), 4.20 (s, major rotamer) and 4.14 (s, minor rotamer) (2H, CH2CO), 3.75 (3H, s, OC//3); 13C NMR (151 MHz, DMSO- d6) (rotamers) δ 174.4 and 173.0 (C=0 ), 159.1 (q. 2JCF= 32.3, CF3COO), 159.0 (4 aryl), 158.8 and 157.7 (N=CN), 129.1 (1 aryl), 127.9 (2, 6 aryl), 116.9 (q, JCF = 298.8, CF3COO), 114.0 (3, 5 aryl). 55.2 (OCH3), 48.3 (CH2CO), 45.4 and 44.2 (NIICI-I2); m/z (CI+) 220 (94%, M+); FIRMS C11H14N302 requires: 220.1086, found: 220.1081.
**tert-Butyl 2-((2-methoxybenzyl)amino)-4-oxo-4,5-dihydro-l//-imidazole-1-carboxylate**

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-l//-imidazole-1-carboxylate (0.204 g, 0.886 mmol) in ethanol (10 mL) was added 2-methoxybenzylamine (0.150 mL, 1.15 mmol) and the resulting mixture was stirred at 50 °C for four days. The solvent was evaporated and the residue purified by flash column chromatography (50% hexane/EtOAc; dry load onto Celite) to afford **tert-butyl 2-((2-methoxybenzyl)amino)-4-oxo-4,5-dihydro-l//-imidazole-1-carboxylate** as a pale yellow solid (0.159 g, 56%); mp 194-197 °C; Rf 0.41 (50% hexane/EtOAc); IR (vmax) 3344 (NH), 3070 (CH), 2970 (CH), 2939 (CM), 1698 (C=O), 1608 (NH bend), 1521 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆) δ 8.75 (1H, br. s, NHCH₂), 7.35 (1H, d, J = 7.3, 6 aryl), 7.29 (1H, t, J = 7.8, 5 aryl), 6.86-6.94 (2H, m, 3, 4 aryl), 4.69 (2H, s, NHCH₂), 4.06 (2H, s, CH₂CO), 3.90 (3H, s, OCH₃), 1.51 (9H, s, (CH₃)₃); 13C NMR (126 MHz, DMSO-d₆) δ 181.4 (CO₂Bu), 167.1 (C=O), 156.7 (2 aryl), 150.2 (N=CN), 128.7 (1 aryl), 128.0 (6 aryl), 125.2 (4 aryl), 120.3 (5 aryl), 110.7 (3 aryl), 83.6 (C(CH₃)₃), 55.4 (OCH₃), 51.6 (CH₂CO), 42.0 (NHCH₂), 27.6 (CH₃)₃; m/z (Cl⁺) 320 (51%, M⁺), 264 (100%, M⁺-?Bu); HRMS C₁₆H₂₂N₃O₃ requires: 320.1610, found: 320.1608.

2-((2-Methoxybenzyl)amino)-1,5-dihydro-4H-imidazol-4-one (lid)

To a solution of tert-butyl 2-((2-methoxybenzyl)amino)-4-oxo-4,5-dihydro-l//-imidazole-1-carboxylate (0.120 g, 0.376 mmol) in DCM (2 mL) was added TFA (1 mL) and the resulting solution stirred at 20 °C until TLC (10% MeOH/EtOAc) indicated consumption of the starting material (~4 h). The solvent was evaporated and the resulting oil azeotroped with toluene (3 x 5 mL) to give a brown oil, which was partitioned between sat. aq. sodium hydrogen carbonate (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer washed with excess brine (3 x 40 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated to give crude 2-((2-methoxybenzyl)amino)-1,5-
dihydro-4//-imidazol-4-one as an off-white solid (0.036 g, 44%); Rf 0.29 (10% MeOH/EtOAc); IRvmax 3378 (Nil), 2951 (CH), 2921 (CH), 1657 (C=O), 1461 (Ar) cm-1; 1H NMR (600 MHz, DMSO-d6) (2:1 mixture of rotamers) δ 8.21 (br. s, minor rotamer), 8.03 (br. s, major rotamer) (IH, 1H-imidazole), 8.01 (br. s, minor rotamer), 7.64 (br. s, major rotamer) (IH, NHC=CH2), 7.25 (IH, t, 4 aryl), 7.18 (1H, d, 5 aryl), 6.98 (1H, d, 3 aryl). 6.91 (IH, t, 4 aryl), 4.39 (s, major rotamer) and 4.32 (s, minor rotamer) (2H, NHC H2), 3.80 (3H, s, OCH3), 3.64 (2H, s, CH2CO); 13C NMR (126 MHz, DMSO-d6) (rotamers) δ 187.2 and 186.7 (C=O), 172.9 and 172.2 (2 aryl). 156.5 (N=C-N), 128.3 (1 aryl). 127.7 (6 aryl), 126.7 (4 aryl), 120.2 (5 aryl), 110.5 (3 aryl), 55.4 (OCH3), 49.9 (CH2CO), 40.6 (NHC=CH2); m/z (Cl+) 220 (100%, M+); HRMS C11H14N3O2 requires: 220.1086, found: 220.1085.

tert-Butyl (R)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate

To a solution of tert-butyl 2-(methylthio)-4-oxo-4,5-dihydro-1 H-imidazole-1 -carboxylate (0.208 g, 0.903 mmol) in ethanol (10 mL) in a nitrogen- Hushed flask was added R-(-)-prolinol (0.101 mL, 1.04 mmol) and the resulting mixture stirred at 20 °C for 2 days, under nitrogen. The solvent was evaporated and the waxy residue purified by flash column chromatography (7% MeOH, 1% NH3/DCM) to give tert-butyl (R)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate as a pale yellow solid (0.161 g, 63%); mp 141-143 °C; Rf 0.29 (7% McOH 1% NH3/EtOAc); IR (vmax) 3178 (OH), 2979 (CH), 1737 (C=O) cm-1; 1H NMR (600 MHz, methanol-d4) δ 4.29 (2H, m, C(10)H), 4.13 (1H, m, C(9)H), 3.88-3.92 (2H, m, C(5)H). 3.44-3.60 (2H, m, C(6)H), 2.13 (2H, m, C(8)H), 2.01 (2H, m, C(7)H). 1.45 (9H, s, (CH3)3): 13C NMR (151 MHz, methanol-d4) δ 190.3 and 190.0 (C2iBu) 170.6 and 170.0 (C=O), 154.8 (N=C-N), 83.5 and 83.1 (C(CH3)3), 67.6 and 67.1 (CIO), 59.7 and 57.8 (C9), 51.4 (C5), 50.1 and 47.9 (C6), 29.4 and 28.8 (C8), 28.0 (Cl-13)3, 24.5 and 23.8 (C7); m/z (EI+) 283 (7%, M+), 210 (27%, M+-Bu), 182 (79%, M+-Boc) 166 (100%, M+-Boc-OH) 152 (94%, M+-Boc-CH2O); HRMS C13H21N3O4 requires: 283.1532, found: 283.1530.
(7?)-2-(2-(Hydroxymethyl)p-trolidin-1-vl)-1,5-dihydro-4/7-imidazol-4-one 2.2.2-trifluoroacetate (TFA)

To a solution of tert-butyl /(-/-)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-4-oxo-4,5-dihydro-1H-imidazole-1-carboxylate (0.100 g, 0.351 mmol) in DCM (1.0 mL) in a nitrogen-flushed flask was added TFA (0.5 mL) and the resulting solution stirred at 20 °C, under nitrogen, until TLC (20% MeOH/EtOAc) indicated consumption of the starting material (~3.5 h). The solvent was evaporated and the resulting oil azeotroped with toluene (3 x 5 mL) to give /R/-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-1,5-dihydro-4H-imidazol-4-one 2,2,2-trifluoroacetate as a TLC pure orange, waxy solid (0.103 g, 99%); Rf 0.19 (20% MeOH/EtOAc); IR (vmax) 3196 (OH), 3079 (NH), 2967 (CH), 2882 (CH), 1669 (C=O) cm⁻¹

HNMR (600 MHz, methanol-/) δ 4.16-4.26 (3H, C(9)H and C(10)H), 3.54-3.73 (4H, C(5)H and C(6)H), 2.10-2.21 (2H, C(8)H), 1.97-2.09 (2H, C(7)H); 13C NMR (151 MHz, methanol-) (rotamers) δ 173.8 and 173.6 (C=O), 158.7 (q, 2JCF = 42.0, CF3COO), 158.4 and 157.9 (N=C-N), 116.2 (q, 1JC = 292.4, CF3COO), 64.1 and 63.6 (C9), 63.7 and 63.6 (C10), 51.2 (C5), 49.6 and 49.5 (C6), 29.0 and 28.8 (C8), 24.5 and 24.3 (C7); m/z (CI+) 184 (100%, M+); HRMS C8H14N302 requires: 184.1007, found: 184.1003.

5.5-Dimethyl-2-methylsulfanyloxazol-4-one

To a solution of 5,5-dimethyl-2-thioxo-4-oxazolidinone (0.45 g, 3.06 mmol, commercial grade: 80% purity) in acetonitrile (25 mL) under nitrogen was added with stirring potassium carbonate (0.516 g, 3.73 mmol) and then methyl iodide (0.284 mL, 4.56 mmol). After stirring at 20 °C for 3 hours, LC-MS showed consumption of starting materials, the desired product eluting after 4.34 min, and side products eluting at 4.65 min and also subsequently. After stirring for an additional 13 hours, the mixture was filtered and the filtrate evaporated to give crude 5,5-Dimethyl-2-methylsulfanyloxazol-4-one as a yellow solid (0.85 g) that was dissolved in dichloromethane, and the solution filtered and
evaporated. The residue was purified by column chromatography, (elution with 1% EtOAc in dichloromethane and then with 1% triethylamine in dichloromethane). The relevant fractions were combined, evaporated and the residue triturated with diethyl ether to give 5,5-Diethyl-2-methylsulfanyloxazol-4-one as yellow microprisms (0.30 g, 61%).

\[ \text{2-[2-(1H-Indol-3-yl)-ethanolamino]-5,5-dimethyloxazol-4-one (Va)} \]

5,5-Dimethyl-2-thiomethyl-4-oxazolidinone (0.30 mg, 1.53 mmol) and tryptamine (0.28 g, 1.53 mmol) were heated at reflux in ethanol (20 ml) for 4 hours. LC-MS showed a single peak for the desired product (m/z 272, elution time 12.0 min). Evaporation afforded a residue that was triturated with 1:1 diethyl ether: hexane to give Va (0.241 g); $^1$H NMR (500 MHz, DMSO-$d_6$) (2:1 tautomers): $\delta$ 10.87 (1H, s), 9.05 (1H, s, NH, minor tautomer), 8.82 (1H, t, J ~ 5.5 Hz NH, major tautomer), 7.55 (1H, m), 7.35 (1H, m), 7.18 (1H, s, minor tautomer), 7.13 (IH, s, major tautomer), 7.08 (IH, m), 6.98 (1H, m), 3.50 (2H, m).

15 \[ \text{13C NMR (125 MHz, DMSO-$d_6$) (major tautomer): } \delta \text{ 190.0, 173.4, 136.3, 127.2, 122.9, 121.0, 118.3, 111.4, 111.0, 85.1, 43.1, 24.8, 23.2; (minor tautomer): } \delta \text{ 189.8, 173.3, 136.2, 127.1, 123.1, 121.0, 118.2, 111.4, 110.8, 85.6, 41.4, 25.3, 23.0.} \]

4,6-Dichloro-1H-pyrimidin-2-one

Aqueous sodium hydroxide (3.8 M, 10 ml, 38.7 mmol) was added to a vigorously stirred solution of 2,4,6-trichloropyrimidine (4.74 g, 25.8 mmol) in THF (80 ml). Progress of the reaction was monitored by LC-MS which showed a product peak (m/z 165, 4.08 min) and residual 2,4,6-trichloropyrimidine (5.28 min). After 48 h, the mixture was concentrated under reduced pressure and filtered (the filtrate being retained) to give a precipitate that was collected and dissolved in hot water (120 ml). After adjusting the solution to pH 2 with hydrochloric acid (3.6 M) it was cooled to 0 °C. The precipitate was filtered, washed with water and dried under reduced pressure to give the first batch of 4,6-dichloro-1H-
pyriniidin-2-one (1.17 g, 27%) as a white solid. The retained filtrate was concentrated almost to dryness and the above purification process repeated to furnish a second batch of 4,6-dichloro-1H-pyrimidin-2-one (2.03 g, 48%) as a white solid (total yield 3.2 g, 75%).

6-Chloro-4-(2-(1H-indol-3-yl)-ethylamino)-1H-pyrimidin-2-one (17)

To a solution of 4,6-dichloro-1H-pyrimidin-2-one (0.21 g, 1.28 mmol) in anhydrous acetonitrile (10 mL) in an oven-dried flask under nitrogen was added Hunig's base (0.423 mL) and tryptamine (0.204 g, 1.28 mmol). The solution was heated at reflux for 18 hours, or until LC-MS showed about 5% of residual 4,6-dichloro-1H-pyrimidin-2-one (m/z 165, 4.10 min). Evaporation under reduced pressure gave a residue that was partitioned between a mixture of ethyl acetate (25 mL) and water (25 mL). The ethyl acetate layer was separated, washed with water (2 x 10 mL) then with brine (10 mL), and dried over anhydrous MgSO₄. Filtered and evaporated. The residue was triturated with di-isopropyl ether several times to give 17 as a beige solid (0.30, 81%) of >95% purity by LC-MS (m/z 289, 4.70 min).

H NMR (500 MHz, DMSO-de): δ 11.05 (s, 1H), 10.87 (s, 1H), 7.64 (d, J = 7.8 Hz), 7.37 (d, J = 8.1 Hz), 7.18 (s, 1H), 7.07 (d, J = 7.3 Hz), 6.97 (d, J = 7.3 Hz), 6.85 (s, 1H), 5.63 (s, 1H), 3.55 (q, J = 7.2 Hz), 2.93 (t, J = 7.2 Hz).

3C NMR (125 MHz, DMSO-d₆) δ 159.2, 153.9, 136.3, 127.1, 123.0, 121.0, 118.4, 118.3, 111.4, 111.1, 41.0, 24.7.

2-[2-(1H-indol-3-yl)-ethylamino]ethanol

A mixture of tryptamine (3.0 g, 18.7 mmol) and 2-chloroethanol (1.2 mL, 18.7 mmol) in DMF (12 mL) was heated under nitrogen at 80 °C for 2 hours. LC-MS showed a major peak at 3.53 min containing overlapping peaks for tryptamine (m/z 161), the title compound (m/z 205) and the M/V-di-alkylated product (m/z 249) which could not be separated on even on a 30 min LC-MS run. The DMF was removed using a high vacuum. Addition of water (40 mL) to the residue, extraction with ethyl acetate (8 x 20 mL) and combining of the
organic layers gave a solution that was washed with water (2 x 20 mL), then with brine (2 x 20 mL), dried over MgSO₄ and evaporated to give crude 2-[2-(1H-indol-3-yl)-ethylaminoethanol (2.13 g) as a brown oil that was used in the next step without further purification.

6-Chloro-4-r2-(hydroxyethyl)-2-(1H-indol-3-yl)-ethylaminol-lH-pyrimidin-2-one (18)

To a solution of 4,6-dichloro-l H-pyrimidin-2-one (0.51 g, 3.09 mmol) in anhydrous acetonitrile (30 mL) in an oven-dried flask under nitrogen was added llinig's base (1.08 mL, 6.18 mmol) followed by crude 2-[2-(1H-indol-3-yl)-ethylaminoethanol (1.58 g, 7.72 mmol). The mixture was heated at reflux for 20 hours. Evaporation of the solvent gave a residue that was dissolved in 1:1 ethyl acetate:water (20 mL). The ethyl acetate layer was separated and washed with water (3 x 10 mL) then with brine (20 mL), dried over MgSO₄, filtered and evaporated to give a brown foam (1.17 g) that was purified by column chromatography, by elution first with 1% triethylamine in ethyl acetate to remove a by-product eluted then with 1:9 methanol: ethyl acetate followed by pure methanol. The relevant fractions were combined and evaporated to give a yellow oil that was dissolved in ethyl acetate (20 mL) and the solution washed with water (5 x 15 mL) then with brine (10 mL), dried over MgSO₄, filtered and evaporated to give 18 (0.15 g, 15%) as a tan solid of >90% purity by LC-MS. 1H NMR (500 MHz, DMSO-d₆): δ 10.83 (1H, br s), 7.75 (1H, br s), 7.37 (1H, d, J=8.1 Hz), 7.18 (1H, s), 7.11 (1H, t, J=7.3 Hz), 6.98 (1H, t, J=7.3 Hz), 5.73 (1H, s), 3.78 (2H, t, J=7.6 Hz), 3.55 (4H, m), 2.97 (2H, t, J=7.6 Hz); 13C NMR (125 MHz, DMSO-d₆) δ 159.2, 136.2, 127.2, 122.9, 120.1, 118.5, 118.2, 111.4, 111.2, 59.0, 50.3, 22.9.
When 4,6-dichloro-1//-pyrimidin-2-one was allowed to stand in air, or when left in a damp or moistened state, partial hydrolysis occurred to give crude 4-chloro-6-hydroxy-1//-pyrimidin-2-one which when treated with tryptamine and Hiiniig’s base according to the above procedure for 17 (or similar quantities or reaction times), a small quantity of 19 was obtained as a beige solid. 1H NMR (500 MHz, DMSO-d6): δ 10.97 (IH, s), 10.18 (1H, s), 9.68 (1H, br s), 7.57 (1H, d, J=7.8 Hz), 7.37 (1H, d, J=8.0 Hz), 7.24 (1H, s), 7.08 (1H, t, J=7.3 Hz), 6.98 (1H, t, J=7.3 Hz), 6.43 (1H, br s), 3.33 (2H, q, J=7.0 Hz), 2.94 (2H, t, J=7.0 Hz); 13C NMR (125 MHz, DMSO-d6) δ 164.6, 154.5, 151.1, 136.5, 127.3, 123.5, 121.4, 118.6, 118.4, 111.8, 111.1, 42.2, 24.3.

References


**Tautomerism of 2-[2-(1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one derivatives** (1)

The structure 1 identifies some of the preferred 2-[2-(1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one derivatives according to the invention.

![Diagram of tautomers](image)

The depiction of any tautomer, therefore, refers to a compound of one molecular formula that may exist as more than one tautomer. Furthermore, the tautomer shown may not necessarily be the major tautomer.

**Modelling of binding site**

Potential modes of binding have been explored using molecular modelling. Using AutoDock3.() (Morris et al., J. Comput. Chem., 1998, 19, 1639), modeling of the binding of imidazolin-4-one 3 in PAD4 (prepared from PDB code 3B1U) suggested a strong preference for a pose of the imidazolin-4-one ring in proximity to PAD4 residues involved in hydrolytic dcimination, including His471, the nucleophilic Cys645, and especially to Asp350 and Asp473 participating in hydrogen bonding. Even an unsubstituted indole ring
proves to be an acceptable replacement for the amide chain present in BAA. This modeling confirms the efficacy of a 2-amino-3,5-dihydroimidazol-4-one moiety as a surrogate for a guanidinc terminus, and also suggests that even more potent, and perhaps selective, inhibition of PADs should result from the addition of appropriate polar substituents to the indole ring present in 3. Thus, although the mechanism of action is not completely understood, and is not limiting on the present invention, the above provides one possible theory for compound inhibition.

**Treatment of cells with compounds**

Imidazolin-4-one 3 was dissolved in (DMSO) and used at 0.1-1000 µM final concentration. Cl-amidine (Cambridge Bioscience Ltd.) was dissolved in phosphate buffer saline (PBS) and used at 0.1-1000 µM final concentration. Thapsigargin (Sigma) was dissolved in ethanol and used at either 1 or 5 µM final concentration. Cells were treated with each compound, or the appropriate vehicle(s) as a control, alone or in combination. In combination experiments. Imidazolin-4-one 3 or Cl-amidine were applied 15 min before addition of thapsigargin.

**Cells and methylene blue assay**

Human Embryonic Kidney 293 (HEK293T) cells were grown and transfected when at 60% confluence with a human recombinant PAD3 plasmid using Lipofectamine LTX (Invitrogen) as previously described (Graham et al., J. Gen. Virol., 1977, 36, 59.). The human embryonic neural stem cell line was grown as previously described (Sun et al., Mol. Cell. Neurosci., 2008, 38, 245). Analysis of cell survival was assessed in 96-well plates after 24 h treatment with the different compounds using the methylene blue assay as previously reported (Lee et al., Biophys. Acta, 2009, 1802, 347).

**PAD enzymatic assay**

The benzoyl L-arginine ethyl ester (BALE) enzymatic assay was used to compare compound 17 and Cl-amidine inhibitory activity in protein extracts from HEK293T expressing human recombinant PAD3. BAEE is a non-natural PAD substrate converted by PAD activity to sodium ben/.oyl-L-citrulline. The BAEE assay detects colorimetrically the amount of citrulline from BAEE produced by PAD activity using carbidino detection reagents and was carried out with minor modifications from published protocols (Cafaro et
The amount of red pigment developed upon heating at 100 °C for 10 min was measured at 550 nm (Sigma Protocol, EC 3.5.3.15) using a microplate reader (Revelation v4.21 Dynex Technologies, inc). The results provided an estimated EC₅₀ value for compound 17 of 824 µM.

**Abbreviations**

Ac₂O, acetic anhydride; Boc, /er/-butoxycarbonyl; Cbz, carboxybenzyl; DCM, dichloromethane; DMSO-d₆, deuterated dimethyl sulfoxide; EtOAc, ethyl acetate; EtOll, ethanol; IR, infrared; MeOH, methanol; Mel, iodomethane; mp, melting point; NH₄SCN, ammonium thiocyanate; NMR, nuclear magnetic resonance; PAD, peptidylarginine deiminase; TFA, trifluoroacetic acid; TLC, thin layer chromatography.
Claims

1. A compound of the formula (I):

\[
\begin{align*}
\text{A} & \xrightarrow{\text{W}} \text{B} \\
\text{R}^1 & \quad \text{Y} \quad \text{R}^2
\end{align*}
\]

wherein

- ring A is an optionally substituted 5- to 7-membered aryl, heteroaryl, or heterocyclyl ring;
- ring B is an optionally substituted 4- to 7-membered heteroaryl, or heterocyclyl ring;
- \( \text{R}^1 \) is a group independently selected from hydrogen, halogen, hydroxyl, cyano optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkylnyl, optionally substituted alkoxyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group;
- \( \text{R}^2 \) is a group independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkylnyl, optionally substituted alkoxyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group;
- or \( \text{R}^1 \) and \( \text{R}^2 \) may be joined together to form an optionally substituted 5- to 7-membered aryl, heteroaryl, or heterocyclyl ring;
- W is a bond or a group selected from optionally substituted alkyne, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heteroalkylene, optionally substituted heterocyclyl, optionally substituted acyl, \( \text{O}, \text{S}(0)_q \), wherein \( q \) is 0, 1, or 2, and \( \text{NR}^4 \), wherein \( \text{R}^4 \) is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; and
- Y is a bond or a group selected from optionally substituted alkyne, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene,
optionally substituted heteroarylene, optionally substituted heterocyclyl, optionally substituted acyl, O, S, S(0),...alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein ring A is an optionally substituted 5- or 6-membered heteroaryl or heterocyclyl ring containing from 1 to 4 heteroatoms selected from O, N and S.

3. A compound according to claim 1 or claim 2, wherein ring A is an optionally substituted 5- or 6-membered heteroaryl ring containing from 1 to 3 heteroatoms selected from O, N and S.

4. A compound according to any preceding claim, wherein ring B is an optionally substituted 5- or 6-membered heteroaryl or heterocyclyl ring containing from 1 to 4 heteroatoms selected from O, N and S.

5. A compound according to any preceding claim, wherein ring B is an optionally substituted 5- or 6-membered heteroaryl or heterocyclyl ring containing from 1 to 3 heteroatoms selected from O, N and S.

6. A compound according to any preceding claim, wherein R¹ and R² are joined together to form an optionally substituted 5- or 6-membered aryl or heteroaryl ring.

7. A compound according to any preceding claim, wherein W is a bond or a group selected from optionally substituted alkyne, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heterocyclyl, and optionally substituted acyl.

8. A compound according to any preceding claim, wherein W is an optionally substituted alkyne group, optionally substituted alkenylene group, an optionally substituted alkynylene group, an optionally substituted arylene group, an optionally substituted heterocyclyl group, or an optionally substituted acyl group.

9. A compound according to any preceding claim, wherein Y is a bond or a group selected from optionally substituted alkyne, O, S, S(0),...alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroarylene, optionally substituted heterocyclyl, and optionally substituted acyl;
substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

10. A compound according to any preceding claim, wherein Y is a group selected from optionally substituted alkyne, O, S, S(O)\(_q\), wherein q is 0, 1, or 2, and NR\(_4\), wherein R\(_4\) is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

11. A compound according to claim 1, wherein ring A is represented by a ring selected from:

![Rings](image_url)

each of which rings may be optionally further substituted.

12. A compound according to claim 1, wherein ring B is represented by a ring selected from:
each of which rings may be optionally further substituted.

13. A compound according to claim 1, of the formula (II):

wherein

R¹ is a group independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl.
optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group;

R\textsuperscript{2} is a group independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted amino, optionally substituted thiol, an oxo group, and a thioxo group;

or R\textsuperscript{1} and R\textsuperscript{2} may be joined together to form an optionally substituted 5- or 6-membered aryl or heteroaryl ring;

W is joined to a substitutable position at either Xi, X\textsubscript{2} or X\textsubscript{3}, and is a bond or a group selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

Y is a group selected from optionally substituted alkylene, O, S, S(0)\_q, wherein q is 0, 1, or 2, and NR\textsuperscript{4}, wherein R\textsuperscript{4} in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl

Xi is a group selected from O, S, NR\textsuperscript{5}, and CR\textsuperscript{6}R\textsuperscript{7}, wherein R\textsuperscript{5}, R\textsuperscript{6}, and R\textsuperscript{7} in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\textsuperscript{6} and R\textsuperscript{7} are taken together to form an oxo group or thioxo group; and

X\textsubscript{2} is a group selected from O, S, N, NR\textsuperscript{5}, CR\textsuperscript{6}R\textsuperscript{7}, and CR\textsuperscript{8}, wherein R\textsuperscript{5}, R\textsuperscript{6}, R\textsuperscript{7}, and R\textsuperscript{8} in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\textsuperscript{6} and R\textsuperscript{7} are taken together to form an oxo group or thioxo group;

X\textsubscript{3} is a group selected from O, S, N, NR\textsuperscript{5}, CR\textsuperscript{6}R\textsuperscript{7}, and CR\textsuperscript{8}, wherein R\textsuperscript{5}, R\textsuperscript{6}, R\textsuperscript{7}, and R\textsuperscript{8} in this context are each independently selected from hydrogen, halogen, hydroxyl,
optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ are taken together to form an oxo group or thioxo group;

$X_4$ is a group selected from O, S, N, NR$^5$, CR$^6$R$^7$, and CR$^8$, wherein $R^5$, $R^6$, $R^7$, and $R^8$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ are taken together to form an oxo group or thioxo group;

$X_5$ is a group selected from O, S, N, NR$^5$, CR$^6$R$^7$, and CR$^8$, wherein $R^5$, $R^6$, $R^7$, and $R^8$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ are taken together to form an oxo group or thioxo group;

U—V is a group which may be saturated or unsaturated, and U and V may be independently selected from O, N, NR$^5$, CR$^6$R$^7$, CR$^8$, S(0)$_q$, wherein $q$ is 0, 1, or 2, and either U or V, but not both, may be a combination of two atoms selected from R$^6$R$^7$C-CR$^6$R$^7$, R$^8$C=CR$^8$, R$^6$R$^7$C-S, R$^8$R$^7$C-NR$^5$, R$^8$C=N, S-NR$^5$, S=N, O-NR$^5$, R$^5$N-NR$^5$, and N=N, wherein $R^5$, $R^6$, $R^7$, $R^7$, and $R^8$ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or $R^6$ and $R^7$ or $R^6'$ and $R^7'$ are taken together to form an oxo group or thioxo group.

14. A compound according claim 1, of the formula (III):

![Diagram](image-url)

wherein
D, E, G, and H are each independently selected from N and CR\(^9\), wherein each R\(^9\) in this context is independently selected from hydrogen, halogen, hydroxyl cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

W is joined to a substitutable position at either Xi, X2 or X3, and is a bond or a group selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heterocyclyle, optionally substituted heterocyclyl, and optionally substituted acyl;

Y is a group selected from optionally substituted alkylene, O, S, S(0)\(^q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl

X1 is a group selected from O, S, NR\(^5\), and CR\(^6\)R\(^7\), wherein R\(^5\), R\(^6\), and R\(^7\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\(^6\) and R\(^7\) are taken together to form an oxo group or thioxo group;

X2 is a group selected from O, S, N, NR\(^5\), CR\(^6\)R\(^7\), and CR\(^8\), wherein R\(^5\), R\(^6\), R\(^7\), and R\(^8\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\(^6\) and R\(^7\) are taken together to form an oxo group or thioxo group;

X3 is a group selected from O, S, N, NR\(^5\), CR\(^6\)R\(^7\), and CR\(^8\), wherein R\(^5\), R\(^6\), R\(^7\), and R\(^8\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R\(^6\) and R\(^7\) are taken together to form an oxo group or thioxo group;
X₄ is a group selected from O, S, N, NR₅, CR₆R₇, and CR₈, wherein R₅, R₆, R₇, and R₈
in this context are each independently selected from hydrogen, halogen, hydroxyl,
only substituted alkyl, optionally substituted alkenyl, optionally substituted aryl,
only substituted aralkyl, optionally substituted heteroaryl, optionally substituted
heterocyclyl, and optionally substituted acyl, or R₆ and R₇ are taken together to form an
oxo group or thioxo group;

X₅ is a group selected from O, S, NR₅, and CR₆R₇, wherein R₅, R₆, and R₇ in this
context are each independently selected from hydrogen, halogen, hydroxyl, optionally
substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heteroaryl, optionally substituted
heterocyclyl, and optionally substituted acyl, or R₆ and R₇ are taken together to form an
oxo group or thioxo group;

U—V is a group which may be saturated or unsaturated, and U and V may be
independently selected from O, N, NR₅, CR₆R₇, CR₈, S(0)₉, wherein q is 0, 1, or 2, and
either U or V, but not both, may be a combination of two atoms selected from R₆R₇C-
CR₆R₇, R₈C=CR₅, R₆R₇C-S, R₆R₇C-NR₅, R₈C=N, S-NR₅, S=N, O-NR₅, R₅N-NR₅,
and N=N, wherein R₅, R₆, R₇, R₉, and R₈ in this context are each independently
selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally
substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally
substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted
acyl, or R₆ and R₇ or R₆ and R₇ are taken together to form an oxo group or thioxo
group.

15. A compound according to claim 1, of the formula (IV):

![Formula (IV)]

wherein

D, E, G, and H are each independently selected from N and CR₉, wherein each R₉ in
this context is independently selected from hydrogen, halogen, hydroxyl, cyano,
only substituted alkyl, optionally substituted alkenyl, optionally substituted
alkoxyl, optionally substituted ary1, optionally substituted aralkyl, optionally substituted
heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;
W is joined to a substitutable position at either \(X_i\), \(X_2\) or \(X_3\), and is a bond or a group selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene, optionally substituted heterocyclyl, and optionally substituted acyl;

\(Y\) is a group selected from optionally substituted alkylene, \(O, S, S(0)\), wherein \(q\) is 0, 1, or 2, and \(NR^4\), wherein \(R^4\) in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

\(X_i\) is a group selected from 0, \(S\), \(NR^5\), and \(CR^6R^7\), wherein \(R^5\), \(R^6\), and \(R^7\) in this context are each independently selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

\(X_2\) is a group selected from \(N\) and \(CR^8\), wherein \(R^8\) in this context is selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

\(X_3\) is a group selected from \(N\) and \(CR^8\), wherein \(R^8\) in this context is selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

\(X_4\) is a group selected from \(N\) and \(CR^8\), wherein \(R^8\) in this context is selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

\(X_5\) is a group selected from \(O, S, NR^5\), and \(CR^6R^7\), wherein \(R^5\), \(R^6\), and \(R^7\) in this context are each independently selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or \(R^6\) and \(R^7\) are taken together to form an oxo group or thioxo group; and
U—V is a group which may be saturated or unsaturated, and U and V may be independently selected from O, N, NR^5, CR^9R^7, CR^8, S(0)q, wherein q is 0, 1, or 2, and either U or V, but not both, may be a combination of two atoms selected from R^8R^7C-CR^6R^7, R^8C=CR^8, R^9R^7C-S, R^6R^7C-NR^i, R^8C=N, S-NR^5, S=N, O-NR^5, R^5N-NR^5, and N=N, wherein R^5, R^6, R^7, R^7, and R^8 in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R^6 and R^7 or R^6 and R^7 are taken together to form an oxo group or thioxo group.

16. A compound according to any of claims 13 to 15, wherein W is joined to a substitutable position at either X_2 or X_3, and X_i is NR^5, wherein R^5 in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

17. A compound according to any of claims 13 to 16, wherein X_5 is NR^5 and R^5 in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

18. A compound according to any of claims 13 to 17, wherein one or two of D, E, G, and H are N and the remaining groups are CR^9, wherein each R^9 in this context is selected from hydrogen, halogen, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

19. A compound according to any of claims 13 to 18, wherein U and V are each independently selected from O, NR^5, CR^9R^7, and S(0)q, wherein q is 0, 1, or 2, and wherein R^5, R^6, and R^7 in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl, or R^6 and R^7 are taken together to form an oxo group or thioxo group.
20. A compound according to any of claims 13 to 19, wherein Y is NR₄ and R₄ in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl.

21. A compound according to claim 1, of the formula (V):

![Chemical Structure](V)

wherein

D, E, G, and H are each CR⁹, and each R⁹ in this context is independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

W is a group selected from optionally substituted alkylene, optionally substituted alkenylene, and optionally substituted acyl;

Y is a group selected from optionally substituted alkylene, O, S, and NR⁴, wherein R⁴ in this context is a group selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

X₁ is NH;

X₂ is CR⁸, wherein R⁸ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

X₄ is N;

X₅ is NR⁵, wherein R⁵ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl,
optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocycyle, and optionally substituted acyl; and

V is CR₆R₇, wherein R₆ and R₇ in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocycyle, and optionally substituted acyl.

22. A compound according to claim 1, of the formula (VI):

![Diagram](image)

wherein

10 R⁹ is a group selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxyl;
(iv) cyano;

(v) C₁-₆ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably C₁ or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁-3 alkoxy (preferably methoxy), (e) C₁-3 alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) C₁-₆ alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably C₁ or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁-3 alkoxy (preferably methoxy), (e) C₁-3 alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carbonyloxy.
including carboxyl (preferably carboxyl or methyl ester), (h) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vii) \textit{C}\textsubscript{6-14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkylene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{i-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{1-6} alkyl, fluoro- or tert-butoxycarbonyl or benzyl, (f) C\textsubscript{i-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(viii) \textit{C}\textsubscript{7-16} aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkylene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{i-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl!; and

(ix) an \textit{ac} group optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkylene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl). (d) cyano. (e) amino, optionally mono-or di-substituted with C\textsubscript{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{i-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carbonyloxy, including carboxyl
(preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

R₈ is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) C₁₋₆ alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(v) C₂₋₆ alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) C₆₋₁₄ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkyne, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C₁₋₆ alkyl, tert-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(vii) C₇₋₁₆ aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkyne, said aryl is
phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifuoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, /<i>tert</i>-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(viii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifuoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C₁₋₆ alkyl, /<i>tert</i>-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

W is a group selected from:

(i) C₁₋₆ alkylene optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifuoromethyl), (c) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, /<i>tert</i>-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyl, including carboxyl (preferably carboxyl or methyl ester), (g) hydroxyl;

(ii) C₂₋₆ alkenylene optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloO₋₃ alkyl (preferably trifuoromethyl), (c) amino, optionally mono- or di-substituted with C₁₋₃ alkyl, /<i>tert</i>-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) C₁₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carbonyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl; and

(iii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkyene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC_{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C_{1-6} alkyl, /c/Y-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

Y is NR_{4}, wherein R_{4} in this context is a group selected from:

(i) hydrogen,

(ii) C_{1-6} alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC_{1-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C_{1-3} alkyl, tert-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{1-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C_{2-6} alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC_{1-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C_{1-3} alkyl, tert-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{1-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl

(iv) C_{6-14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkyene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3}
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) halo-C1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C7,i6 aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) halo-C1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) halo-C1-3 alkyl (preferably trifluoromethyl), (d) cyano. (e) amino, optionally mono-or di-substituted with C1-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

X5 is NR5, wherein R5 in this context is a group selected from:
(i) hydrogen,

(ii) C_i-6 alkyl optionally substituted with one to three substituents selected from
(a) halogen (preferably Cl or Br), (b) haloC_i-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C_1-3 alkyl, /tri-butoxycarbonyl or benzyl, (d) C_1-3 alkoxy (preferably methoxy), (e) C_i-3 alkyl carbonyl (preferably acetyl), (f) C_1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_i-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl:

(iii) C_2-6 alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC_i-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with C_1-3 alkyl, /tert-butoxycarbonyl or benzyl, (d) C_1-3 alkoxy (preferably methoxy), (e) C_i-3 alkyl carbonyl (preferably acetyl), (f) C_1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_i-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl

(iv) C_6-14 aryl optionally substituted with (1) a group selected from -J-aryl and -J-C_3-6 cycloalkyl, wherein J represents a bond or C_1-3 alkylene, said aryl is phenyl, and said C_3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC_i-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C_i-6 alkyl, /tert-butoxycarbonyl or benzyl, (f) C_1-3 alkoxy (preferably methoxy), (g) C_i-3 alkyl carbonyl (preferably acetyl), (h) C_1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C_i-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C_7-16 aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C_3-6 cycloalkyl, wherein J represents a bond or C_1-3 alkylene, said aryl is phenyl, and said C_3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_i-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC_i-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C_i-6 alkyl, /tert-butoxycarbonyl or
benzyl, (f) Ci-3 alkoxy (preferably methoxy), (g) Ci-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci-6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; and

V is CR6R7, wherein R6 and R7 in this context are each independently selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxyl;
(iv) Ci-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC1-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, tert-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(v) Ci-6 alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, tert-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy),


(e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxy:

(vi) C4,44 aryl optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C1-6 alkyl, /tri-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy;

(vii) C7-16 aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C1,6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; and

(viii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC1-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with C1,6 alkyl, /terZ-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1,3 alkyl carbonyl
23. A compound according to claim 1, of the formula (VII):

![Chemical Structure]

wherein

R^9 is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) cyano;

(v) C_{1-6} alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC_{1-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{1-3} alkyl, /e/7-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{1-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{1,3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) C_{1-6} alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC_{1-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{1-3} alkyl, /e/7-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{1-3} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vii) C_{14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkylcne. said aryl is
phenyl, and said C$_{3-6}$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C$_{1-3}$ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC$_{3-6}$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C$_{1-6}$ alkyl, tert-butoxycarbonyl or benzyl, (f) C$_{1-3}$ alkoxy (preferably methoxy), (g) C$_{1-3}$ alkyl carbonyl (preferably acetyl), (h) C$_{1-3}$ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C$_{1-3}$ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; and

(viii) C$_{7-16}$ aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C$_{3-6}$ cycloalkyl, wherein J represents a bond or C$_{1-3}$ alkylene, said aryl is phenyl, and said C$_{3-6}$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C$_{1-3}$ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC$_{3-6}$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C$_{1-6}$ alkyl, tert-butoxycarbonyl or benzyl, (f) C$_{1-3}$ alkoxy (preferably methoxy), (g) C$_{1-3}$ alkyl carbonyl (preferably acetyl), (h) C$_{1-3}$ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C$_{1-3}$ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy; and

(ix) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C$_{3-6}$ cycloalkyl, wherein J represents a bond or C$_{1-3}$ alkylene, said aryl is phenyl, and said C$_{3-6}$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C$_{1-3}$ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC$_{3-6}$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C$_{1-6}$ alkyl, tert-butoxycarbonyl or benzyl, (f) C$_{1-3}$ alkoxy (preferably methoxy), (g) C$_{1-3}$ alkyl carbonyl (preferably acetyl), (h) C$_{1-3}$ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C$_{1-3}$ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy;

R$^8$ is a group selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxy 1;
(iv) C₁₋₆ alkyl optionally substituted with one to three substituents selected from
(a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) Ci₋₉ alkoxy (preferably methoxy), (e) Ci₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C₁₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(v) C₂₋₆ alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC₁₋₃ alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C₁₋₃ alkyl, tert-butoxycarbonyl or benzyl, (d) C₁₋₃ alkoxy (preferably methoxy), (e) Ci₋₃ alkyl carbonyl (preferably acetyl), (f) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) Ci₋₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(vi) C₆₋₁₄ aryl optionally substituted with (1) a group selected from J-aryl and J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C₁₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci₋₆ alkyl, tert-butoxycarbonyl or benzyl, (f) C₁₋₃ alkoxy (preferably methoxy), (g) C₁₋₃ alkyl carbonyl (preferably acetyl), (h) C₁₋₃ alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C₁₋₃ alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;
(vii) C₇₋₁₆ aralkyl optionally substituted with (1) a group selected from J-aryl and J-C₃₋₆ cycloalkyl, wherein J represents a bond or C₁₋₃ alkylene, said aryl is phenyl, and said C₃₋₆ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) Ci₋₃ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC₁₋₃ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino,
optionally mono-or di-substituted with C_{1-6} alkyl, \textit{tert}-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and (viii) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkylene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) haloC_{3-6} alkyl (preferably trifluoromethyl), (d) cyano. (e) amino, optionally mono-or di-substituted with C_{1-6} alkyl, \textit{tert}-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; 

R^{10} is a group selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxyl;
(iv) cyano;
(v) C_{1-6} alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC_{3-6} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{1-3} alkyl, \textit{tert}-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{3-6} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(vi) C_{6} alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably Cl or Br), (b) haloC_{3-6} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C_{3-6} alkyl, \textit{tert}-butoxycarbonyl or benzyl, (d) C_{1-3} alkoxy (preferably methoxy), (e) C_{3-6} alkyl carbonyl (preferably acetyl), (f) C_{1-3} alkyl carboxyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C_{1-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxy-1:

(vii) Ce-14 aryl optionally substituted with (1) a group selected from -J-aryl and -J-alkyl, wherein J represents a bond or C_{1-3} alkylene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC_{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C_{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carboxyl, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(viii) C_{7-16} aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkylene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC_{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C_{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carboxyl, including carboxyl (preferably carboxyl or methyl ester), (i) C_{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(ix) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C_{3-6} cycloalkyl, wherein J represents a bond or C_{1-3} alkylene, said aryl is phenyl, and said C_{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C_{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC_{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C_{1-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C_{1-3} alkoxy (preferably methoxy), (g) C_{1-3} alkyl carbonyl (preferably acetyl), (h) C_{1-3} alkyl carboxyl, including carboxyl
(preferably carboxyl or methyl ester), (i) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

\( R^4 \) is a group selected from:

(i) hydrogen,

(ii) C\textsubscript{i-6} alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC\textsubscript{i-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C\textsubscript{i-3} alkyl, tert-butoxy carbonyl or benzyl, (d) C\textsubscript{i-3} alkoxy (preferably methoxy), (e) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (f) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C\textsubscript{2-6} alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloC\textsubscript{i-3} alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C\textsubscript{i-3} alkyl, tert-butoxy carbonyl or benzyl, (d) C\textsubscript{i-3} alkoxy (preferably methoxy), (e) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (f) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, and (g) hydroxyl

(iv) C\textsubscript{6-14} aryl optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{i-3} alkyne, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{i-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{i-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{i-3} alkoxy (preferably methoxy), (g) C\textsubscript{i-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{i-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C\textsubscript{7-16} aralkyl optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{i-3} alkyne, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{i-3}
alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci,6 alkyl, tert-butoxycarbonyl or benzyl, (f) Ci-3 alkoxy (preferably methoxy), (g) Ci,3 alkyl carbonyl (preferably acetyl), (h) Ci,3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) Ci,3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy!

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with Ci,6 alkyl, tert-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1,3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl;

R5 is a group selected from:

(i) hydrogen,

(ii) C1,6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloG-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, tert-butoxycarbonyl or benzyl, (d) C1,3 alkyl oxoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(iii) C2-6 alkenyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifluoromethyl), (c) amino, optionally mono-or di-substituted with C1-3
alkyl, teri-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy),
(e) C1-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carbonyloxy,
including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxyl

(iv) C6-H ary1 optionally substituted with (I) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC3-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, teri-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(v) C7-16 aralkyl optionally substituted with (I) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC3-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, teri-butoxycarbonyl or benzyl, (f) C1-3 alkoxy (preferably methoxy), (g) C1-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl; and

(vi) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C3-6 cycloalkyl, wherein J represents a bond or C1-3 alkylene, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC3-3 alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C1-6 alkyl, teri-butoxycarbonyl or
benzyl, (f) Ci-3 alkoxy (preferably methoxy), (g) Ci-3 alkyl carbonyl (preferably acetyl), (h) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C1-3 alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted acyl; and

R⁶ and R⁷ are each independently selected from:

(i) hydrogen;
(ii) halogen;
(iii) hydroxy 1;
(iv) Ci-6 alkyl optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloG-3 alkyl (preferably trifuoromethyl), (c) amino, optionally mono-or di-substituted with C1-3 alkyl, /er7-butoxycarbonyl or benzyl, (d) C1-3 alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) C1-3 alkyl carbamoyl, including carbamoyl, and (g) hydroxy 1;
(v) Ci-6 alkoxy optionally substituted with one to three substituents selected from (a) halogen (preferably CI or Br), (b) haloCi-3 alkyl (preferably trifuoromethyl), (c) amino, optionally mono-or di-substituted with Ci-3 alkyl, fert-butoxycarbonyl or benzyl, (d) Ci₃ alkoxy (preferably methoxy), (e) Ci-3 alkyl carbonyl (preferably acetyl), (f) C1-3 alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) Ci₃ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;
(vi) C₆₋₁₄ aryl optionally substituted with (1) a group selected from -J-aryl and -J-C₃₋₆ cycloalkyl, wherein J represents a bond or Ci₃ alkylenc, said aryl is phenyl, and said C3-6 cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C1-3 alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloCi-3 alkyl (preferably trifluoromethyl), (d) cyano. (e) amino, optionally mono-or di-substituted with Ci-₆ alkyl, fert-butoxycarbonyl or benzyl, (f) Ci-3 alkoxy (preferably methoxy), (g) Ci₃ alkyl carbonyl
(preferably acetyl), (h) \( \text{C}_{1-3} \) alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) \( \text{C}_{1-3} \) alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy. 

(vii) \( \text{C}_{7-i_6} \) aralkyl optionally substituted with (1) a group selected from \(-J\)-aryl and \(-J\)-\text{C}3.6 cycloalkyl, wherein \( J \) represents a bond or \( \text{C}_{1-3} \) alkyne, said aryl is phenyl, and said \( \text{C}_{3-6} \) cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) \( \text{C}_{1-3} \) alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) halo\( \text{C}_{1-3} \) alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with \( \text{C}_{i-6} \) alkyl, tert-butoxycarbonyl or benzyl, (f) \( \text{C}_{1-3} \) alkoxy (preferably methoxy), (g) \( \text{C}_{1-3} \) alkyl carbonyl (preferably acetyl), (h) \( \text{C}_{1-3} \) alkyl carbamoyl, including carboxyl (preferably carboxyl or methyl ester), (i) \( \text{C}_{1-3} \) alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy. 

(viii) an acyl group optionally substituted with (1) a group selected from \(-J\)-aryl and \(-J\)-\text{C}3.6 cycloalkyl, wherein \( J \) represents a bond or \( \text{C}_{1-3} \) alkyne, said aryl is phenyl, and said \( \text{C}_{3-6} \) cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) \( \text{C}_{1-3} \) alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) halo\( \text{C}_{1-3} \) alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono- or di-substituted with \( \text{C}_{i-6} \) alkyl, ieri-butoxycarbonyl or benzyl, (f) \( \text{C}_{1-3} \) alkoxy (preferably methoxy), (g) \( \text{C}_{1-3} \) alkyl carbonyl (preferably acetyl), (h) \( \text{C}_{1-3} \) alkyl carbamoyl, including carboxyl (preferably carboxyl or methyl ester), (i) \( \text{C}_{1-3} \) alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxy. 

\( n \) is 0, 1, 2, or 3.

24. A compound according to claim 1, of the formula (VIII):
wherein

$R^9$ is a group selected from:

(i) hydrogen;

(ii) halogen;

(iii) hydroxyl;

(iv) cyano;

(v) $C_1-6$ alkyl optionally substituted with one to three substituents selected from
   (a) halogen (preferably CI or Br), (b) halo$C_1-3$ alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with $C_1-3$ alkyl, tert-butoxycarbonyl or benzyl, (d) $C_1-3$ alkoxy (preferably methoxy), (e) $C_1-3$ alkyl carbonyl (preferably acetyl), (f) $C_1-3$ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) $C_1-3$ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vi) $C_1-6$ alkoxy optionally substituted with one to three substituents selected from
   (a) halogen (preferably CI or Br), (b) halo$C_1-3$ alkyl (preferably trifluoromethyl), (c) amino, optionally mono- or di-substituted with $C_1-3$ alkyl, tert-butoxycarbonyl or benzyl, (d) $C_1-3$ alkoxy (preferably methoxy), (e) $C_1-3$ alkyl carbonyl (preferably acetyl), (f) $C_1-3$ alkyl carbonyloxy, including carboxyl (preferably carboxyl or methyl ester), (h) $C_1-3$ alkyl carbamoyl, including carbamoyl, and (g) hydroxyl;

(vii) $C_6-14$ ary1 optionally substituted with (1) a group selected from -J-aryl and -J-$C_3-6$ cycloalkyl, wherein J represents a bond or $C_1-3$ alky1ene, said aryl is phenyl, and said $C_3.6$ cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) $C_1-3$ alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably Cl or Br), (c) halo$C_1-3$ alkyl (preferably trifluoromethyl), (d) cyano, (e) amino.
optionally mono-or di-substituted with C\textsubscript{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{1-3} alkoxy (preferably methoxy), (g) C\textsubscript{1-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(viii) C\textsubscript{7-16} aralkyl optionally substituted with (1) a group selected from -j-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkyene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{1-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{1-3} alkoxy (preferably methoxy), (g) C\textsubscript{1-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl;

(ix) an acyl group optionally substituted with (1) a group selected from -J-aryl and -J-C\textsubscript{3-6} cycloalkyl, wherein J represents a bond or C\textsubscript{1-3} alkyene, said aryl is phenyl, and said C\textsubscript{3-6} cycloalkyl is selected from cyclopropyl, cyclopentyl and cyclohexyl, and/or (2) one to three substituents selected from (a) C\textsubscript{i-3} alkyl (preferably methyl, ethyl or isopropyl), (b) halogen (preferably CI or Br), (c) haloC\textsubscript{1-3} alkyl (preferably trifluoromethyl), (d) cyano, (e) amino, optionally mono-or di-substituted with C\textsubscript{i-6} alkyl, tert-butoxycarbonyl or benzyl, (f) C\textsubscript{1-3} alkoxy (preferably methoxy), (g) C\textsubscript{1-3} alkyl carbonyl (preferably acetyl), (h) C\textsubscript{i-3} alkyl carboxyloxy, including carboxyl (preferably carboxyl or methyl ester), (i) C\textsubscript{1-3} alkyl carbamoyl, including carbamoyl, (j) nitro, and (k) hydroxyl.

25. A compound according to claim 1, of the formula (IX):

![Chemical Structure](image)

(IX)

wherein
ring A is an optionally substituted aryl ring;
W is an optionally substituted alkylene group;
Y is a group selected from O, S, S(0)\(^q\), wherein q is 0, 1, or 2, and NR\(^4\), wherein R\(^4\) is a group selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl;

\(X_4\) is a group selected from N and CR\(^8\), wherein R\(^8\) in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl;

\(X_5\) is a group selected from O, S, NR\(^5\), and CR\(^6\)R\(^7\), wherein R\(^5\), R\(^6\), and R\(^7\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl, or R\(^6\) and R\(^7\) are taken together to form an oxo group or thioxo group; and

U—V is a group which may be saturated or unsaturated, and U and V may be independently selected from 0, N, NR\(^5\), CR\(^6\)R\(^7\), CR\(^8\), S(0)\(^q\), wherein q is 0, 1, or 2, and either U or V, but not both, may be a combination of two atoms selected from R\(^5\)R\(^7\)C-CR\(^6\)R\(^7\), R\(^8\)C=CR\(^8\), R\(^6\)R\(^7\)C-S, R\(^6\)R\(^7\)C-NR\(^5\), R\(^8\)C=N, S-NR\(^5\), S=N, O-NR\(^5\), R\(^3\)N-NR\(^5\), and N=N, wherein R\(^5\), R\(^6\), R\(^6\)', R\(^7\), R\(^7\)', and R\(^8\) in this context are each independently selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl, or R\(^6\) and R\(^7\) or R\(^6\)' and R\(^7\)' are taken together to form an oxo group or thioxo group.

26. A compound according to claim 1, of the formula (X):

![Diagram](attachment:diagram.png)

wherein

ring B is an optionally substituted 6-membered heterocyclyl or heteroaryl ring;
D, E, G, and H are each independently selected from N and CR\(^9\), wherein each R\(^9\) in this context is independently selected from hydrogen, halogen, hydroxyl, cyano, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, and optionally substituted aralkyl;
W is joined to a substitutable position at either $X_2$ or $X_3$, and is an optionally substituted alkylene group;

Y is a group selected from O, S, S(0)$_q$ wherein q is 0, 1, or 2, and NR$^4$, wherein R$^4$ is a group selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl;

$X_i$ is a group selected from O, S, and NR$^5$, wherein R$^5$ in this context is selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl;

$X_2$ is a group selected from N and CR$^8$, wherein R$^8$ in this context is selected from hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl; and

$X_3$ is a group selected from N and CR$^8$, wherein R$^8$ in this context is selected from hydrogen, halogen, hydroxyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted aralkyl.

27. A compound according to claim 1, which is 2-[(1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one:

![](image)

28. A compound according to claim 1, which is 3-Acetyl-2-[(5-hydroxy-1H-indol-3-yl)-ethylamino]-3,5-dihydroimidazol-4-one:

![](image)
29. A compound according to claim 1, which is 2-[2-(1H-Indol-3-yl)-ethanolamino]-5,5-dimethylloxazol-4-one:

![Chemical Structure](image)

30. A compound according to claim 1, which is 2-( Phenethylamino)-1,5-dihydro-4H-5-imidazol-4-one:

![Chemical Structure](image)

31. A compound according to claim 1, which is 6-Hydroxy-4-[1H-indol-3-yl]-ethylamino]-1/-pyrimidin-2-one:

![Chemical Structure](image)

32. A composition comprising a compound according to any preceding claim, and one or more pharmaceutically acceptable excipients.

33. A compound according to any one of claims 1 to 31, or a composition according to claim 32, for use in therapy.
34. A compound according to any one of claims 1 to 31, or a composition according to claim 32, for use in the prophylaxis or treatment of neural injury.

35. A compound according to any one of claims 1 to 31, or a composition according to claim 32, for use in the prophylaxis or treatment of cancer, multiple sclerosis, glaucoma, arthritis, rheumatoid arthritis, lupus, Alzheimer's disease, and ulcerative colitis.

36. A compound or composition for use according to claim 35, wherein the cancer is ovarian or prostate cancer.

37. A composition according to claim 32, containing one or more additional active pharmaceutical ingredients.

38. A method of preventing or treating neural injury, cancer, multiple sclerosis, arthritis, rheumatoid arthritis, lupus, Alzheimer's disease, and/or ulcerative colitis in a subject comprising administering a prophylactically or therapeutically effective amount of a compound according to any one of claims 1 to 31 or a composition according to claim 32 or claim 37.
Figures

**Figure 1**

**Imidazolin-4-one 3**

% cell survival

Concentration (µM)

**Cl-amidine**

% cell survival

Concentration (µM)

**Figure 2**

**Imidazolin-4-one 3**

Abs 490nm

control 10nM 100nM 1µM 10µM 100µM

**Cl-amidine**

Abs 490nm

control 10nM 100nM 1µM 10µM 100µM

**Notes:**
- **control**
- **10nM**
- **100nM**
- **1µM**
- **10µM**
- **100µM**

**Significance levels:**
- **NS**
- ****
- ****
- ****
Figure 7

% CELL SURVIVAL

TREATMENTS
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/12 C07D233/88 A61K31/4178 A61K31/4168 A61K31/506
A61P35/00 A61P25/28 A61P19/02

ADD.

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

B. FIELDS SEARCHED

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

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

EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2012/127032 AI (CHEMI LIA AB [SE]; HOEGBERG MARITA [SE]; DAHLSTEDT EMMA [SE]; SMITT 0L0) 27 September 2012 (2012-09-27) claims 1,38,42</td>
<td>1,35,38</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
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*"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

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Date of the actual completion of the international search

26 August 2014

Date of mailing of the international search report

02/09/2014

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Schuemacher, Anne

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>EP 2 395 001 Al (CHEMIA AB [SE]) 14 December 2011 (2011-12-14) claims 1.34; examples 1-42</td>
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<td>SUTIN ET AL: &quot;Oxazolones as potent inhibitors of llbeta-hydroxysteroid dehydrogenase type 1&quot;, BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 17, no. 17, 4 August 2007 (2007-08-04), pages 4837-4840, XP022184919, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2007.06.054 table 2; compounds 18, 19</td>
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**INTERNATIONAL SEARCH REPORT**

**PCT/GB2014/051563**

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<td>W0 2009/127048 AI (HOSPITAL FOR SICK CHILDREN [CA]; MASTRONARDI FABRIZIO [CA]; MOSCARELLO) 22 October 2009 (2009-10-22) claims 1</td>
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