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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HURST, David, Nigel** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **KING, Nigel, Paul** [GB/SG]; GlaxoSmithKline, Biopolis at One-North, The Helios Block, #03-01/02, 11 Biopolis Way, Singapore 138667 (SG). **MAK, Sing, Yeung** [CN/SG]; GlaxoSmithKline, Biopolis at One-North, The Helios Block, #03-01/02, 11 Biopolis Way, Singapore 138667 (SG). **SCOCCITTI, Tiziana** [IT/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **SKIDMORE, John** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB).

(74) Agents: **MUELLER, Philippe** et al.; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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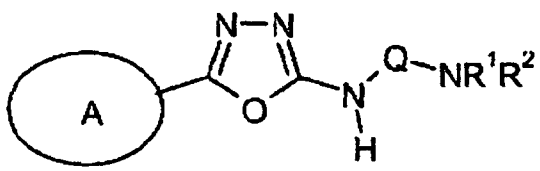
(54) **Title:** OXADIAZOLE DERIVATIVES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RECEPTOR MODULATORS



(I)

(57) **Abstract:** Oxadiazole derivatives of formula (I) where ring A is a bicyclic or tricyclic system. Claimed compounds are active on nicotinic acetylcholine receptors (nAChRs), and are useful to treat neurological, psychiatric, and gastrointestinal disorders, as well as sepsis and obesity.

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OXADIAZOLE DERIVATIVES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RECEPTOR MODULATORS

The present invention relates to novel oxadiazole derivatives having pharmacological activity, processes for their preparation, compositions containing them and their use in the treatment of neurological, psychiatric disorders and gastrointestinal disorders.

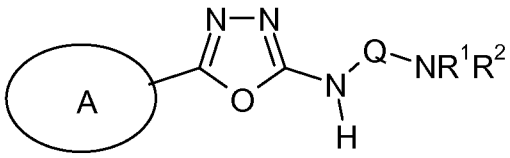
Nicotinic acetylcholine receptors (nAChRs) are cation-specific, excitatory ligand-gated ion channels that are widely expressed throughout the central and peripheral nervous systems. To date, 16 mammalian nAChR subunit genes have been cloned: 5 encoding muscle receptor subunits, and 11 encoding neuronal receptor subunits. The nicotinic α7 receptor subunit is predominantly expressed in the mammalian central nervous system (CNS), where it is thought to assemble as a functional homopentameric complex, and is also expressed in peripheral tissues including the sympathetic nervous system, immune cells and the GI tract. Activation of neuronal nicotinic α7 receptors by selective agonists or the endogenous ligand acetylcholine can modulate the release of various neurotransmitters including glutamate, GABA, dopamine, and noradrenaline and, thus, has the potential to modulate a range of neurological functions. Additionally, *in vivo* studies have shown that α7 nAChR agonists can modulate neurotransmitter release in brain areas such as the cortex and hippocampus that are relevant to cognition (Paterson D *et al*, (2000) Prog Neurobiol **61**:75-111.

A number of literature reports have demonstrated the cognitive enhancing properties of α7 nAChR agonists (e.g. GTS-21 (3-(2,4-dimethoxybenzylidene)anabaseine), AR-R 17779 ((-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazoldin-2'-one] 4-propyl-benzylidene anabaseine) and SSR-180771 (4-bromophenyl 1,4-diazabicyclo[3.2.2]nonane-4-carboxylate hydrochloride) in rodent and primate cognition models including the radial arm maze (Levin E.D. *et al.* (1999), Behavioural Pharmacology. **10(6-7)**:675-80), social recognition (Van Kampen M. *et al.* (2004) Psychopharmacology. **172(4)**:375-83), elevated plus maze/delayed matching-to-sample test (Briggs C.A. *et al.* (1997) Pharmacology, Biochemistry & Behavior. **57(1-2)**:231-41), active avoidance and radial arm maze (Arendash G.W. *et al.* (1995) Brain Research. **674(2)**:252-9).

Consistent with these animal studies, recent data from small clinical trials demonstrates that the α7 nAChR partial agonist GTS-21 enhanced memory and attention in healthy volunteers (Kitagawa H. *et al.* (2003) Neuropsychopharmacology. **28(3)**:542-51). Furthermore, beneficial effects of nicotine on attention parameters have also been

demonstrated in Alzheimer's disease (Potter A. and Levin E.D. (1997) Drugs & Aging. **11(3)**:206-28), age-associated memory impairments (White H.K. and Levin E.D. (2004), Psychopharmacology. **171(4)**:465-71) and attention deficit disorder (Levin E.D. *et al.* (1996) Psychopharmacology. **123(1)**:55-63). Activation of α7 nAChRs has also been reported to ameliorate sensory gating deficits in both preclinical (Simosky J.K. *et al.*, (2001) Biological Psychiatry. **50(7)**:493-500) and small clinical studies. These data suggest that novel α7 nAChR agonists and/or partial agonists such as the current series could be useful for the treatment of cognitive impairments in neurological and psychiatric disorders such as Alzheimer's disease, related neurodegenerative disorders and schizophrenia.

The present invention provides, in a first aspect, compounds of formula (I) or a salt thereof:



(I)

wherein

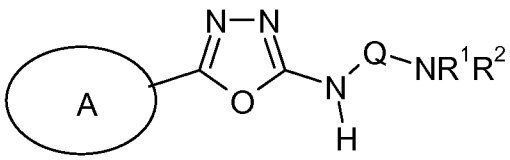
R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or C_{3-6}cycloalkyl;

or R^1 and R^2 together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclyl group which is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro;

Q represents $-(CH_2)_n-$ wherein n represents 3 or 4;

A is selected from a 9 to 10 membered fused bicyclic ring system containing 0, 1, 2 or 3 heteroatoms selected from O, N and S with a maximum of 2 heteroatoms present in the same ring, which fused bicyclic ring system which can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl or if at least two substituents are present two of the substitutents can together form a third ring, and 9*H*-β-carbolinyl.

In one embodiment of the invention, the compounds of the invention are compounds of formula (I) or a salt thereof:



(I)

wherein

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or C_{3-6}cycloalkyl;

or R^1 and R^2 together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclyl group which is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro;

Q represents $-(CH_2)_n-$ wherein n represents 3 or 4;

A represents a 9 to 10 membered fused bicyclic ring system containing 0, 1, 2 or 3 heteroatoms selected from O, N and S with a maximum of 2 heteroatoms present in the same ring, which fused bicyclic ring system which can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl or if at least two substituents are present two of the substitutents can together form a third ring.

The term 'C_{1-6} alkyl' as used herein as a group or a part of the group refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like. Unless a particular structure is specified, the terms propyl, butyl etc include all straight and branched chain forms having the appropriate number of carbon atoms e.g. propyl includes n-propyl and isopropyl.

The term 'C_{1-6} alkoxy' as used herein refers to an $-O-C_{1-6}$ alkyl group wherein C_{1-6} alkyl is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy and the like. As for alkyl unless a particular stucture is specified the terms propoxy, butoxy etc include all straight and branched chain forms having the appropriate number of carbon atoms e.g. propoxy includes n-propoxy and isopropoxy.

The term 'halo' as used herein refers to a fluorine, chlorine, bromine or iodine atom.

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

The term "nitrogen containing heterocyclyl group" includes a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system, a 6-9 membered saturated or partially unsaturated bridged ring system or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing a nitrogen atom in addition to

1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl, morpholinyl, hexahydroazepanyl, hexahydrodiazepanyl and homomorpholinyl. Examples of such bridged ring systems are azabicycloheptanyl and azabicyclononanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepinyl or tetrahydroisoquinolinyl.

The term 9 to 10 membered fused bicyclic ring system includes but is not limited to the following ring systems indolinyl, indolyl, isoindolinyl, isoindolyl, indenyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzoxazinyl, benzopyranyl, benzothiopyranyl, quinolinyl, isoquinolinyl, chromenyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, naphthyl, dihydrobenzoxazinyl, dihydrochromenyl, dihydrobenzodioxinyl, tetrahydroquinolinyl, tetrahydroquinoxalinyl, tetrahydronaphthalenyl dihydrobenzofuranyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, dihydrobenzothienyl, dihydrodioxinopyridinyl, dihydroindenyl, dihydropyrrolopyridinyl, dihydropyrrolopyrimidinyl, dihydropyrrolopyrazinyl, dihydropyrrolopyridazinyl, pyrrolopyridinyl, pyrrolopyrazinyl, pyrrolopyridazinyl, pyrrolopyrimidinyl, furopyrimidinyl, furopyrazinyl, furopyridazinyl, thienopyridinyl, thienopyrazinyl, thienopyridazinyl, thienopyrimidinyl, pyrazolopyridinyl, pyrazolopyrazinyl, pyrazolopyridazinyl, pyrazolopyrimidinyl, imidazopyridinyl, imidazopyrazinyl, imidazopyridazinyl, imidazopyrimidinyl, thiazolopyridinyl, thiazolopyrazinyl, thiazolopyridazinyl, thiazolopyrimidinyl, oxazolopyridinyl, oxazolopyrazinyl, oxazolopyridazinyl, oxazolopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, pyridopyrimidinyl, pyridooxazinyl, pyrazinooxazinyl, pyridazinooxazinyl, pyrimidooxazinyl, dihydropyridooxazinyl, dihydropyrazinooxazinyl, dihydropyridazinooxazinyl, dihydropyrimidooxazinyl, dihydropyranopyridinyl, dihydropyranopyrazinyl, dihydropyranopyridazinyl, dihydropyrimidinyl, pyranopyridinyl, pyranopyrimidinyl, pyranopyrazinyl, pyranopyridazinyl, dihydrodioxinopyridinyl, dihydrodioxinopyrazinyl, dihydrodioxinopyridazinyl, dihydrodioxinopyrimidinyl, tetrahydronaphthyridinyl, tetrahydropyridopyridazinyl, tetrahydropyridopyrazinyl, tetrahydropyridopyrimidinyl, tetrahydropyrazinopyridazinyl, tetrahydropteridinyl, tetrahydropyrazinopyrazinyl, tetrahydroquinolinyl, tetrahydrocinnolinyl, tetrahydroquinazolinyl, tetrahydroquinoxalinyl, thiinopyridinyl, thiinopyrazinyl, thiinopyridazinyl, thiinopyrimidinyl, dihydrothiinopyridinyl, dihydrothiinopyrazinyl, dihydrothiinopyridazinyl, dihydrothiinopyrimidinyl, dihydrofuropyridinyl, dihydrofuropyrazinyl, dihydrofuropyridazinyl, dihydrofuropyrimidinyl, dihydrothienopyridinyl, dihydrothienopyrazinyl, dihydrothienopyridazinyl,

dihydrothienopyrimidinyl, dihydrocyclopentapyridinyl, dihydrocyclopentapyrazinyl, dihydrocyclopentapyridazinyl and dihydrocyclopentapyrimidinyl.

Alternatively, the term "fused bicyclic ring system" includes but is not limited to the following ring systems thienofuranyl, indolizinyl, indolinyl, isoindolinyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzothiazolyl, imidazopyridinyl, benzoxazolyl, quinolinyl, quinolizinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl and naphthyl.

It will be appreciated that the fused bicyclic ring system can be bonded to the oxadiazole core through either ring in the ring system.

In one embodiment A represents a 9 to 10 membered fused bicyclic ring system containing 0, 1 or 2 heteroatoms selected from O, N and S.

In one embodiment Q represents $-(CH_2)_n-$ wherein n is 4. In another embodiment, Q represents $-(CH_2)_n-$ wherein n is 3.

In one embodiment, R^1 and R^2 together with the nitrogen atom which they are attached form a nitrogen containing heterocyclyl group e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the heterocyclyl group is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro.

In one embodiment, R^1 and R^2 together with the nitrogen atom which they are attached form a nitrogen containing heterocyclyl group e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the heterocyclyl group is unsubstituted.

In one embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur, and which monocyclic ring system is unsubstituted.

In one embodiment A is selected from indolinyl, benzofuranyl, benzothienyl, benzothiazolyl, imidazopyridinyl, benzimidazolyl, benzoxazolyl and quinolinyl.

In one embodiment where A is substituted by at least two substituents and two substituents form a third ring this may be a C5-6 carbocyclic or 5-6 membered heterocyclic ring, e.g. pyrrolidinyl or piperidinyl.

In one embodiment when A is substituted the substituents are independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo and phenyl.

In one embodiment, A may be selected from indolinyl, benzofuranyl, benzothienyl, benzothiazolyl, imidazopyridinyl, benzimidazolyl, benzoxazolyl and quinolinyl and A is bonded to the oxadiazole core through the phenyl ring of the bicyclic ring system.

In one embodiment A is selected from indolinyl, benzofuranyl, quinolinyl and benzothienyl and A is bonded to the oxadiazole core through the ring containing the heteroatom.

In one embodiment, A represents a 9 to 10 membered fused bicyclic ring system selected from indolyl, benzothiazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl and pyrrolopyridinyl, each of which 9 to 10 membered fused bicyclic ring system can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo and phenyl.

In one embodiment , A is selected from
- indolyl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl, C_{1-6} alkyl and C_{1-6} alkoxy;
- benzothiazolyl which is unsubstituted or substituted with 1 substituent selected from C_{1-6} alkyl and halo;
- unsubstituted imidazopyridinyl;
- unsubstituted benzothienyl;
- unsubstituted benzofuranyl;
- unsubstituted quinolinyl;
- unsubstituted isoquinolinyl;
- benzimidazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl and C_{1-6} alkyl;
- benzoxazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolopyridinyl which is unsubstituted or substituted with 1 substituent selected from C_{1-6} alkyl.

In one embodiment , A is selected from
- indolyl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl, methyl and methoxy;
- benzothiazolyl which is unsubstituted or substituted with 1 substituent selected from methyl and chloro;
- unsubstituted imidazopyridinyl;
- unsubstituted benzothienyl;
- unsubstituted benzofuranyl;
- unsubstituted quinolinyl;
- unsubstituted isoquinolinyl;
- benzimidazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl and methyl;
- benzoxazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolopyridinyl which is unsubstituted or substituted with 1 substituent selected from methyl. In a more particular embodiment, benzothiazolyl is unsubstituted or substituted with 1 substituent selected from methyl.

In one embodiment of the invention, A is selected from
- indol-5-yl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl and methyl;
- unsubstituted indol-7-yl;
- indol-3-yl which is unsubstituted or substituted with 1 substituent selected from phenyl, methyl and methoxy;
- indol-6-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- indol-4-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted indol-2-yl;
- benzothiazol-6-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted benzothiazol-2-yl;
- unsubstituted imidazopyridin-6-yl;
- unsubstituted benzothien-2-yl;
- unsubstituted benzothien-3-yl;
- unsubstituted benzofuran-5-yl;
- unsubstituted benzofuran-2-yl;

- unsubstituted quinolin-3-yl;
- unsubstituted isoquinolin-4-yl;
- benzimidazol-5-yl which is unsubstituted or substituted with 1 substituent selected from phenyl and methyl;
- benzoxazol-6-yl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolo[2,3-b]pyridin-4-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted pyrrolo[2,3-b]pyridin-5-yl;
- unsubstituted pyrrolo[2,3-b]pyridin-2-yl; and
- unsubstituted pyrrolo[2,3-b]pyridin-3-yl.

In a more particular embodiment, benzothiazol-2-yl is unsubstituted or substituted with 1 substituent selected from methyl.

In one embodiment, A is indol-5-yl which is substituted with 1or 2 substituents selected from phenyl and methyl or unsubstituted indol-3-yl.

In one embodiment, A represents a 9 to 10 membered fused bicyclic ring system containing 0, 1 or 2 heteroatoms selected from O, N and S, which is substituted with at least two substituents which form a third ring, said third ring is selected from C5-6 carbocyclic or 5-6 membered heterocyclic ring, e.g. pyrrolidinyl or piperidinyl. In a particular embodiment, A is unsubstituted dihydro-pyrrolo-[1,2-a]-benzimidazolyl.

In one embodiment, A is unsubstituted 9*H*-β-carbolinyl.

In one embodiment, A represents a 9 to 10 membered fused bicyclic ring system selected from indolyl, benzothiazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl and pyrrolopyridinyl, each of which fused bicyclic ring system can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo and phenyl, and Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur,

e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted.

In one embodiment, A is selected from
- indolyl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl, C_{1-6} alkyl and C_{1-6} alkoxy;
- benzothiazolyl which is unsubstituted or substituted with 1 substituent selected from C_{1-6} alkyl and halo;
- unsubstituted imidazopyridinyl;
- unsubstituted benzothienyl;
- unsubstituted benzofuranyl;
- unsubstituted quinolinyl;
- unsubstituted isoquinolinyl;
- benzimidazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl and C_{1-6} alkyl;
- benzoxazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolopyridinyl which is unsubstituted or substituted with 1 substituent selected from C_{1-6} alkyl

and

Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur,
e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted.

In one embodiment, A is selected from
- indolyl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl, methyl, methoxy and chloro;
- benzothiazolyl which is unsubstituted or substituted with 1 substituent selected from methyl and chloro;
- unsubstituted imidazopyridinyl;
- unsubstituted benzothienyl;

- unsubstituted benzofuranyl;
- unsubstituted quinolinyl;
- unsubstituted isoquinolinyl;
- benzimidazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl and methyl;
- benzoxazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolopyridinyl which is unsubstituted or substituted with 1 substituent selected from methyl; and

wherein Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur,
e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted. In a more particular embodiment, benzothiazolyl is unsubstituted or substituted with 1 substituent selected from methyl.

In one embodiment, A is selected from
- indol-5-yl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl and methyl;
- unsubstituted indol-7-yl;
- indol-3-yl which is unsubstituted or substituted with 1 substituent selected from phenyl, methyl and methoxy;
- indol-6-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- indol-4-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted indol-2-yl;
- benzothiazol-6-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted benzothiazol-2-yl;
- unsubstituted imidazopyridin-6-yl;
- unsubstituted benzothien-2-yl;
- unsubstituted benzothien-3-yl;
- unsubstituted benzofuran-5-yl;
- unsubstituted benzofuran-2-yl;
- unsubstituted quinolin-3-yl;

- unsubstituted isoquinolin-3-yl;
- benzimidazol-5-yl which is unsubstituted or substituted with 1 substituent selected from phenyl and methyl;
- benzoxazol-6-yl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolo[2,3-b]pyridin-4-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted pyrrolo[2,3-b]pyridin-5-yl;
- unsubstituted pyrrolo[2,3-b]pyridin-2-yl; and
- unsubstituted pyrrolo[2,3-b]pyridin-3-yl;

and wherein Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur, e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted.

In one embodiment, A is indol-5-yl which is substituted with 1or 2 substituents selected from phenyl and methyl or unsubstituted indol-3-yl, and Q represents $-(CH_2)_n-$ wherein n represents 4, and R^1 and R^2 together with the nitrogen atom which they are attached form a nitrogen containing heterocyclyl group selected from piperidinyl, morpholinyl and pyrrolidinyl wherein the heterocyclyl group is unsubstituted.

In one embodiment, A represents a 9 to 10 membered fused bicyclic ring system containing 0, 1 or 2 heteroatoms selected from O, N and S, which is substituted with at least two substituents which form a third ring, said third ring is selected from C5-6 carbocyclic or 5-6 membered heterocyclic ring, e.g. pyrrolidinyl or piperidinyl; and Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur,
e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted. In one embodiment, the 4-7 membered monocyclic

saturated or partially unsaturated aliphatic ring system containing a nitrogen atom is selected from piperidinyl, morpholinyl and pyrrolidinyl.

In one embodiment, A is unsubstituted dihydro-pyrrolo-[1,2-a]-benzimidazolyl, Q represents $-(CH_2)_n-$ wherein n represents 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur,
e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted.

In one embodiment, A is unsubstituted 9*H*-β-carbolinyl, Q represents $-(CH_2)_n-$ wherein n represents 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur, e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted.

In one embodiment A is selected from indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzamidazolyl and benzoxazolyl wherein A is unsubstituted or substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo and phenyl, and A is bonded to the oxadiazole core through the phenyl ring of the bicyclic ring system, Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur,
e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the monocyclyl ring is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro, particularly the monocyclic ring is unsubstituted.

In one embodiment, A is selected from indolyl, benzofuranyl, benzothiazolyl, quinolinyl, isoquinolinyl, imidazopyridinyl, pyrolopyridinyl and benzothienyl wherein A is unsubstituted or substituted with 1 to 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo and phenyl, and A is bonded to the oxadiazole core through a ring containing a

heteroatom, and Q represents $-(CH_2)_n-$ wherein n represents 3 or 4, and R^1 and R^2 together with the nitrogen atom which they are attached form a nitrogen containing heterocyclyl group e.g. piperidinyl, morpholinyl, pyrrolidinyl wherein the heterocyclyl group is unsubstituted.

Compounds of formula (I) and salts thereof include the compounds of Examples 1 to 38 and salts thereof.

In one embodiment, a compound of formula (I) or a salt thereof is selected from a compound of Examples 1, 2, 8, 22, 26 and 28, or a salt thereof.

It is to be understood that the present invention encompasses all isomers of formula (I) and their salts including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The present invention may also includes isotopically-labelled compounds, which are identical to the compounds of formula (I), except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{35}S, ^{123}I and ^{125}I.
Compounds of the present invention and salts and solvates of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and/or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. ^{3}H and ^{14}C are considered useful due to their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are considered useful in PET (positron emission tomography), and ^{125}I isotopes are considered useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Substitution with heavier isotopes such as ^{2}H may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced

dosage requirements and, hence, are considered useful in some circumstances. In one embodiment, the compounds of formula (I) are not isotopically labelled.

Certain compounds of formula (I) may be prepared in crystalline or non-crystalline form, and may be optionally solvated, e.g. hydrated. Where solvates exist, this invention includes within its scope stoichiometric solvates as well as compounds containing variable amounts of solvate.

Because of the potential use of compounds of formula (I) in medicine, salts of compounds of formula (I) are preferably pharmaceutically acceptable.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, ethanedisulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In some circumstances some salts may be non-stoichiometric.

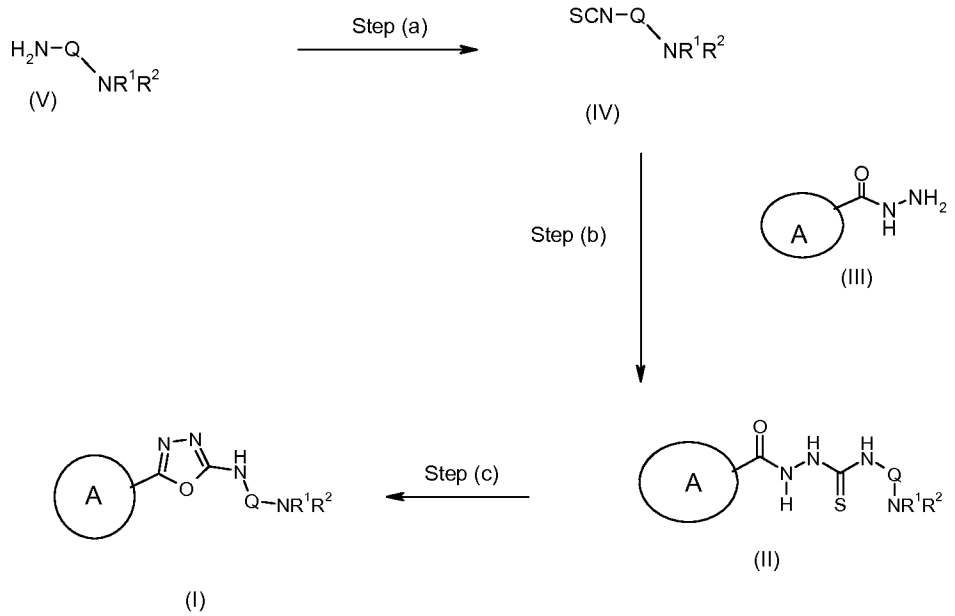
Compounds of formula (I) can be prepared as set forth in the following Schemes and in the Examples. The following processes form another aspect of the present invention.

The present invention also provides processes for the preparation of a compound of formula (I) or a salt thereof:

Process (a):

Compounds of formula (I) may be prepared in accordance with the following Scheme 1:

Scheme 1



wherein A, Q, R^1 and R^2 are as defined for compounds of formula (I).

Step (a) typically comprises the use of a suitable reagent, such as 1,1-thiocarbonyldiimidazole or both carbon disulfide and a coupling agent such as dicyclohexylcarbodiimide in a suitable solvent such as ether, THF or DMF and at a suitable temperature such as room temperature.

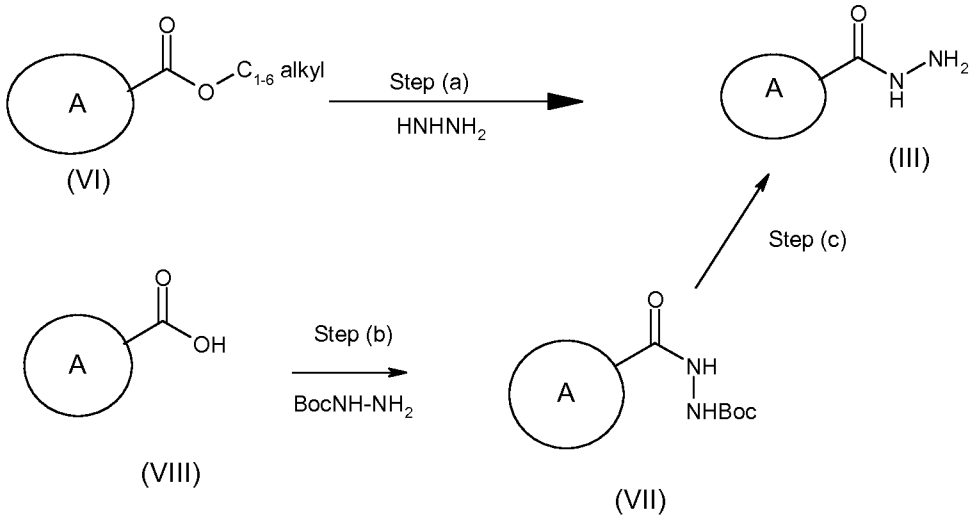
Step (b) typically comprises the reaction of a compound of formula (IV) with a compound of formula (III) in a suitable solvent such as DCM, DMF or THF at a suitable temperature such as 60 to 65°C.

Step (c) is a cyclisation reaction that typically comprises addition of a suitable reagent such as EDAC.HCl or dicyclohexylcarbodiimide to a compound of formula (II) in a suitable solvent such as DMF. A suitable temperature, for example, would be 60 to 80 °C.

The above steps can be carried out separately with isolation after step (a) and/or step (b) or carried out sequentially in a one pot reaction .

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

Scheme 2



wherein A is as defined for compounds of formula (I).

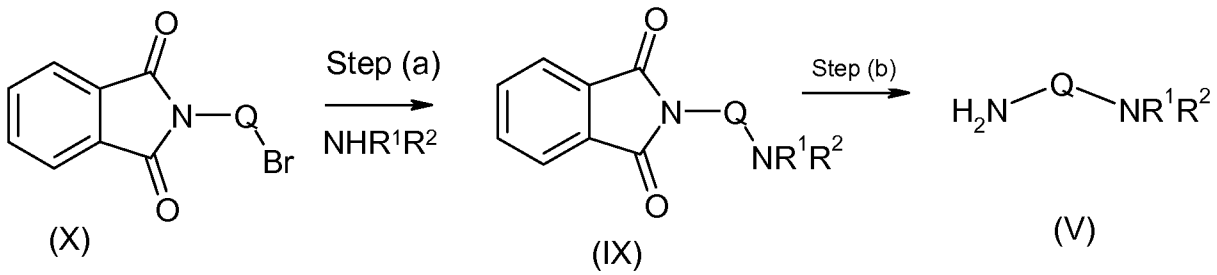
Step (a) typically comprises the use of a suitable reagent, such as hydrazine monohydrate in the presence of a suitable solvent, such as methanol at a suitable temperature, e.g. from room temperature to reflux. Typically compounds of formula (VI) are used as the methyl ester.

Step (b) typically comprises the reaction of a compound of formula (VIII) with $BocNHNH_2$ in a suitable solvent e.g. CH_2Cl_2 using a suitable coupling agent such as EDAC.HCl and optionally HOBt.The reaction is typically conducted at room temperature.

In Step (c) the Boc protecting group can be removed by conventional means, for example by treatment with HCl in dioxane.

Compounds of formula (V) may be prepared in accordance with the following Scheme 3:

Scheme 3



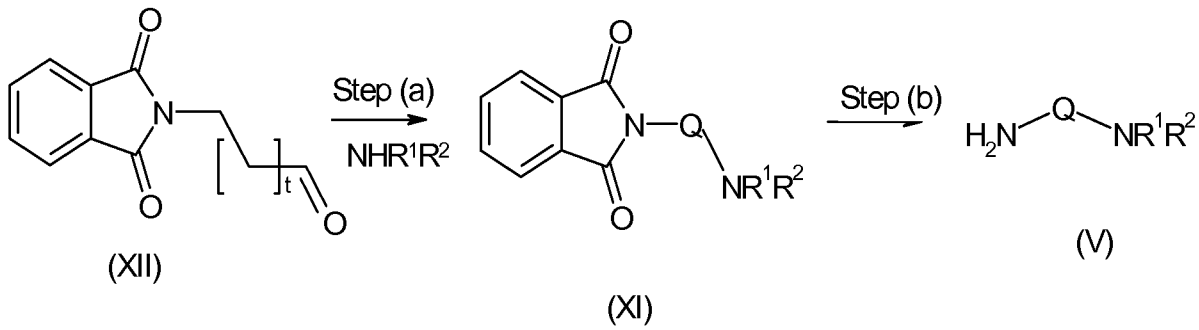
wherein Q, R^1 or R^2 are as described for compounds of formula (I).

Step (a) is a reaction of NHR^1R^2 in the presence of a suitable base e.g. triethylamine in a suitable solvent such as ethanol at a suitable temperature, e.g. reflux.

Step (b) typically comprises the use of $MeNH_2$ in a suitable solvent such as ethanol at a suitable temperature such as room temperature or the use of $NH_2NH_2.H_2O$ in a suitable solvent such as ethanol at a suitable temperature such as reflux.

Compounds of formula (V) may also be prepared in accordance with the following Scheme 4:

Scheme 4



wherein R^1, R^2, and Q are as defined for compounds of formula (I) and t is 1 or 2.

Step (a) is a reaction of NHR^1R^2 in the presence of a suitable reducing agent e.g. $NaBH(OAc)_3$ in a suitable solvent such as DCM at a suitable temperature, e.g.room temperature.

Step (b) typically comprises the use of $MeNH_2$ in a suitable solvent such as ethanol at a suitable temperature such as room temperature or the use of $NH_2NH_2.H_2O$ in a suitable solvent such as ethanol at a suitable temperature such as reflux.

Process (b): Compounds of formula (I) may also be prepared by deprotecting a protected compound of formula (I).

Examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include acyl (e.g. acetyl, removed by hydrolysis), carbonyls (e.g. 2',2',2'-trichloroethoxycarbonyl, removed with zinc in acetic acid, benzyloxycarbonyl, removed by acidolysis or hydrogenolysis or t-butoxycarbonyl, removed by acidolysis e.g. using an acid such as HCl or TFA) and arylalkyl (e.g. benzyl, removed by hydrogenolysis) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

The term "protected compound of formula (I)" is used herein to refer to a compound which includes a protecting group, for example those referred to above.

Process (c): Compounds of formula (I) may also be prepared by interconversion of a compound of formula (I) to another compound of formula (I).

Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution or amide bond formation.

A further process is the preparation of pharmaceutically acceptable salts, and solvates of compounds of formula (I).

Compounds of formula (VI), (VIII), (X), and (XII) are either commercially available, or may be prepared by known methods.

Compounds of formula (I) and their pharmaceutically acceptable salts may have affinity for and be agonists at the nicotinic α7 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease (particularly cognitive deficit of Alzheimer's disease), dementia (including Lewy body dementia and vascular dementia), age-related memory dysfunction, cognitive impairment as listed below, cognitive deficit especially cognitive deficit of schizophrenia, Parkinson's disease and Tourette's syndrome, psychiatric disorders including schizophrenia as listed below, attention deficit/hyperactivity disorder as listed below, depression as listed below, anxiety as listed

below and addiction, pain related disorders including pain of neuropathic origin including neuralgias, neuritis and back pain, and inflammatory pain including osteoarthritis, rheumatoid arthritis, acute inflammatory pain and back pain, migraine; and other diseases including obesity, sepsis and gastro-intestinal disorders (including irritable bowel syndrome and inflammatory bowel disease). Further neurological diseases for which these compounds may be of potential use is epilepsy and learning & memory disorders.

The following disease classification refer to the classification code in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10):

i) Psychotic disorders for example Schizophrenia (including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60)); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) (including the subtypes Bipolar Type and Depressive Type); Delusional Disorder (297.1) (including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type); Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder due to a General Medical Condition (including the subtypes with Delusions and with Hallucinations); Substance-Induced Psychotic Disorder (including the subtypes with Delusions (293.81) and with Hallucinations (293.82)); and Psychotic Disorder Not Otherwise Specified (298.9).

ii) cognitive impairment including for example the treatment of impairment of cognitive functions including attention, orientation, learning disorders, memory (i.e. memory disorders, amnesia, amnesic disorders, transient global amnesia syndrome and age-associated memory impairment) and language function; cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, Aids-related dementia or other dementia states such as Multiinfarct dementia, alcoholic dementia, hypothyroidism-related dementia, and dementia associated to other degenerative disorders such as cerebellar atrophy and amyotropic lateral sclerosis; other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states) trauma, head trauma, age related cognitive decline, stroke, neurodegeneration, drug-induced states, neurotoxic agents, mild cognitive impairment, age related cognitive impairment, autism related cognitive impairment, Down's syndrome, cognitive deficit related to psychosis, and post-electroconvulsive treatment related cognitive disorders; and

dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism, and tardive dyskinesias.

iii) Depression and mood disorders for example Depressive Episodes (including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode); Depressive Disorders (including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311)); Bipolar Disorders (including Bipolar I Disorder, Bipolar II Disorder (i.e. Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80)); Other Mood Disorders (including Mood Disorder due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features); Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features); and Mood Disorder Not Otherwise Specified (296.90).

iv) Anxiety disorders for example Social Anxiety Disorder; Panic Attack; Agoraphobia, Panic Disorder; Agoraphobia Without History of Panic Disorder (300.22); Specific Phobia (300.29) (including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type); Social Phobia (300.23); Obsessive-Compulsive Disorder (300.3); Posttraumatic Stress Disorder (309.81); Acute Stress Disorder (308.3); Generalized Anxiety Disorder (300.02); Anxiety Disorder Due to a General Medical Condition (293.84); Substance-Induced Anxiety Disorder; and Anxiety Disorder Not Otherwise Specified (300.00).

v) Attention-Deficit /Hyperactivity Disorder (including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified (314.9)); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder (including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23).

A compound of formula (I) or a pharmaceutically acceptable salt thereof may be useful in the treatment or prophylaxis of pain. More particularly, a compound of formula (I) or a pharmaceutically acceptable salt thereof may be useful in the treatment of pain.

When used herein the term pain, includes pain of neuropathic origin including neuralgias, neuritis and back pain; acute pain, chronic pain, chronic articular pain, musculoskeletal pain, inflammatory pain including osteoarthritis, and rheumatoid arthritis, acute inflammatory pain and back pain, visceral pain, pain associated with cancer, pain associated with migraine, tension headache and cluster headaches, pain associated with functional gastrointestinal disorders, lower back and neck pain, pain associated with sprains and strains, sympathetically maintained pain; myositis, pain associated with influenza or other viral infections such as the common cold, pain associated with rheumatic fever, pain associated with myocardial ischemia, post operative pain, headache, toothache and dysmenorrhea.

In one embodiment a compound of formula (I) or a pharmaceutically acceptable salt thereof may be useful in the treatment or prophylaxis of chronic pain, post-operative pain, chronic lower back and neck pain, cancer pain, sprains and strains. More particularly, a compound of formula (I) or a pharmaceutically acceptable salt thereof may be useful in a treatment of these pain conditions.
In the context of the present invention, treatment refers to symptomatic treatment.

Chronic articular pain conditions include rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

Pain associated with functional gastrointestinal disorders includes non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in therapy for example in the treatment or prophylaxis of the above disorders, in particular pain, neurological (e.g. cognitive deficit of Alzheimer's disease) and psychiatric disorders (e.g. cognitive deficit of schizophrenia). More particularly, a compound of formula (I) or a pharmaceutically acceptable salt thereof may be useful in the treatment or pain.

The invention further provides a method of treatment of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

When used in therapy, a compound of formula (I) or a pharmaceutically acceptable salt thereof is usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment or prophylaxis of the above disorders which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

When used in the treatment of Alzheimer's disease, the compound of formula (I) or a pharmaceutically acceptable salt thereof may be used in combination with other medicaments indicated to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease.
Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_{1A} antagonists, (e.g. lecozotan), 5-HT6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonist, acetylcholinesterase inhibitors (e.g tetrahydroaminoacridine, donepezil or rivastigmine), or allosteric modulators, nicotinic receptor agonists or allosteric modulators, symptomatic agents such as 5-HT6 receptor antagonists, e.g. SB742457, H3 receptor antagonists e.g. GSK189254 and GSK239512, 5-HT4 receptor agonist, PPAR agonists, also NMDA receptor antagonists or modulators, also disease modifying agents such as β or γ-secretase inhibitors (e.g. R-flurbiprofen), also AMPA positive modulators and Glycine Transporter Reuptake inhibitors.

When used in the treatment of pain, the compound of formula (I) or a pharmaceutically acceptable salt thereof may be used in combination with other medicaments indicated to be useful in the treatment of pain of neuropathic origin including neuralgias, neuritis and back pain, and inflammatory pain including osteoarthritis, rheumatoid arthritis, acute inflammatory pain, back pain and migraine. Such therapeutic agents include for example COX-2 (cyclooxygenase-2) inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib, COX-189 or 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (WO99/012930); 5-lipoxygenase inhibitors; NSAIDs (non-steroidal anti-inflammatory drugs) such as diclofenac, indomethacin, nabumetone or ibuprofen; bisphosphonates, leukotriene receptor antagonists; DMARDs (disease modifying anti-rheumatic drugs) such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA (N-methyl-D-aspartate) receptor modulators, such as glycine receptor antagonists or memantine; ligands for the $\alpha_2\delta$-subunit of voltage gated calcium channels, such as gabapentin and pregabalin; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; cholinesterase inhibitors such as galantamine; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B subtype; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 agonists and EP_2 agonists; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabinoid receptor ligands; bradykinin receptor ligands; vanilloid receptor ligand; and purinergic receptor ligands, including antagonists at $P2X_3$, $P2X_{2/3}$, $P2X_4$, $P2X_7$ or $P2X_{4/7,}$. Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995, US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

When a compound of formula (I) or a pharmaceutically acceptable salt thereof is used in combination with another therapeutic agent, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms may be prepared utilising a compound of the invention or pharmaceutically acceptable salt or solvate thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and

buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in a similar manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10% to 60% by weight, of the active material, depending on the method of administration. The dose of the compound of formula (I) or a pharmaceutically acceptable salt thereof used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks, months, years or even life.

A further aspect to the invention is a pharmaceutical composition comprising 0.05 to 1000mg of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and 0 to 3 g more suitably 0 to 2g of at least one pharmaceutically acceptable carrier.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

DMF: *N,N*-dimethylformamide
THF: Tetrahydrofuran
EDAC.HCl/EDAC: 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
EtOAc: Ethyl acetate
HOBt: 1-Hydroxybenzotriazole
Boc: t-butyl carbonate
DCM: Dichloromethane
MeOH: Methanol
h: Hour(s)
MDAP: Mass Directed Auto-Purification System

DMSO:	Dimethyl sulfoxide
HEPES:	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
LCMS:	Liquid Chromatography Mass Spectrometry
Biotage SP4:	Four column sequential FLASH purification system with expanded fraction bed designed for multiple sample purification, Website: http://www.biotage.com/
SCX	Strong Cationic Exchange Resin used for isolation of amines, Website: http://www.biotage.com/

Conditions used on the MDAP system:

Basic:

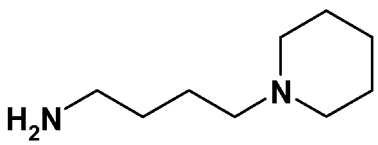
Mobile phase: water 0.2% diethylamine - acetonitrile 0.2% diethylamine
Column: Xbridge™ C18 30X100 mm - 5 microns
Detection: MS and photodiode array detector (PDA)

Acidic:

Mobile phase: water 0.2% formic acid - acetonitrile 0.2% formic acid
Column: Xbridge™ C18 30X100 mm - 5 microns
Detection: MS and photodiode array detector (PDA)

The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

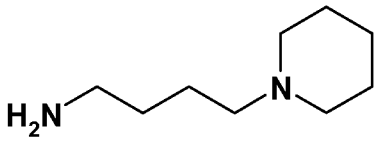
Description 1 (Method A): [4-(1-Piperidinyl)butyl]amine



A solution of piperidine (3.1ml, 31.6mmol), 4-bromobutylphthalimide (8.1g, 28.7mmol), and triethylamine (7.99ml, 57.4mmol) in ethanol (60ml) was refluxed for 6.5h. The reaction was cooled to room temperature, ethanol (20ml) and hydrazine hydrate (6.9ml, 66mmol) were added and refluxed for 20min, by which time a white precipitate crashed out. The white solid was filtered off and washed with DCM. The filtrate was passed through SCX using

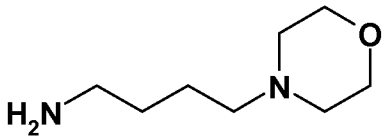
methanol followed by 2M ammonia in methanol. Solvents removed in vacuo to afford bright yellow oil. To the yellow oil was added THF, causing more white precipitate to crash out. The white precipitate was filtered off and the filtrate was concentrated in vacuo to afford [4-(1-Piperidinyl)butyl]amine as a yellow oil (2.7g).
ELSD LCMS: (MH^+=157)

Description 1 (Method B): [4-(1-Piperidinyl)butyl]amine



To a solution of N-(4-bromobutyl)phthalimide (7.63g, 27.03mmol) in ethanol (80ml) was added piperidine (3.2ml, 32.4mmol) followed by triethylamine (7.5ml, 54.1mmol). The reaction mixture was then brought to reflux at 90°C for 5h. The reaction was cooled to room temperature and hydrazine hydrate (2.6ml, 54.1mmol) was then added to the mixture. After heating for 2h, an off-white precipitate was produced. The reaction was cooled to room temperature and allowed to stir overnight. The off-white precipitate was then filtered off and the filtrate passed through a SCX column (eluting with 10% ammonia in methanol) to provide [4-(1-piperidinyl)butyl]amine (2.4g, 56%) as a yellow oil.

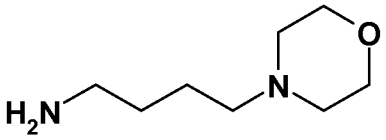
Description 2 (Method A): 4-(4-Morpholinyl)butyl]amine



To a solution of N-(4-bromobutyl)phthalimide (8g, 0.03mol) in ethanol (50ml) was added morpholine (2.97ml, 0.034mol) and triethylamine (7.9ml, 0.06mol). The reaction was then refluxed under N_2 atmosphere for 20h after which LC-MS indicated the clean formation of 2-[4-(4-morpholinyl)butyl]-1H-isoindole-1,3(2H)-dione. The reaction mixture was cooled to ambient temperature followed by the addition of hydrazine hydrate (3.26ml, 0.057mol). The reaction mixture was brought up for reflux again for 30min during which a white precipitate was formed. The reaction mixture was cooled to room temperature before the white precipitate was filtered and the filtrate passed through an SCX column (eluting with 100%

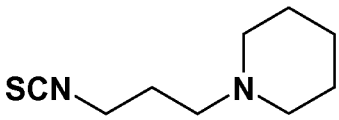
methanol followed by 10% 2M ammonia in methanol) to afford 4-(4-morpholinyl)butyl]amine (1.8g, 41%).

Description 2 (Method B): 4-(4-Morpholinyl)butyl]amine



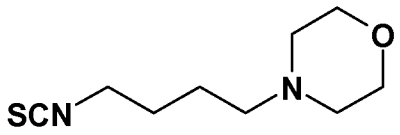
A solution of morpholine (3ml, 34.9mmol), N-(4-bromobutyl)phthalimide (8g, 29mmol) and triethylamine (8ml, 58mmol) in ethanol (55ml) was refluxed for 16h, by which the LC-MS showed reaction completion. The reaction was cooled to room temperature. Ethanol (10ml) and hydrazine hydrate (6ml, 58mmol) were added and the mixture refluxed for 20min, by which a white solid crashed out. The reaction was filtered and the filtrate passed through SCX with methanol followed by 10% 2M ammonium hydroxide in methanol. The latter fractions eluted with 10% ammonium hydroxide in methanol were combined and concentrated in vacuo to afford a bright yellow oil (3g). ELSD LC-MS, (MH^+=159).

Description 3: 1-(3-Isothiocyanatopropyl)piperidine



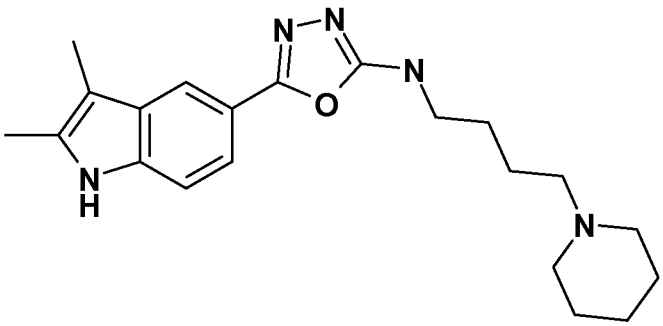
A solution of carbon disulphide (4.3ml, 70.4mmol) in dry ether (75ml) was added dropwise to an ice cooled solution of [3-(1-piperidinyl)propyl]amine (10g, 70.4mmol) and N,N′-dicyclohexylcarbodiimide (14.5g, 70.4mmol) in ether (300ml). The mixture was allowed to warm to room temperature and the precipitate formed was filtered and the filtrate evaporated to dryness to yield an orange oil. The orange oil was dissolved in hexane, the solid formed was filtered and filtrate evaporated to dryness to yield an orange oil. The orange oil was re-dissolved in hexane and stood in the fridge overnight until no more solid was formed. Hexane was evaporated to give an orange oil (13.6g).

Description 4: 4-(4-Isothiocyanatobutyl)morpholine



4-(4-Morpholinyl)butyl]amine (0.83g, 5.25mmol) was dissolved in THF (20ml). 1,1-Thiocarbonyldiimidazole (0.935g, 5.245mmol) was added and reaction stirred for 70min, LC-MS: (MH^+=201.1). The solvent was removed in vacuo, residue taken up in DCM (30ml) and washed with water (15ml). The aqueous layer was further extracted with DCM (3 x 20ml). The combined organic layers were dried over sodium sulfate and reduced in vacuo to give a yellow oil (1.266g).

Example 1: 5-(2,3-Dimethyl-1H-indol-5-yl)-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine

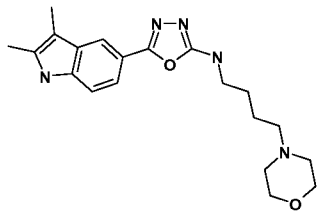
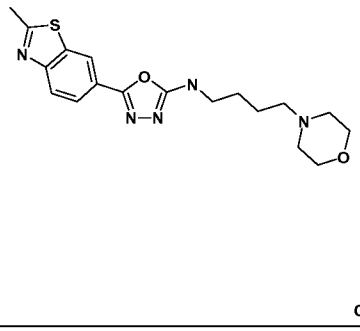
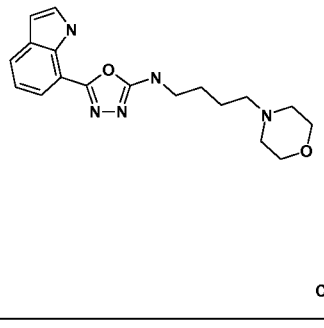
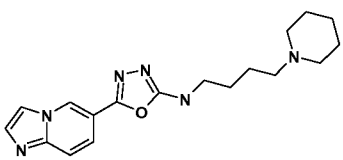


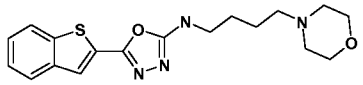
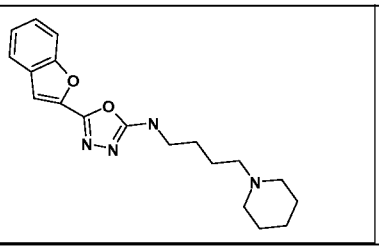
A solution of [4-(1-piperidinyl)butyl]amine (0.85g, 5.44mmol) and 1,1-thiocarbonyldiimidazole (0.97g, 5.44mmol) in THF (14ml) was stirred at room temperature for 4h, after which ELSD LC-MS showed no trace of starting material. Solvents were removed and diluted with ethyl acetate (20ml) and brine (5ml). The organics were separated and the aqueous layer was extracted further with ethyl acetate (3 x 10ml). The organics were combined, dried with magnesium sulfate, filtered and concentrated in vacuo to afford isothiocyanate residue (MH^+=199.4). The residue was diluted with THF (16ml) and a 4ml aliquot was added to 2,3-dimethyl-1H-indole-5-carbohydrazide (162mg), and refluxed at 60°C for 11.5h. The reaction was cooled and concentrated in vacuo. DMF (6ml) and EDAC.HCl (230mg, 1.2mmol) were added and heated at 80°C for 5h, at which time, the LC-MS showed that the reaction was completed The reaction was concentrated in vacuo and diluted with ethyl acetate (15ml) and water (10ml). The organics were separated; the aqueous layer was further extracted with DCM (3 x 10ml). The combined organics were dried over sodium sulfate, filtered, concentrated in vacuo and purified by SP4 silica column

using 10% methanol in DCM/DCM and 10% methanol in DCM + 1% triethylamine/DCM solvent systems. The residue collected was purified again using MDAP (C18 column under basic conditions) and then triturated with ether to afford 5-(2,3-dimethyl-1H-indol-5-yl)-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine as a solid (110mg).
LCMS: (MH^+=368)

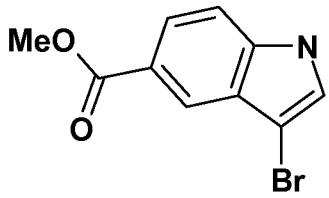
Table 1

Examples 2-7 were prepared in an analogous manner to Example 1. Where mentioned, hydrochloride salts were prepared.

No	Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+ (Acidic)	LC/MS (ES+ve) m/z [M+H]+ Basic
2	5-(2,3-Dimethyl-1H-indol-5-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine		C20H27N5O2	370	370
3	5-(2-Methyl-1,3-benzothiazol-6-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine hydrochloride		C18H23N5O2S. HCl	374	374
4	5-(1H-Indol-7-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine hydrochloride		C18H23N5O2. HCl	343	343
5	5-Imidazo[1,2-a]pyridin-6-yl-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine		C18H24N6O	NA	341

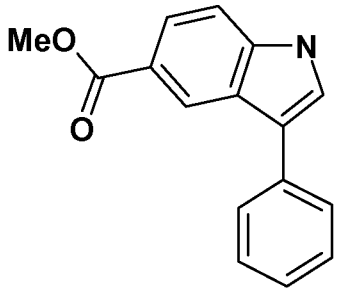
6	5-(1-Benzothien-2-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine		C18H22N4O2S	359	359
7	5-(1-Benzofuran-2-yl)-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine		C19H24N4O2	341	341

Description 5: Methyl 3-bromo-1H-indole-5-carboxylate



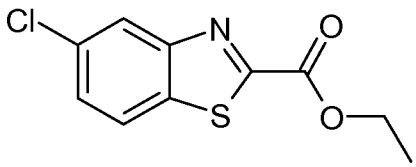
Methyl-5-indole carboxylate (1g, 5.7mmol) was added to a round bottom flask and dissolved in DMF (10ml) and cooled to 0°C with an ice bath. N-Bromosuccinimide (1.07g, 5.99mmol) dissolved in DMF (20ml) was added slowly. The reaction mixture was stirred at 0°C for 30min then at room temperature overnight. After stirring for 17.5h, LC-MS showed no starting material and one peak corresponding to methyl 3-bromo-1H-indole-5-carboxylate. The solvent was removed under vacuum to give a brown solid. To this was added 40ml water and 50ml ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 40ml) and the combined organic layers washed with brine (50ml) then dried over sodium sulfate and concentrated in vacuo. The crude residue was washed with DCM to give an orange solid which was removed by filtration and dried under vacuum. (1.25g, 86%)

Description 6: Methyl 3-phenyl-1H-indole-5-carboxylate



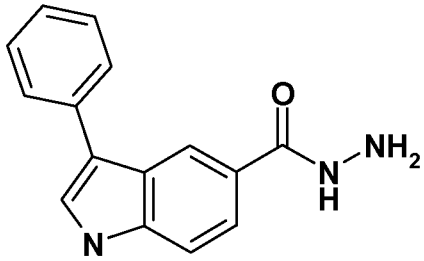
Methyl 3-bromo-1H-indole-5-carboxylate (1.24g, 4.88mmol) and palladium-tetrakis(triphenylphosphine) (0.169g, 0.146mmol) were added to a round bottom flask along with toluene (20ml). To this was added a solution of phenyl boronic acid (0.89g, 7.32mmol) in methanol (20ml) and 2M sodium carbonate solution (9.75ml, 19.52mmol). The reaction mixture was heated at reflux at 100°C for 48h. After cooling, the reaction mixture was concentrated in vacuo to give a brown solid. This was dissolved in DCM/methanol and subjected to SP4 column using 1% (2M ammonia in methanol) in DCM to give a white solid. LC-MS,: (MH^+=252)

Description 7: Ethyl 5-chloro-1,3-benzothiazole-2-carboxylate



A mixture of 2-amino-4-chlorothiophenol (10.0g, 61.4mmol) and diethyl oxalate (19.0g, 129mmol) was heated under nitrogen for 6h, during which the temperature decreased from 150°C to 95°C. After cooling, the mixture was poured into a solution consisting of concentrated HCl (50ml), water (150ml) and 95% EtOH (70ml). After stirring for 5min, the mixture was cooled to 8°C and filtered. The solid was washed with 25% EtOH (2 x 40ml), dried under vacuum and purified by preparative HPLC to yield the titled compound as a solid.

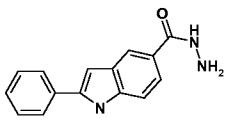
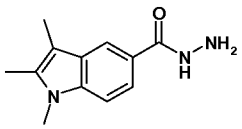
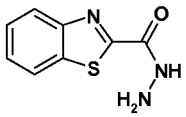
Description 8: 3-Phenyl-1H-indole-5-carbohydrazide

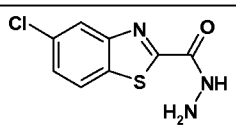


Methyl 3-phenyl 1-H indole-5-carboxylate (0.65g, 2.59mmol) was added to a round bottom flask and dissolved in methanol (20ml). To this was added hydrazine hydrate (1.5ml, 25.9mmol) and the reaction mixture heated at 80°C for 42h. The reaction was further heated at 90°C for 63h after adding additional hydrazine hydrate (1.2ml, 48.4mmol). The reaction was passed through a 70g SCX column using methanol followed by 2M ammonia in methanol. The fractions eluted with 2M ammonia in methanol were collected. TLC showed most fractions were not pure. The collected fractions were concentrated and purified by SP4 silica column (Solvent systems: DCM and 10% 2M ammonia in methanol/DCM). The target product was eluted at 5% 2M ammonia in methanol/DCM gradient. The purified fractions were collected and dried down to afford product. The product (230mg) was then dissolved in 2 ml methanol and 10ml 1M HCl. The solution was heated at 60°C for 3h. The solvents were removed in vacuo to afford 3-phenyl-1H-indole-5-carbohydrazide as a light beige solid (220mg).

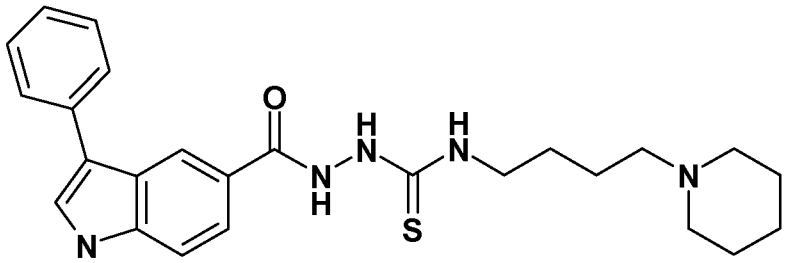
LCMS: (MH^+=252)

Table 2. The following hydrazides were prepared in an analogous manner to Description 7.

Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+
2-phenyl-1H-indole-5-carbohydrazide		C15H13N3O	252
1,2,3-trimethyl-1H-indole-5-carbohydrazide		C12H15N3O	218
1,3-benzothiazole-2-carbohydrazide		C8H7N3OS	194

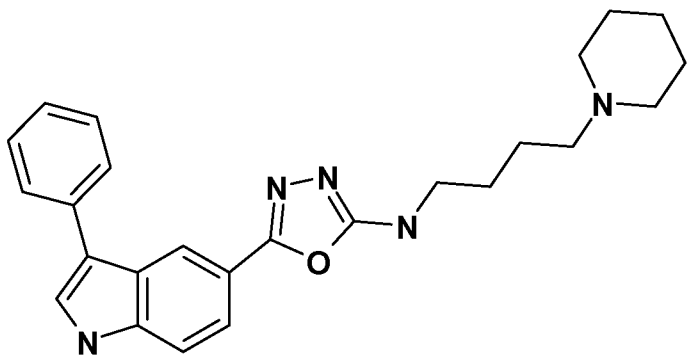
5-chloro-1,3-benzothiazole-2-carbohydrazide		C8H6ClN3OS	228

Description 9: 2-[(3-Phenyl-1H-indol-5-yl)carbonyl]-N-[4-(1-piperidinyl)butyl]hydrazinecarbothioamide



[4-(1-Piperidinyl)butyl]amine (0.16g, 1.05mmol) was dissolved in 3.5ml THF. 1,1-Thiocarbonyldiimidazole (0.19g, 1.05mmol) was added and the reaction stirred for 1.5h. LC-MS: (MH^+=199) showed no trace of starting material. Solvent was removed in vacuo. The residue was taken up in 15ml DCM and washed with 8ml of water. The aqueous layer was further extracted with DCM (3 x 10ml). The combined organic layers were dried over sodium sulfate and reduced in vacuo to give 322 mg yellow oil. LC-MS: (MH^+=199). 3-Phenyl-1H-indole-5-carbohydrazide (115mg, 0.46mmol) was added to the yellow oil and dissolved in 3.5ml THF. The reaction was heated at 60°C for 3h. LC-MS: (MH^+=450).The reaction mixture was used without further purification.

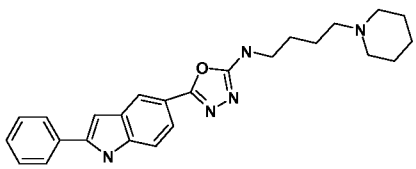
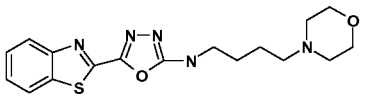
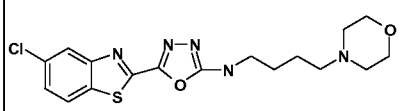
Example 8: 5-(3-Phenyl-1H-indol-5-yl)-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine



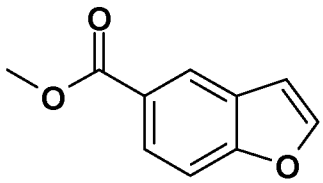
EDAC.HCl (96mg, 0.5mmol) was added to 2-[(3-phenyl-1H-indol-5-yl)carbonyl]-N-[4-(1-piperidinyl)butyl]hydrazinecarbothioamide. DMF (2ml) was added and the mixture heated at 80°C for 4h. LC-MS, (MH^+ =416). Solvent was removed in vacuo, residue taken up in 15ml DCM and washed with 8ml water. The aqueous layer was further extracted with DCM (3 x 10ml). The combined organic layers were dried over sodium sulfate, filtered and reduced in vacuo to afford 800mg yellow oil. LC-MS: (MH^+=416). Purification was done on MDAP by reverse phase C18 in basic conditions. Solvent was removed in vacuo to afford 133mg of yellow oil. It was dissolved in methanol (1ml), followed by the addition of of 1M HCl in ether (0.35ml, 1.1eqv). The mixture was stirred at room temperature for 5min. Solvent was removed in vacuo. Toluene (3 x 25ml) was added and removed in vacuo. The residue was dissolved in minimum amount of methanol and few drops of ether were added to form a cloudy solution. It was sonicated and dried under vacuum to produce a yellow solid. The sample was dried in vacuum oven overnight at 40°C to afford 93mg yellow solid.
LC-MS: (MH^+=416).

Table 3.

Examples 9-12 were prepared in an analogous manner to Example 8

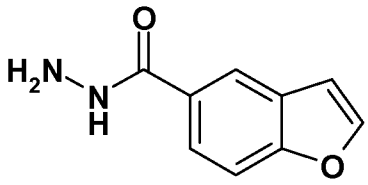
No	Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+ (Acidic)	LC/MS (ES+ve) m/z [M+H]+ Basic
9	5-(2-Phenyl-1H-indol-5-yl)-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine		C25H29N5O	NA	416
10	5-(1,3-Benzothiazol-2-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine		C17H21N5O2S	NA	360
11	5-(5-Chloro-1,3-benzothiazol-2-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine		C17H20ClN5O2S	NA	394/396

Description 10: Methyl 1-benzofuran-5-carboxylate



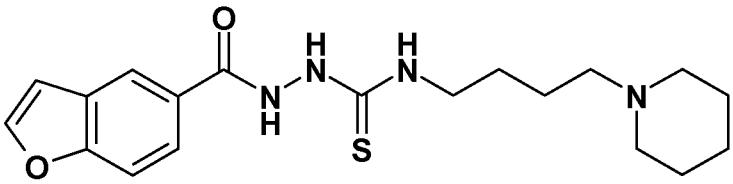
To a stirred solution of 1-benzofuran-5-carboxylic acid (486mg, 3mmol) in methanol (10ml), conc sulfuric acid (1 drop) was added. The reaction mixture was heated under reflux for 48h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and poured into saturated potassium carbonate solution (50ml). The mixture was extrated with ethyl acetate (3 x 10ml). The organic layers were combined, washed with brine (20ml), dried over sodium sulphate, filtered and evaporated. The residue was purified by SP4 column eluting with ethyl acetate/hexane solvent system to yield 400mg of white solid.
LC-MS: (MH^+=177)

Description 11: 1-Benzofuran-5-carbohydrazide



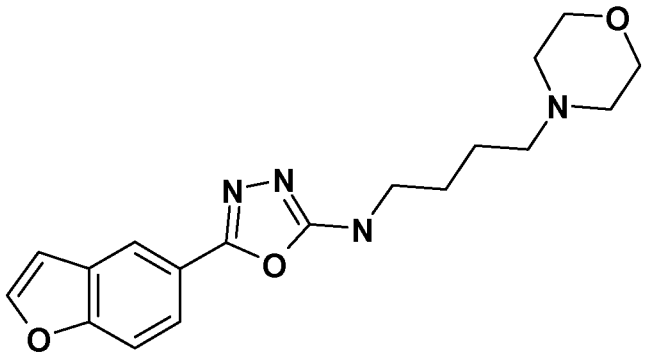
The title compound was prepared as in an analogous manner to Description 7.

Description 12: 2-(1-Benzofuran-5-ylcarbonyl)-N-[4-(1-piperidinyl)butyl]hydrazinecarbothioamide



The title compound was prepared in an analogous manner to Description 8.

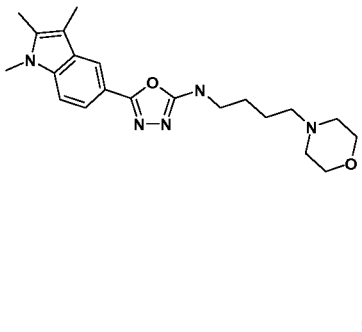
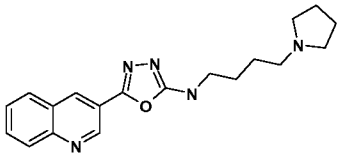
Example 12: 5-(1-Benzofuran-5-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine

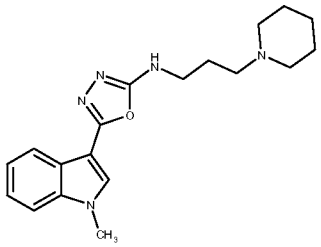
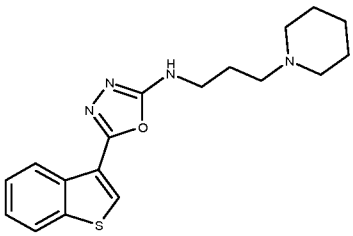
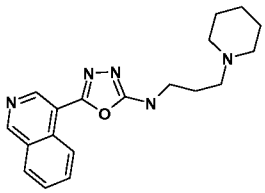


The title compound was prepared in a analogous manner to Example 8.
LC/MS (ES+ve) m/z [M+H]+ (Acidic) (MH^+=343) C18H22N4O3.

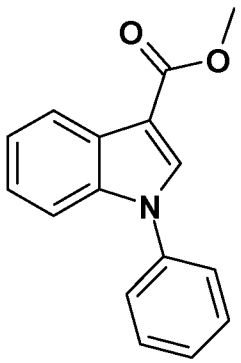
Table 4.

Example 13-17 were prepared in an analogous manner to Example 12. Where indicated, hydrochloride salts of the compounds were prepared.

No	Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+ (Acidic)	LC/MS (ES+ve) m/z [M+H]+ Basic
13	N-[4-(4-morpholinyl)butyl]-5-(1,2,3-trimethyl-1H-indol-5-yl)-1,3,4-oxadiazol-2-amine hydrochloride	 Cl	C21H29N5O2. HCl	384	384
14	N-[4-(1-pyrrolidinyl)butyl]-5-(3-quinolinyl)-1,3,4-oxadiazol-2-amine		C19H23N5O	338	NA

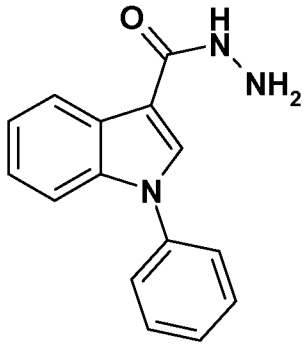
15	5-(1-methyl-1H-indol-3-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C19H25N5O	340	NA
16	5-(1-benzothien-3-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C18H22N4OS	343	NA
17	5-(4-isoquinolinyl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C19H23N5O	338	NA

Description 13: Methyl 1-phenyl-1H-indole-3-carboxylate



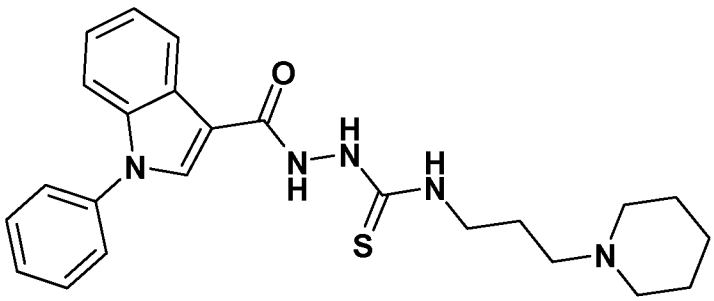
Methyl 1H-indole-3-carboxylate (1g, 5.7mmol), K_3PO_4 (2.54g, 11.97mmol), copper iodide (54.27mg, 0.29mmol), trans N-N-dimethyl-1,2-cyclohexanediamine (6.38mg, 0.06mmol) and iodobenzene (1.4g, 6.8mmol) were added to a 25ml round bottom flask with toluene (12ml) as a solvent. The reaction mixture was stirred at 110°C under argon overnight. The reaction lasted 2 days. The reaction mixture was diluted with ethyl acetate and washed with sodium hydroxide (100ml) followed by water (3 x100ml). The organic phase was evaporated to give product 1.7g.

Description 14: 1-Phenyl-1H-indole-3-carbohydrazide



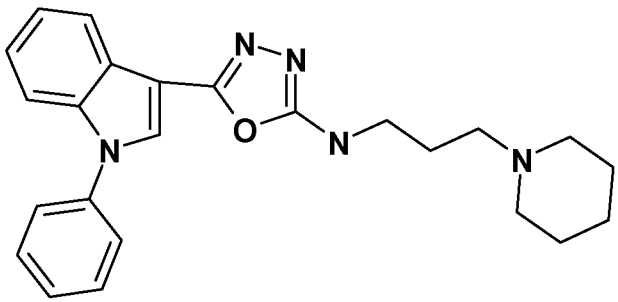
The title compound was prepared as in an analogous manner to Description 7.

Description 15: 2-[(1-phenyl-1H-indol-3-yl)carbonyl]-N-[3-(1-piperidinyl)propyl]hydrazinecarbothioamide



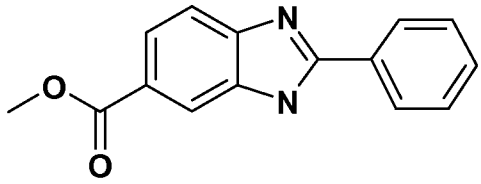
The title compound was prepared as in an analogous manner to Description 8.

Example 18: 5-(1-Phenyl-1H-indol-3-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine



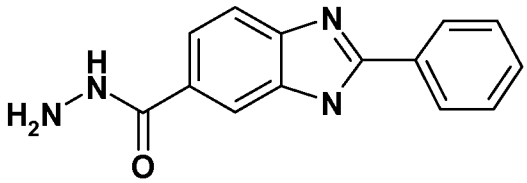
The title compound was prepared in an analogous manner to Example 8.

Description 16: Methyl 2-phenyl-1H-benzimidazole-5-carboxylate



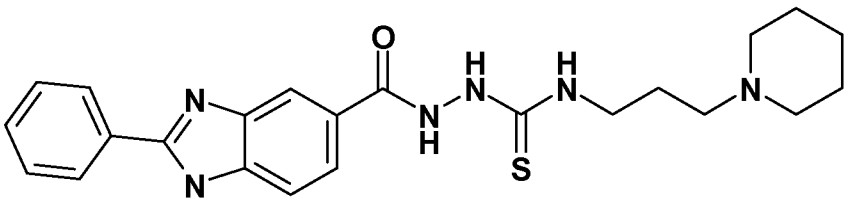
Methyl 3,4-diaminobenzoate (2.5g, 15mmol), ytterbium(III) trifluoromethanesulfonate (466.8mg, 0.8mmol) and benzaldehyde (4.7ml, 46.3mmol) were mixed and stirred at room temperature for 30min. DCM (10ml) was added. Ytterbium(III) trifluoromethanesulfonate crystallised and was filtered onto celite and washed with DCM. The organic layer was evaporated and purified by SP4 using ethyl acetate/hexane solvent system to yield an orange solid (1.29g)

Description 17: 2-Phenyl-1H-benzimidazole-5-carbohydrazide



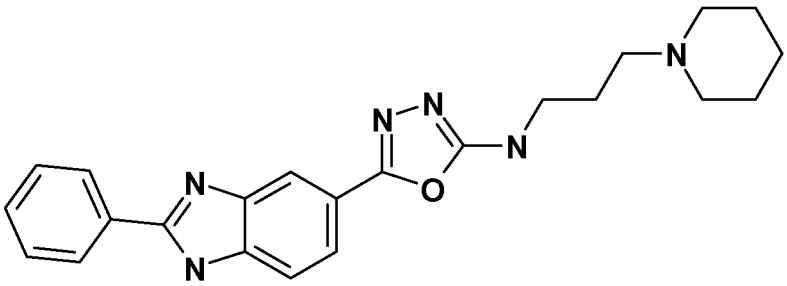
The title compound was prepared as in an analogous manner to Description 7.

Description 18: 2-[(2-Phenyl-1H-benzimidazol-5-yl)carbonyl]-N-[3-(1-piperidinyl)propyl]hydrazinecarbothioamide



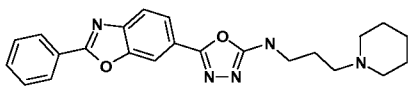
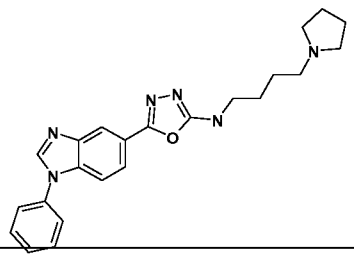
The title compound was prepared as in an analogous manner to Description 8.

Example 19: 5-(2-Phenyl-1H-benzimidazol-5-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine

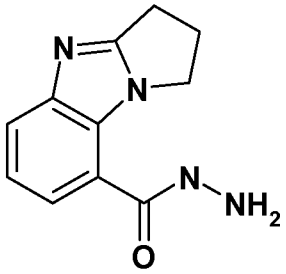


The title compound was prepared in an analogous manner to Example 8.

Example 20 was prepared in a similar manner to Example 19, however in the preparation of the methyl 2-phenyl-1,3-benzoxazole-6-carboxylate intermediate, a different catalyst $Pb(OAc)_2$, conditions and solvents were used. Example 21 was prepared in a similar manner however the methyl 3-amino-4-(phenylamino)benzoate was prepared from the corresponding nitro compound by reduction, which in turn was prepared from methyl 4-bromo-3-nitrobenzoate and phenylamine.

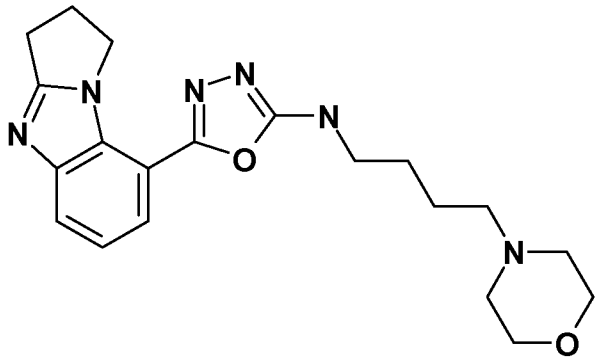
No	Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+ (Acidic)
20	5-(2-phenyl-1,3-benzoxazol-6-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C23H25N5O2	404
21	5-(1-phenyl-1H-benzimidazol-5-yl)-N-[4-(1-pyrrolidinyl)butyl]-1,3,4-oxadiazol-2-amine		C23H26N6O	403

Description 19: 2,3-Dihydro-1H-pyrrolo[1,2-a]benzimidazole-8-carbohydrazide



To a stirred solution of ethyl 2-methyl-1-propyl-1H-benzimidazole-7-carboxylate (which may be prepared as described in: Libeer et al. US3931156 (1976)) (0.23g, 0.98mmol) in methanol (5ml) was added hydrazine hydrate solution (0.5ml, 9.7mmol). The reaction mixture was refluxed for 20h and was allowed to cool to room temperature. The resulting precipitate was filtered and washed with hexane to give an off-white powder (209mg, 93%). The product was used without further purification.
LC-MS (Acidic): (MH^+=217).

Example 22: 5-(2,3-Dihydro-1H-pyrrolo[1,2-a]benzimidazol-8-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine and HCl salt

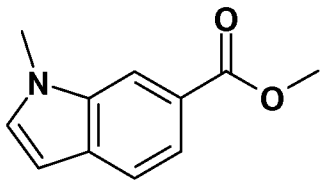


To a stirred solution of 4-(4-morpholinyl)butyl]amine (101mg, 0.6mmol) in DMF (3ml) was added 1,1'-thiocarbonyldiimidazole (120mg, 0.7mmol). The reaction mixture was stirred for 16h at room temperature, followed by the addition of water (5ml) and DCM (5ml). The aqueous phase was extracted with DCM (3 x 5ml) and the combined organic extracts dried with a phase separating column. Removal of the solvent in vacuo furnished a crude residue which was then dissolved in DMF (3ml) and transferred to a stirred solution of 2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole-8-carbohydrazide (110mg, 0.478mmol) in DMF (2ml). The reaction mixture was heated at 65°C for 3h followed by the addition of EDAC.HCl (114mg, 0.6mmol). The reaction was constantly stirred at 65°C for 22h and was then allowed to cool

to room temperature. Toluene (15ml) was added and the solvent was removed in vacuo to give the crude residue. Purification by SP4 (DCM followed by 10% methanol in DCM) furnished the desired product as a colourless oil (55mg, 30%).
LC-MS (Acidic) (MH^+=383).

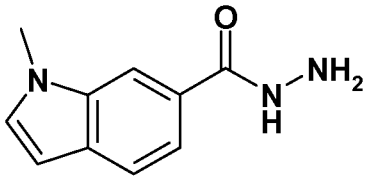
It was redissolved in DCM (4ml), followed by the addition of a 4.0M HCl solution in dioxane (0.5ml). The solvent was removed in vacuo to give a white solid as the corresponding HCl salt.
LC-MS (Acidic) (MH^+=383)

Description 20: Methyl 1-methyl-1H-indole-6-carboxylate



To a stirred solution of methyl 1H-indole-6-carboxylate (0.76g, 4.34mmol) in DMF (10ml) at room temperature was added sodium hydride (0.35g, 8.75mmol). The resultant suspension was stirred for 30min at room temperature followed by the addition of methyl iodide (0.54ml, 8.67mmol). The reaction mixture was stirred for 20h at room temperature and was then quenched by the addition of water (20ml) and ethyl acetate (20ml). The aqueous layer was extracted with ethyl acetate (3 x 30ml) and the combined extracts were dried with a phase separating column. The solvent was then removed in vacuo to give the desired product as an off-white solid (0.85g, 100%).
LC-MS (Acidic) (MH^+=190). The product was used without further purification.

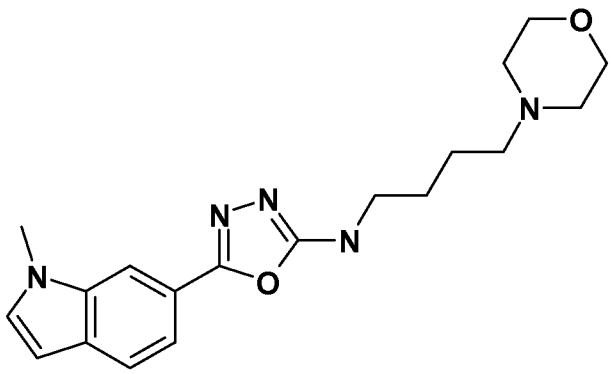
Description 21: 1-Methyl-1H-indole-6-carbohydrazide



To a solution of methyl 1-methyl-1H-indole-6-carboxylate (0.9g, 4.5mmol) in methanol (15ml) was added hydrazine hydrate solution (1.6ml, 28.3mmol). The reaction mixture was

heated at 75°C for 20h, followed by the addition of another portion of hydrazine hydrate solution (1.2ml). The reaction mixture was continually heated at 75°C for another 20h and was then cooled to room temperature. Water (20ml) and DCM (20ml) was added and the aqueous layer extracted with DCM (3 x 25ml). The combined organic extracts were dried with a phase separating column and concentrated in vacuo to give the desired product as an off white solid (0.86g, 100%).
LC-MS (Acidic): (MH^+=190).

Example 23: 5-(1-Methyl-1H-indol-6-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine and HCl salt

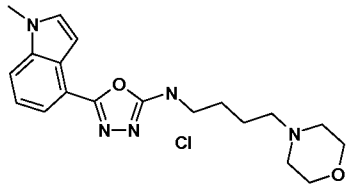
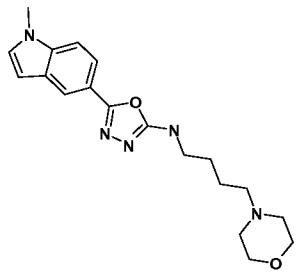


To a stirred solution of 4-[(4-morpholinyl)butyl]amine (126mg, 0.8mmol) in DMF (2.5ml) was added 1,1'-thiocarbonyldiimidazole (139mg, 0.8mmol). The reaction mixture was stirred at room temperature for 16h, followed by the addition of water (5ml) and DCM (5ml). The aqueous phase was extracted with DCM (3 x 10ml) and the combined organic extracts washed with water (15ml). The organic phase was then dried with a phase separating column and concentrated in vacuo to give a crude residue which was then dissolved in DMF (3ml) and transferred to a stirred solution of 1-methyl-1H-indole-6-carbohydrazide (102mg, 0.6mmol) dissolved in DMF (2ml). The reaction mixture was heated at 65°C for 3h followed by the addition of EDAC.HCl (126mg, 0.7mmol). The reaction was stirred at 65°C for 18h and then cooled to room temperature. Toluene (10ml) was added and the solvent was removed in vacuo to give the crude product. Purification by SP4 (DCM followed by 10% methanol in DCM) furnished the desired product, as a single pure component along with some sample contaminated with a yellow residue. 5-(1-Methyl-1H-indol-6-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine obtained: 50mg.
LC-MS (Acidic) (MH^+=356).

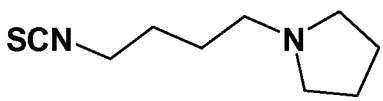
To a solution of 5-(1-methyl-1H-indol-6-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine 50mg in DCM (2ml) was added a 4.0M HCl solution in dioxane (0.5ml). The solvent was removed in vacuo to give an off-white solid.
LC-MS (Acidic): (MH^+=356).

Table 5

Examples 24-25 were prepared in an analogous manner to Example 23. Where indicated, the hydrochloride salt was prepared.

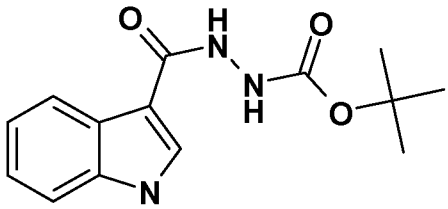
No	Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+ (Acidic)	LC/MS (ES+ve) m/z [M+H]+ Basic
24	5-(1-Methyl-1H-indol-4-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine hydrochloride		C19H25N5O2. HCl	356	356
25	5-(1-Methyl-1H-indol-5-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine		C19H25N5O2	356	356

Description 22: 1-(4-Isothiocyanatobutyl)pyrrolidine



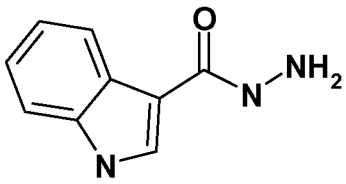
The reaction mixture comprising 1,1'-thiocarbonyldiimidazole (178mg, 1mmol) and pyrrolidinylbutylamine (142.mg, 1mmol) in THF (3ml) was stirred for 3h at room temperature with a stopper on top of the flask. It was then dissolved in ethyl acetate and washed with water. The organic phase was then removed in vacuo. 160mg of brown oil was obtained.

Description 23: 1,1-Dimethylethyl 2-(1H-indol-3-ylcarbonyl)hydrazinecarboxylate



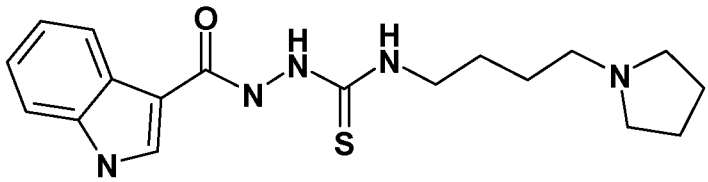
Indole-3-carboxylic acid (3g, 18.6mmol), 1,1-dimethylethyl hydrazinecarboxylate (2.95g, 22.32mmol), EDAC.HCl (3.9g, 20.5mmol) and HOBt hydrate (3.1g, 20.5mmol) were mixed together in a 50ml round bottom flask. DCM was used as the solvent. The reaction mixture was stirred at room temperature overnight. To make the reaction complete, 1,1-dimethylethyl hydrazinecarboxylate (2g) and EDAC.HCl (2g) were added. The reaction lasted 4 days. DCM was removed in vacuo. The product was dissolved in ethyl acetate and washed with sodium bicarbonate solution (2 x 50ml) and 2M HCl (3 x 50ml) in a separating funnel. It was filtered and 3.56g of white/pink solid was obtained.

Description 24: 1H-Indole-3-carbohydrazide



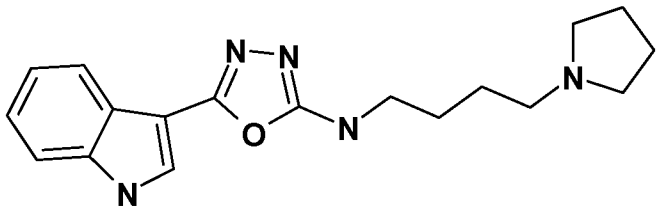
1,1-Dimethylethyl 2-(1H-indol-3-ylcarbonyl)hydrazinecarboxylate (3.56g, 1eq) was first dissolved in dioxane (30ml). Then HCl in dioxane (20ml) was added. The flask used was a 100ml round flask. The reaction mixture was stirred at room temperature. The reaction lasted 15h. The product was filtered, and then partitioned between sodium hydroxide (100ml) and ethyl acetate (300ml). The organic phase was dried and evaporated. The product was triturated and filtered to obtain 1.48g pink/white solid.

Description 25: 2-(1H-Indol-3-ylcarbonyl)-N-[4-(1-pyrrolidinyl)butyl]hydrazinecarbothioamide



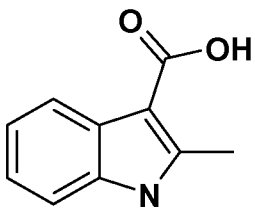
1H-Indole-3-carbohydrazide (250mg, 1.4mmol) and 1-(4-isothiocyanatobutyl)pyrrolidine (342.5mg, 1.9mmol) was stirred at 60°C under argon with THF (10ml) as a solvent. The reaction lasted 1h. THF was evaporated. The product was triturated with ether. Then it was filtered to obtain 414mg yellow solid.

Example 26: 5-(1H-Indol-3-yl)-N-[4-(1-pyrrolidinyl)butyl]-1,3,4-oxadiazol-2-amine



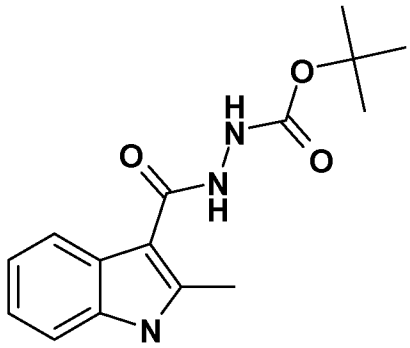
2-(1H-Indol-3-ylcarbonyl)-N-[4-(1-pyrrolidinyl)butyl]hydrazinecarbothioamide (414mg, 1.2mmol) was stirred in a 100ml round bottom flask and EDAC.HCl (264mg, 1.4mmol) dissolved in DMF (10ml) was added. The reaction was carried out under argon with a condenser at 90°C. The reaction lasted 2h. The reaction mixture was passed through a SCX column (1st solvent used: methanol, 2nd solvent used: 2M ammonia in methanol). The fraction containing the product was evaporated. The residue was dissolved in ethyl acetate and washed with water (3 x 40ml). The organic phase was dried and evaporated. Then the product was triturated with ether to give 185mg of a yellow/pink solid.

Description 26: 2-Methyl-3H-indole-3-carboxylic acid



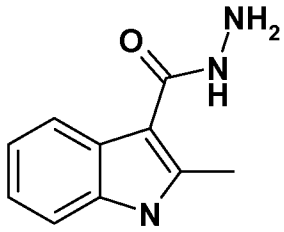
Ethyl 2-methyl-3H-indole-3-carboxylate (1g, 4.9mmol) was dissolved in ethanol (20ml) and 2M sodium hydroxide (6ml) was added. The solution was stirred at room temperature for 2h. No product was observed and the solution was refluxed for 4 days at which 76% of product was formed. The reaction was stopped. Upon cooling, the solvent was evaporated and residue diluted with water, acidified with 2M HCl and extracted with ethyl acetate (2 x 50ml). The organics were dried over magnesium sulphate and evaporated to give a dark solid. This was purified by SP4 eluting with 2-10% methanol in DCM to yield 611mg of a dark solid.

Description 27: 1,1-Dimethylethyl 2-[(2-methyl-3H-indol-3-yl)carbonyl]hydrazinecarboxylate



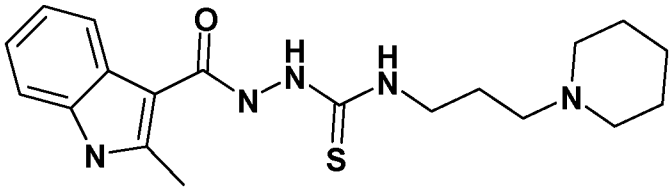
The title compound was prepared as in an analogous manner to Description 22.

Description 28: 2-Methyl-3H-indole-3-carbohydrazide



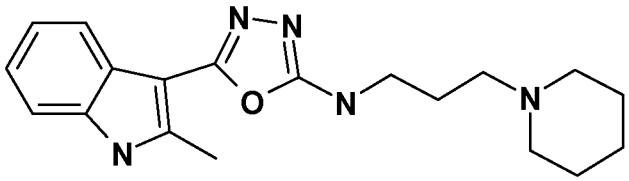
The title compound was prepared as in an analogous manner to Description 23.

Description 29: 2-[(2-Methyl-3H-indol-3-yl)carbonyl]-N-[3-(1-piperidinyl)propyl]hydrazinecarbothioamide



The title compound was prepared as in an analogous manner to Description 24.

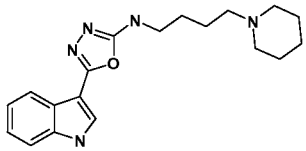
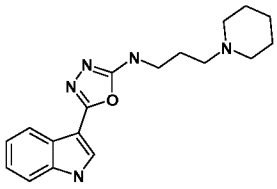
Example 27: 5-(2-Methyl-1H-indol-3-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine

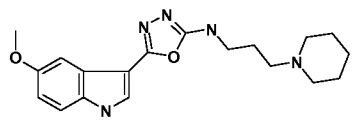
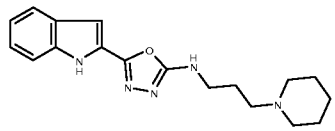
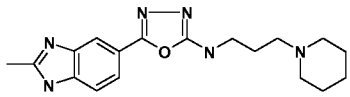


The title compound was prepared as in an analogous manner to Example 26.

Table 6

Examples 28-32 were prepared in an analogous manner to Example 26. In the preparation of the compound of Example 32, the appropriate acid was used to make the hydrazide rather than via the Boc protected intermediate.

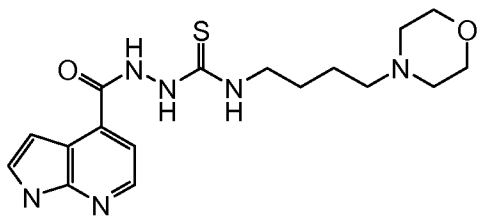
No	Name	Structure	Mol Formula	LC/MS (ES+ve) m/z [M+H]+ (Acidic)
28	5-(1H-indol-3-yl)-N-[4-(1-piperidinyl)butyl]-1,3,4-oxadiazol-2-amine		C19H25N5O	340
29	5-(1H-indol-3-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C18H23N5O	326

30	5-[5-(methyloxy)-1H-indol-3-yl]-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C19H25N5O2	356
31	5-(1H-indol-2-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C18H23N5O	326
32	5-(2-methyl-1H-benzimidazol-5-yl)-N-[3-(1-piperidinyl)propyl]-1,3,4-oxadiazol-2-amine		C18H24N6O	341

Description 30: 1*H*-Pyrrolo[2,3-*b*]pyridine-4-carbohydrazide

A solution of methyl 1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (0.5g, 2.84mmol) in methanol (10ml) was added in hydrazine (50-60% in H_2O) (1.95ml, 19.87mmol). The mixture was refluxed at 80°C for 4h. After cooling to room temperature, the solvent was removed. Trituration with ether gave the desired product as a solid (467mg).

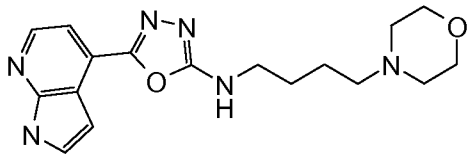
Description 31: *N*-[4-(4-Morpholinyl)butyl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-4-ylcarbonyl) hydrazinecarbothioamide



A solution of 1*H*-pyrrolo[2,3-*b*]pyridine-4-carbohydrazide (100mg, 0.57mmol) and 4-(4-isothiocyanatobutyl)morpholine (159mg, 0.79mmol) in THF (10ml) was heated at 60°C for 16h. After cooling to room temperature, the solvent was removed under reduced

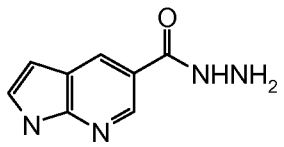
pressure to give the title compound as a solid. Quantitative yield was assumed and the compound was used in the next step reaction.

Example 33: *N*-[4-(4-Morpholinyl)butyl]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1,3,4-oxadiazol-2-amine



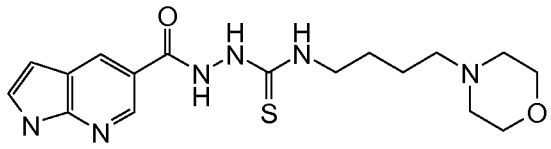
EDAC.HCl (0.21g, 1.11mmol) was added to a solution of *N*-[4-(4-morpholinyl)butyl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-4-ylcarbonyl)hydrazinecarbothioamide (0.21g, 0.56mmol) in DMF (3ml). The reaction mixture was heated at 80°C for 2h. After cooling to room temperature, the reaction mixture was poured into water (50ml) and extracted with ethyl acetate (20ml x3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. Purification via SP4 Biotage (25M, silica gel), eluting with MeOH/DCM (0-10%) gave the title compound as a solid (119mg).
[LCMS = 343.3; Acidic]

Description 32: 1*H*-Pyrrolo[2,3-*b*]pyridine-5-carbohydrazide



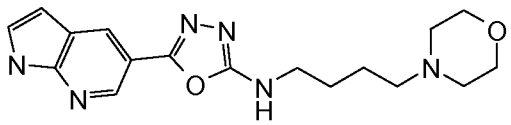
To a solution of methyl 1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (0.5g, 2.84mmol) in methanol (10ml) was added hydrazine (50-60% in H_2O) (1.95ml, 19.87mmol). The mixture was refluxed at 80°C for 6h. After cooling to room temperature, the solvent was removed. Trituration with ether gave the title compound as a solid (425mg).

Description 33: *N*-[4-(4-Morpholinyl)butyl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-ylcarbonyl) hydrazinecarbothioamide



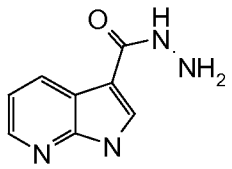
A solution of 1*H*-pyrrolo[2,3-*b*]pyridine-5-carbohydrazide (100mg, 0.57mmol) and 4-(4-isothiocyanatobutyl)morpholine (159mg, 0.79mmol) in THF (10ml) was heated at 60°C for 16h. After cooling to room temperature, the solvent was removed under reduced pressure to give the title compound as a solid. Quantitative yield was assumed and the compound was used in the next reaction.

Example 34: *N*-[4-(4-Morpholinyl)butyl]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1,3,4-oxadiazol-2-amine



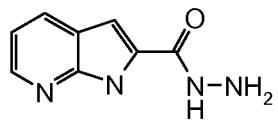
EDAC.HCl (108 mg, 0.57mmol) was added to a solution of *N*-[4-(4-morpholinyl)butyl]-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-ylcarbonyl)hydrazinecarbothioamide (213mg, 0.57mmol) in DMF (3ml). The reaction mixture was heated at 80°C for 2.5h. After cooling to room temperature, the reaction mixture was loaded to SP4 Biotage (25M, silica gel) eluting with MeOH/DCM (0-10%) to give the title compound as a solid (149mg).
[LCMS = 343.3; Acidic]

Description 34: 1*H*-Pyrrolo[2,3-*b*]pyridine-3-carbohydrazide



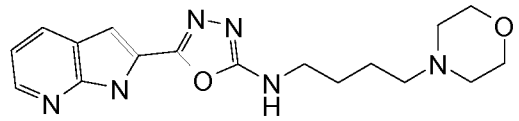
To a solution of methyl 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate (100mg, 0.57mmol) in methanol (10ml) was added hydrazine hydrate (50-60%) (0.39ml, 3.97mmol). The mixture was refluxed at 80°C for 21h. After cooling to room temperature, the solvent was removed. Trituration with ether gave the title compound as a solid (85mg).

Description 35: 1*H*-Pyrrolo[2,3-*b*]pyridine-2-carbohydrazide



To a solution of methyl 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (100mg, 0.57mmol) in methanol (10ml) was added hydrazine hydrate (50-60%) (0.39ml, 3.97mmol). The mixture was refluxed at 80°C for 2h. After cooling to room temperature, the solvent was removed. Trituration with ether gave the title compound as a solid (91mg).

Example 35: *N*-[4-(4-Morpholinyl)butyl]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1,3,4-oxadiazol-2-amine

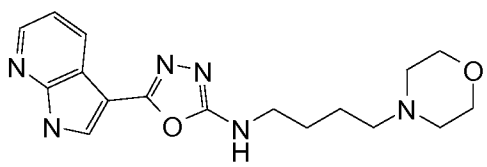


A solution of 1*H*-pyrrolo[2,3-*b*]pyridine-2-carbohydrazide (88 mg, 0.500 mmol) and 4-(4-isothiocyanatobutyl)morpholine (140mg, 0.70mmol) in THF (10ml) was heated at 60°C for 6h. After cooling to room temperature, the solvent was removed under reduced pressure to give a solid (solid A). A quantitative yield was assumed and solid A was used directly in the EDAC coupling reaction.

EDAC.HCl (192mg, 1.00mmol) was added to a stirred solution of solid A (180mg) in DMF (3ml). The reaction mixture was heated at 80°C for 2h. After cooling to room temperature, the reaction mixture was loaded to a SP4 Biotage (25M, silica gel) eluting with MeOH/DCM (0-10%) to give the title compound as a solid (75mg).

[LCMS = 343.3; Acidic]

Example 36: *N*-[4-(4-Morpholinyl)butyl]-5-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1,3,4-oxadiazol-2-amine



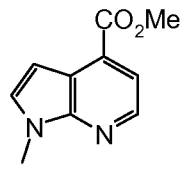
A solution of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbohydrazide (89 mg, 0.50mmol) and 4-(4-isothiocyanatobutyl)morpholine (142mg, 0.71mmol) in THF (10ml) was heated at 60°C for 4h. After cooling to room temperature, the solvent was removed under reduced pressure to give a solid (solid B). A quantitative yield was assumed and solid B was used directly in the EDAC coupling reaction.

EDAC.HCl (194mg, 1.01mmol) was added to a stirred solution of solid B (190mg) in DMF (3ml). The reaction mixture was heated at 80°C for 2.5h.

After cooling to room temperature, the reaction mixture was purified using SP4 Biotage (25M, silica gel) eluting with MeOH/DCM (0-10%), followed by MDAP (Basic) to give the title compound as a solid (46.5mg).

[LCMS = 343.3; Acidic]

Description 36: Methyl 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate

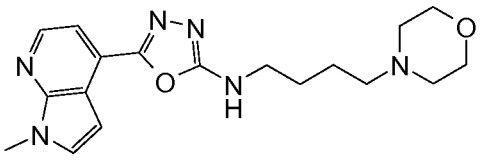


To a stirred solution of methyl 1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (0.15g, 0.85mmol) in THF (10ml) at 0°C was added sodium hydride (60%) (0.07g, 1.70mmol). After 15min, methyl iodide (0.07ml, 1.11mmol) was added to the reaction mixture and the ice bath was removed. The mixture was stirred at room temperature for 2 days. The reaction mixture was quenched with saturated ammonium chloride (10ml), and then extracted with ethyl acetate (10ml x3). The organic layers were combined and washed with brine (30ml), then dried over sodium sulphate, filtered and concentrated. The crude product was used in the next step without further purification.

Description 37: 1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-carbohydrazide

To a solution of methyl 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (60mg, 0.31mmol) in methanol (5ml) was added hydrazine (50-60% in H_2O) (0.22ml, 2.21mmol). The mixture was refluxed at 80°C for 4.5h. After cooling to room temperature, the solvent was removed and dried under vacuum to give the title compound as an oil (53mg).

Example 37: 5-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-N-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine



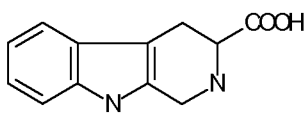
A solution of 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-carbohydrazide (50mg, 0.26mmol) and 4-(4-isothiocyanatobutyl)morpholine (74mg, 0.37mmol) in THF (5ml) was heated at 60°C for 16h. After cooling to room temperature, the solvent was removed under reduced pressure to give a solid (solid C). A quantitative yield was assumed and solid C was used directly in the EDAC coupling reaction.

EDAC.HCl (101mg, 0.53mmol) was added to a stirred solution of solid C in DMF (3ml). The reaction mixture was heated at 80°C for 2.5h.

After cooling to room temperature, the reaction mixture was purified using SP4 Biotage (25M, silica gel) eluting with MeOH/DCM (0-10%), followed by MDAP (Basic) to give the title compound as an oil (7.5mg).

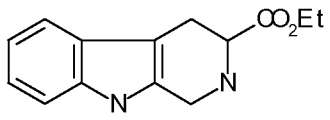
[LCMS = 357.3; Acidic]

Description 38: 2,3,4,9-Tetrahydro-1*H*-β-carboline-3-carboxylic acid



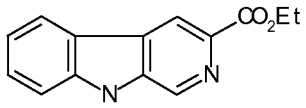
A mixture of (*d,l*) tryptophan (60g), NaOH (12g) and water (120ml) was stirred until clear; then methanol (36ml) was added. This mixture was stirred at room temperature for 2h, then refluxed for 3h. The solution was cooled to room temperature and then neutralized with 5M HCl (aq) and left at 5°C overnight. The resulting solid was filtered off and washed with water, methanol and DCM then dried in vacuo at 100°C to give the title compound (62.7g).

Description 39: Ethyl 2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate



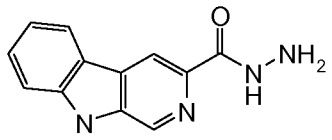
The 2,3,4,9-Tetrahydro-1*H*-β-carboline-3-carboxylic acid (50g) was dissolved in saturated ethanolic HCl (800ml) and refluxed under nitrogen for ~8h. The solvent was removed under reduced pressure and the residue suspended in aq NH_3 (480ml, 14%). This suspension was extracted with trichloromethane (2x480ml) and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue recrystallised from EtOAc to give 9.53g of product.

Description 40: Ethyl 9*H*-β-carboline-3-carboxylate



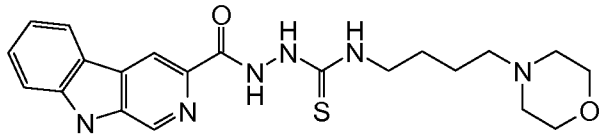
Sulphur (19.2g) was added to ethyl 2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (16.08g) in a solution of xylene and dioxane (600ml each) and refluxed. Further additions of sulphur (13.26g) were made after 2h and 48h time refluxing and refluxing was then continued for a further 3 days. The solvent was removed under reduced pressure and the residue suspended in 1M HCl (aq) (~700ml). This was filtered and the precipitate washed with water (~700ml). The combined aqueous fractions were extracted with tetrachloromethane and then basified with conc. NH_3 (aq) to yield the precipitated product which was left at 5°C over a weekend before filtering and drying in vacuo at 40°C to give a solid (12.04g). The solid was purified on a silica gel column (140g) with 6% EtOH/$CHCl_3$ as eluant. Appropriate fractions were collected and those containing the pure product combined and recrystallised from acetonitrile to yield a crystal powder which was dried in vacuo to give 5.99g of the title compound.

Description 41: 9*H*-β-Carboline-3-carbohydrazide



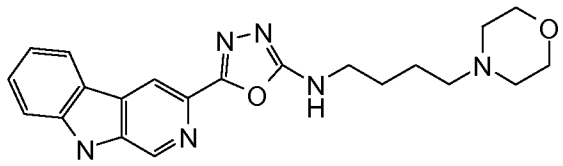
A solution of ethyl 9*H*-β-carboline-3-carboxylate (500mg, 2.08mmol) in methanol (10ml) was added in hydrazine hydrate (50-60%) (1.43ml, 14.57mmol). The mixture was refluxed at 80°C for 21h. After cooling to room temperature, the solvent was removed. Trituration with ether gave the title compound as a solid (452mg).

Description 42: 2-(9*H*-β-Carbolin-3-ylcarbonyl)-*N*-[4-(4-morpholinyl)butyl]hydrazinecarbothioamide



A solution of 9*H*-β-carboline-3-carboxylate (100mg, 0.44mmol) and 4-(4-isothiocyanatobutyl)morpholine (124mg, 0.62mmol) in THF (10ml) was heated at 60°C for 16h. After cooling to room temperature, the solvent was removed under reduced pressure to give the crude product as a solid. A quantitative yield was assumed and the title compound was directly used in the next step reaction.

Example 38: 5-(9*H*-β-Carbolin-3-yl)-*N*-[4-(4-morpholinyl)butyl]-1,3,4-oxadiazol-2-amine



EDAC.HCl (169mg, 0.88mmol) was added to a solution of 2-(9*H*-β-carbolin-3-ylcarbonyl)-*N*-[4-(4-morpholinyl) butylhydrazinecarbothioamide (188mg, 0.44mmol) in DMF (3ml). The reaction mixture was heated at 80°C for 2h. After cooling to room temperature, the reaction mixture was purified using SP4 Biotage (25M, silica gel)

eluting with MeOH/DCM (0-10%), followed by MDAP (Basic) to give the title compound as a solid (22mg).
[LCMS = 393.2; Acidic]

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

Assay 1.

α7 nAChR FLIPR® (Fluorometric Imaging Plate Reader) assay
Function of the heterologous expressed α7 nAChR was assessed by a FLIPR-Ca^{2+} assay. Since nAChRs are non-selective cation channels with high permeability to Ca^{2+}, these studies were carried out by measuring changes of intracellular Ca^{2+} concentration using the Ca^{2+}-chelating fluorescent dye Fluo-4 and FLIPR® (Fluorometric Imaging Plate Reader) technology.

GH4C1cells (pituitary tumor, immortalized cell line) stably transfected with human α7 nAChR (Biocat ID 96986), were thawed, suspended in growth medium (Ham's Nutrient Mixture F10 - Ham's F10, Invitrogen 31550-023, 15% Horse Serum heat inactivated - Invitrogen 26050-047, 2.5% Foetal Bovine Serum - FBS, Gibco 10500-064, 200 µg/ml Hygromycin B - Invitrogen, 10687-010, 10 mg/L Phenol Red - Sigma, P 0290, 1 mM Glutamine - Invitrogen, 25030-024) and plated in 500 cm^2 Triple Flask.
72 hours before an experiment, cells growing in suspension were harvested, centrifuged, resuspended in growth medium at a density of 1.8 x 10^5/mL and plated in coated clear bottom black 384 wells plates (Pierce) at 9000 cells/well. Cells were then incubated at 30°C, 5% CO_2 for 72 hours.

On the day of the experiment, cells were washed twice with Assay Buffer (AB) (145 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 20 mM HEPES, 5.5 mM Glucose pH=7.3) containing 2.5 mM Probenecid. Changes in the intracellular Ca^{2+} content of stably transfected cells were measured using the Ca^{2+} chelating dye Fluo-4 (Tef Labs 0152) in conjunction with a FLIPR® (Molecular Devices). The cell permeant dye Fluo-4 was prepared to a concentration of 1 mM in 100% DMSO and 10% Pluronic acid. The dye was then diluted with AB to a final concentration of 2 µM and placed on the cells. After 45-60 minutes dye loading incubation at 37°C, the unincorporated dye was removed from the cells by washing (80 µL, 3 times) with AB, and a final volume of 30 µL/well of AB was left in each well.

Plates containing test compounds (dissolved in 100% DMSO at 2 mM and serially diluted with DMSO) were copied into "daughter" plates (1 µL/well dispensation). Just prior to starting the assay, the "daughter" plate was diluted with 50 µL/well of AB.

The plates were then placed in the FLIPR®, and cell fluorescence was determined before drug addition (30 seconds) and monitored (excitation 488 nm, emission 510-580 nm) immediately following exposure to compounds. Maximum fluorescence values were recorded and fitted for agonist EC50 calculations.

Results

Compounds of Examples 3, 4, 13, 23 and 24 were tested as HCl salts, the other compounds were tested as free bases.

The compounds of Examples 1, 4-11, 14-18, 21, 24- 32 were tested in the α7 nAChR FLIPR® assay and had a pEC50 of $\geq$ than 5.

The compounds of Examples 1, 26 and 28 were tested in the α7 nAChR FLIPR® assay and had a pEC50 of $\geq$ than 7.

The results are expressed as pEC50 values. A pEC50 is the negative logarithm of the agonist EC50 calculation as determined in the α7 nAChR FLIPR® assay. Certain Examples have been tested more than once. Variations in pEC50 may arise between tests.

Assay 2

α7 nAChR FLIPR® (Fluorometric Imaging Plate Reader) assay

Function of the heterologous expressed α7 nAChR was assessed by a FLIPR-Ca^{2+} assay. Since nAChRs are non-selective cation channels with high permeability to Ca^{2+}, these studies were carried out by measuring changes of intracellular Ca^{2+} concentration using the Ca^{2+}-chelating fluorescent dye Fluo-4 and FLIPR^{TETRA}® (Fluorometric Imaging Plate Reader) technology.

GH4C1cells (pituitary tumor, immortalized cell line) stably transfected with human α7 nAChR (Biocat ID 96986), were thawed, suspended in growth medium (Ham's Nutrient

Mixture F10 - Ham's F10, Invitrogen 11550-043, 15% Horse Serum heat inactivated - Invitrogen 26050-088, 2.5% Foetal Bovine Serum heat inactivated - FBS, Gibco 10500-064, 200 µg/ml Hygromycin B - Invitrogen, 10687-010, 10 mg/L Phenol Red - Sigma, P 0290, 1 mM Glutamine - Invitrogen, 25030-024) and seeded in 175 cm^2 Flasks.
72 hours before an experiment, cells growing in semi-suspension were harvested, centrifuged, resuspended in growth medium at a density of 8 x 10^5/mL and plated in poly-D-lysine coated clear bottom, black wall, 96 well plates (BD Bioscience) at 80,000 cells/well. Cells were then incubated at 30°C, 5% CO_2 for 72 hours.

On the day of the experiment, cells were washed twice with Assay Buffer (AB) (145 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 20 mM HEPES, 5.5 mM Glucose pH 7.4) containing 2.5 mM Probenecid. Changes in the intracellular Ca^{2+} content of stably transfected cells were measured using the Ca^{2+} chelating dye Fluo-4 (Tef Labs 0152) in conjunction with a FLIPR® (Molecular Devices). The cell permeant dye Fluo-4 was prepared to a concentration of 1 mM in 100% DMSO and 20% Pluronic acid. The dye was then diluted with AB to a final concentration of 2 µM and placed on the cells. After 45 minutes dye loading incubation at 37°C, the unincorporated dye was removed from the cells by washing (200 µL, 3 times) with AB, and a final volume of 150 µL/well of AB was left in each well.

Plates containing test compounds, dissolved in AB, at 40µM (from 10 mM, 100% DMSO stock) and serially diluted with AB were placed onto the FLIPR^{TETRA}®. Cell plates were then placed in the FLIPR®, and cell fluorescence was determined before drug addition (30 seconds) and monitored (excitation 488 nm, emission 510-580 nm) immediately following exposure to compounds. Maximum fluorescence values were recorded and fitted for agonist EC50 calculations.

Results

Compounds of Examples 3, 4, 13, 23 and 24 were tested as HCl salts, the other compounds were tested as free bases.

The compounds of Examples 1-6, 8-10, 12, 13, 22-25, 33-38 were tested in the α7 nAChR FLIPR® assay and had a pEC50 of $\geq$ than 5.

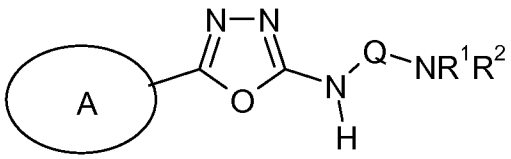
More particularly, the compounds of Examples 1, 2, 8 and 22 exhibited a pEC50 value ≥ 7.

The compound of Example 11, did not appear to have activity in this assay.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

Claims:

1. A compound of formula (I):



(I)

wherein

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or C_{3-6}cycloalkyl;

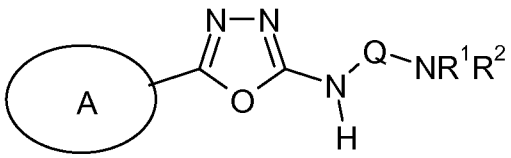
or R^1 and R^2 together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclyl group which is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro;

Q represents $–(CH_2)_n-$ wherein n represents 3 or 4;

A is selected from a 9 to 10 membered fused bicyclic ring system containing 0, 1, 2 or 3 heteroatoms selected from O, N and S with a maximum of 2 heteroatoms present in the same ring, which fused bicyclic ring system which can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl or if at least two substituents are present two of the substitutents can together form a third ring, and 9*H*-β-carbolinyl;

or a salt thereof.

2. A compound as claimed in claim 1 of formula (I)



(I)

wherein

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or C_{3-6}cycloalkyl;

or R^1 and R^2 together with the nitrogen atom to which they are attached form a nitrogen containing heterocyclyl group which is unsubstituted or substituted with 1, 2, or 3 substituents selected from methyl or fluoro;

Q represents $–(CH_2)_n-$ wherein n represents 3 or 4;

A represents a 9 to 10 membered fused bicyclic ring system containing 0, 1, 2 or 3 heteroatoms selected from O, N and S with a maximum of 2 heteroatoms present in the same ring, which fused bicyclic ring system which can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl or if at least two substituents are present two of the substitutents can together form a third ring; or a salt thereof.

3. A compound or salt as claimed in claim 1 or 2 wherein Q represents $-(CH_2)_n-$ wherein n is 4.

4. A compound or salt as claimed in any one of claims 1 to 3 wherein R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system containing a nitrogen atom in addition to 1 or 2 optional additional heteroatoms selected from oxygen, nitrogen or sulphur, and wherein the 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring system is unsubstituted.

5. A compound or salt as claimed in any one of claims 1 to 4, wherein A represents a 9 to 10 membered fused bicyclic ring system selected from indolyl, benzothiazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl and pyrrolopyridinyl, each of which 9 to 10 membered fused bicyclic ring system can be unsubstituted or substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, halo and phenyl.

6. A compound or salt as claimed in any one of claims 1 to 4, wherein A is selected from

- indolyl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl, C_{1-6} alkyl and C_{1-6} alkoxy;
- benzothiazolyl which is unsubstituted or substituted with 1 substituent selected from C_{1-6} alkyl and halo;
- unsubstituted imidazopyridinyl;
- unsubstituted benzothienyl;
- unsubstituted benzofuranyl;
- unsubstituted quinolinyl;
- unsubstituted isoquinolinyl;

- benzimidazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl and C_{1-6} alkyl;
- benzoxazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolopyridinyl which is unsubstituted or substituted with 1 substituent selected from C_{1-6} alkyl.

7. A compound or salt as claimed in any one of claims 1 to 4, wherein A is selected from
- indolyl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl, methyl and methoxy;
- benzothiazolyl which is unsubstituted or substituted with 1 substituent selected from methyl and chloro;
- unsubstituted imidazopyridinyl;
- unsubstituted benzothienyl;
- unsubstituted benzofuranyl;
- unsubstituted quinolinyl;
- unsubstituted isoquinolinyl;
- benzimidazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl and methyl;
- benzoxazolyl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolopyridinyl which is unsubstituted or substituted with 1 substituent selected from methyl.

8. A compound or salt as claimed in any one of claims 1 to 4, wherein A is selected from
- indol-5-yl which is unsubstituted or substituted with 1 to 3 substituents selected from phenyl and methyl;
- unsubstituted indol-7-yl;
- indol-3-yl which is unsubstituted or substituted with 1 substituent selected from phenyl, methyl and methoxy;
- indol-6-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- indol-4-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted indol-2-yl;

- benzothiazol-6-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted benzothiazol-2-yl;
- unsubstituted imidazopyridin-6-yl;
- unsubstituted benzothien-2-yl;
- unsubstituted benzothien-3-yl;
- unsubstituted benzofuran-5-yl;
- unsubstituted benzofuran-2-yl;
- unsubstituted quinolin-3-yl;
- unsubstituted isoquinolin-4-yl;
- benzimidazol-5-yl which is unsubstituted or substituted with 1 substituent selected from phenyl and methyl;
- benzoxazol-6-yl which is unsubstituted or substituted with 1 substituent selected from phenyl; and
- pyrrolo[2,3-b]pyridin-4-yl which is unsubstituted or substituted with 1 substituent selected from methyl;
- unsubstituted pyrrolo[2,3-b]pyridin-5-yl;
- unsubstituted pyrrolo[2,3-b]pyridin-2-yl; and
- unsubstituted pyrrolo[2,3-b]pyridin-3-yl.

9. A compound or salt as claimed in any one of claims 1 to 4, wherein A is indol-5-yl which is substituted with 1 or 2 substituents independently selected from phenyl and methyl or unsubstituted indol-3-yl.

10. A compound or salt as claimed in any one of claims 1 to 4, wherein A represents a 9 to 10 membered fused bicyclic ring system containing 0, 1 or 2 heteroatoms selected from O, N and S, which is substituted with at least two substituents which form a third ring, said third ring is selected from C5-6 carbocyclic and 5-6 membered heterocyclic ring.

11. A compound or salt as claimed in any one of claims 1 to 4, wherein A is selected from
- unsubstituted dihydro-pyrrolo-[1,2-a]-benzimidazolyl; and
- unsubstituted 9*H*-β-carbolinyl.

12. A compound or salt as claimed in any one of the previous claims wherein the salt is a pharmaceutically acceptable salt.

13. A compound or salt as claimed in claim 1 selected from the compounds of Example 1 to 38 or a salt thereof.

14. A compound or salt as claimed in claim 1 or 2 selected from the compounds of Example 1, 2, 8, 22, 26 and 28, or a salt thereof.

15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition as claimed in claim 15 further comprising a pharmaceutical carrier or diluent.

17. A compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

18. A compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof for use in the treatment of neurological diseases, psychiatric disorders, pain related disorders, obesity, sepsis and gastro-intestinal disorders.

19. A method of treating a human or animal subject suffering from neurological diseases, psychiatric disorders, pain related disorders, obesity, sepsis and gastro-intestinal disorders which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

20. Use of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of neurological diseases, psychiatric disorders, pain related disorders, obesity, sepsis and gastro-intestinal disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/066699

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D417/14 C07D471/04 C07D487/04 A61K31/4245
A61P25/00 C07D413/04 C07D417/04 C07D271/113

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 2005/020599 A1 (GALLI FREDERIC [FR] ET AL) 27 January 2005 (2005-01-27) claim 1	

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2009	18/03/2009

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/066699

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	WO 2008/049864 A (NEUROSEARCH AS [DK]; DAHL BJARNE H [DK]; PETERS DAN [DK]; OLSEN GUNNAR) 2 May 2008 (2008-05-02) the whole document	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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