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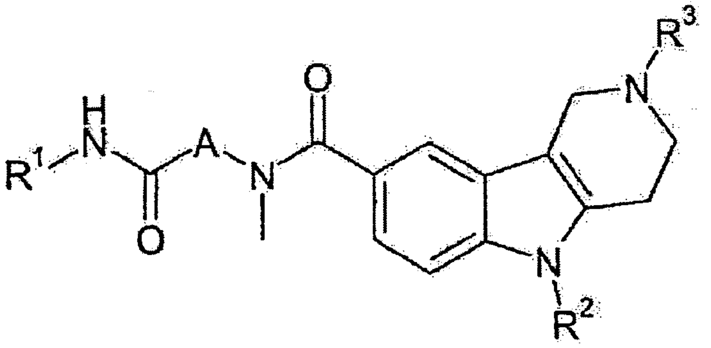

(I)

(57) Abstract: The present invention provides tetrahydro-1H-pyrido [3,4- b] indole derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy. The compounds act as cannabinoid receptor ligands (CB1) and thus may be used in the treatment of pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

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Tetrahydro-1H-pyrido[3,4-b]indole derivatives as CB1 receptor ligands

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., CB_1 receptor, CB_2 receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominately in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB_1 receptor agonists, such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB_1 receptors located in CNS. There are lines of evidence, however, suggesting that CB_1 agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB_1 receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB_1 receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

The term "C_{m-n}" or "C_{m-n} group" refers to any group having m to n carbon atoms.

The term "alkyl" refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-6}alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl can be unsubstituted or substituted with one or two suitable substituents.

The term "cycloalkyl" refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7}cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

The term "cycloalkenyl" refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "aryl" refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "heterocycle" refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" refers to a heterocyclyl having aromatic character.

The term "heterocylcoalkyl" refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 3 to 6 carbon atoms and form 1 to 3 heteroatoms, referred to herein as C_{3-6}heterocycloalkyl.

The term "six-membered" refers to a group having a ring that contains six ring atoms.

The term "five-membered" refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

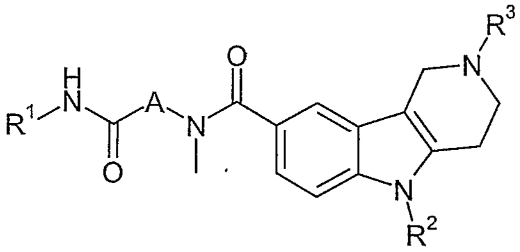
In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

A is $-(CH_2)_n-$ optionally substituted with one or more groups selected from methyl, ethyl, phenyl, benzyl and halogen, wherein n is 2, 3 or 4;

R^1 is selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl and C_{3-6}cycloalkyl;

R^2 is selected from –H, C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)-NR^9R^{10}$, $-S(=O)_2-NR^9R^{10}$, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2-C_{6-10}$aryl, $-S(=O)_2-C_{3-5}$heteroaryl, $-C(=O)-C_{1-6}$alkyl; C_{6-10}aryl-C_{1-4}alkyl; and C_{3-5}heteroaryl-C_{1-4}alkyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2-C_{6-10}$aryl, $-S(=O)_2-C_{3-5}$heteroaryl, $-C(=O)-C_{1-6}$alkyl; C_{6-10}aryl-C_{1-4}alkyl; and C_{3-5}heteroaryl-C_{1-4}alkyl used in defining R^2 is optionally substituted with one or more group selected from -OR, R, $-CO_2H$, $-CO_2-R$; $-SO_2-R$; halogen, $-NO_2$, -OH, $-NH_2$, -NHR, $-C(=O)-NH_2$, and -C(=O)-NHR;

R^3 is selected from C_{3-6}heterocycloalkyl, C_{3-6}heterocycloalkyl-C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl-C_{1-4}alkyl, C_{3-6}heteroaryl-C_{1-4}alkyl, -C(=O)-C_{1-6}alkyl, -C(=O)-C_{3-6}cycloalkyl and -C(=NH)-C_{1-6}alkyl, wherein said C_{3-6}heterocycloalkyl, C_{3-6}heterocycloalkyl-C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl-C_{1-4}alkyl, C_{3-6}heteroaryl-C_{1-4}alkyl, -C(=O)-C_{1-6}alkyl, -C(=O)-C_{3-6}cycloalkyl and -C(=NH)-C_{1-6}alkyl used in defining R^3 is optionally substituted with one or more groups selected from -OR, R, NO_2, $-CO_2H$, $-CO_2$-R; $-SO_2$-R; halogen; -OH; $-NH_2$; -NHR, -C(=O)-NH_2, and -C(=O)-NHR;

R is C_{1-6}alkyl; and

R^9 and R^{10} are independently selected from –H, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}aryl-C_{1-4}alkyl, C_{3-6}heterocyclyl, C_{3-6}heterocyclyl-C_{1-4}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, and C_{3-6}cycloalkyl-C_{1-4}alkyl; N,N-di(C_{1-4}alkyl)amido-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl and C_{1-6}alkoxy-C_{1-6}alkyl.

In another embodiment, A is $-(CH_2)_3-$.

In a further embodiment, A is $-(CH_2)_2-$.

In an even further embodiment, A is $-(CH_2)_4-$.

In another embodiment, A is $-CH_2-CH_2-CH(-Ph)-$.

In another embodiment, A is $-CH_2-CH_2-CH(-CH_2Ph)-$.

In another embodiment, R^1 is selected from methyl, ethyl, 2-fluoroethyl, isopropyl, tert-butyl and cyclopropyl.

In a further embodiment, R^2 is selected from methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, t-butyl, allyl, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2CH_3$, 2-methoxyethyl, tetrahydropyran-4-yl-methyl, 1-propylsulfonyl, methylsulfonyl, ethylsulfonyl, cyclopropylsulfonyl, phenyl, phenylsulfonyl, 2-(methoxycarbonyl)-phenylsulfonyl; 2-(hydroxycarbonyl)-phenylsulfonyl, 1-methyl-1H-imidazol-4-yl-sulfonyl, 1H-imidazol-1-yl-sulfonyl, furylsulfonyl, (5-methylisoxazol-4-yl)sulfonyl, morpholin-4-ylcarbonyl, 4-amino-phenyl, $-CH_2-C(=O)-N(CH_3)_2$, $-C(=O)-N(CH_3)_2$, $-S(=O)_2-N(CH_3)_2$, $-S(=O)_2-NHCH_2CH_3$, $-C(=O)-CH_2CH_2CH_3$, $-CH_2-C(=O)-OCH_3$, $-CH_2-C(=O)-OCH_2CH_3$, $-CH_2-CO_2H$, benzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-methylsulfonyl-benzyl, 4-methylthio-benzyl, 4-acetylamino-benzyl, 4-methoxy-benzyl, 4-ethoxy-benzyl, 2,6-difluorobenzyl, (6-chloro-1,3-benzodioxol-5-yl)methyl, (5-ethoxycarbonyl)-fur-2-yl-methyl, (2-methyl-1,3-thiazol-4-yl)-methyl, (5-methyl-isoxazol-4-yl)-methyl, pyridin-2-ylmethyl, cyclobutylmethyl, and cyclopropylmethyl.

In another embodiment, R^2 is selected from methyl, methylsulfonyl and ethylsulfonyl.

In another embodiment, R^3 is selected from ethyl, isopropyl, propyl, 2-methy-propyl, 1-butyl, 1-pentyl, 1-acetyl-piperidin-4-yl, tetrahydrothien-3-yl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-tetrahydro-2H-pyranyl, tetrahydro-thiopyran-4-yl, 2-pyrimidinyl, 1-iminoethyl, 2-pyridinyl, 3,4,5,6-tetrahydropyrdin-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, 2-pyridinyl-methyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 1-methyl-4-piperidinyl, 4-piperidinyl, (6-methyl-pyridin-2-yl)methyl, (2-ethyl-4-methyl-1H-imidazol-5-yl)methyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-3-ylmethyl, 1-ethyl-1H-pyrazol-4-yl, 1,3-dimethyl-1H-pyrazol-5-yl, (3-methylpyridin-4-yl)methyl, 1,3-oxazol-2-ylmethyl, 1,3-oxazol-5-ylmethyl, 2-(tetrahydro-2H-pyran-4-yl)ethyl, tetrahydro-2H-pyran-4-ylmethyl, 2-phenylethyl, 2-methoxybenzyl, 3,3,3-trifluoropropyl, 2,2-difluoroethyl, 2-hydroxycyclopentyl, (1-ethyl-3-methyl-1H-pyrazol-5-yl)methyl, 2,1,3-benzoxadiazol-5-ylmethyl, 3-thienylmethyl, 2-trifluoromethyl-benzyl, 3-methylbutyl, cyclohex-3-en-1-ylmethyl, 2-fluoro-6-methoxybenzyl, 2-phenyl-propyl, 2-ethyl-butyl, cyclobutylcarbonyl, 2,2-difluoropropanoyl, cyclopentylcarbonyl, tetrahydro-2H-pyran-4-ylcarbonyl, cyclopropylcarbonyl, propylcarbonyl, N-ethylaminocarbonyl, N-isopropylaminocarbonyl, cyclopropylsulfonyl, and ethylsulfonyl.

In a further embodiment, R^3 is selected from ethyl, isopropyl, propyl, 2-methy-propyl, 1-butyl, 1-pentyl, 1-acetyl-piperidin-4-yl, tetrahydrothien-3-yl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-tetrahydro-2H-pyranyl, tetrahydro-thiopyran-4-yl, 1-iminoethyl, 3,4,5,6-tetrahydropyrdin-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, tetrahydrofuran-3-ylmethyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methyl-4-piperidinyl, 2-(tetrahydro-2H-pyran-4-yl)ethyl, tetrahydro-2H-pyran-4-ylmethyl, 3,3,3-trifluoropropyl, 2,2-difluoroethyl, 2-hydroxycyclopentyl, 3-methylbutyl, cyclohex-3-en-1-ylmethyl, and 2-ethyl-butyl.

In an even further embodiment, R^3 is selected from cyclopentyl and 4-tetrahydro-2H-pyranyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB_1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB_1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, obesity, gastrointestinal disorders and cardiovascular disorders. Even furthermore, the compounds of the invention may be useful in enhancing smoking cessation.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, obesity, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

Biological Evaluation

hCB_1 and hCB_2 receptor binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor from BioSignal (hCB_2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 μl. The total and non-specific binding are determined in the absence and presence of 0.2 μM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 μl/well of MS-20 scintillation liquid.

hCB_1 and hCB_2 GTPγS binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM

NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, 0.1% BSA). The EC_{50} and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of $GTPg^{35}S$ per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB_2) or 10 µM (hCB_1) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB2) or 112.5 µM (hCB_1) GDP prior to distribution in plates (15 µM (hCB_2) or 30 µM (hCB_1) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$Ki = IC_{50}/(1+[rad]/Kd),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

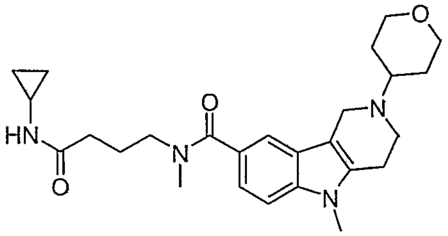
Using the above-mentioned assays, the compounds of the invention are found to be active towards human CB_1 receptors.

EXAMPLES

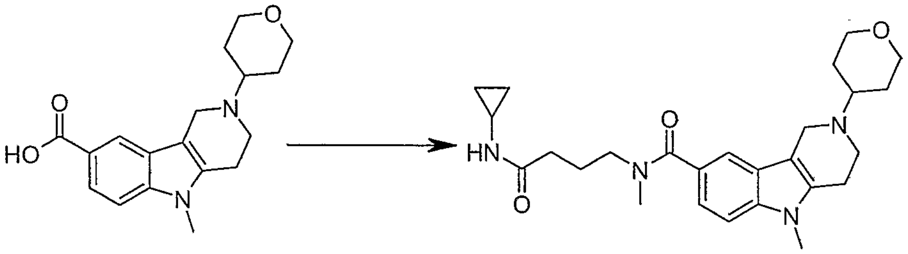
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

_N_-[4-(Cyclopropylamino)-4-oxobutyl]-_N_,5-dimethyl-2-(tetrahydro-2_H_-pyran-4-yl)-2,3,4,5-tetrahydro-1_H_-pyrido[4,3-_b_]indole-8-carboxamide

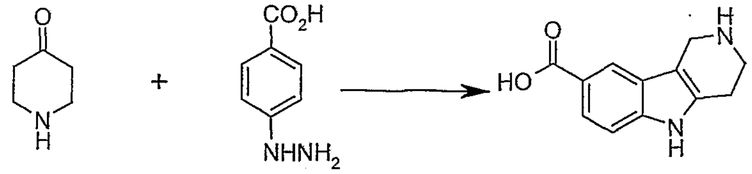


Step A: _N_-[4-(Cyclopropylamino)-4-oxobutyl]-_N_,5-dimethyl-2-(tetrahydro-2_H_-pyran-4-yl)-2,3,4,5-tetrahydro-1_H_-pyrido[4,3-_b_]indole-8-carboxamide



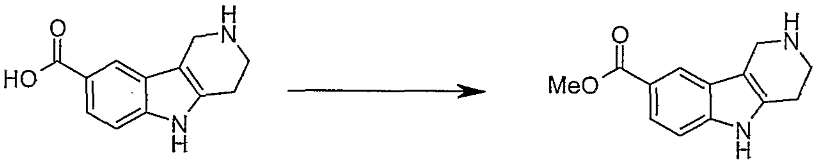
HATU(146 mg, 0.38 mmol) was added portionwise into a mixture of 5-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylic acid (100 mg, 0.32 mmol) (see following steps B, C, D, E, F, G, and H for its preparation), 4-(methylamino) butyric acid hydrochloride (50 mg, 0.32 mmol) and *N*,*N*-diisopropylethylamine (0.3 uL, 1.3 mmol) in dry DMF (5 mL) at 0 °C. The reaction was stirred at room temperature for 2 hours, followed by addition of cyclopropylamine (37 mg, 0.64 mmol) and HATU (146 mg, 0.38 mmol). After stirred overnight, the reaction mixture was concentrated, extracted with EtOAc, washed with water then brine. The crude product was purified by LCMS using high pH column 40-65% acetonitrile gradient to give the title compound as a white solid (TFA salt, 20 mg, 37%). ^{1}H NMR (400 MHz, METHANOL-D4) δ 0.09 - 0.19 (m, 2 H) 0.35 - 0.41 (m, 2 H) 1.73 - 1.93 (m, 6 H) 2.05 - 2.13 (m, 1 H) 2.89 - 3.02 (m, 3 H) 3.12 - 3.19 (m, 3 H) 3.35 - 3.53 (m, 6 H) 3.64 (s, 6 H) 4.03 (dd, *J*=11.72, 4.30 Hz, 4 H) 7.37 (s, 2 H) 7.40 (s, 1 H); MS (APPI) $(M+H)^+$=453.3

Step B. 2,3,4,5-Tetrahydro-1H-pyrido[4-3b]indole-8-carboxylic acid



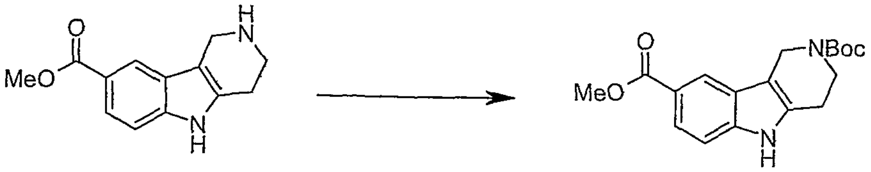
In a 3L round bottom flask with a mechanical stirrer, 3-hydrazinoic acid hydrochloride (55.3 g, 0.29 mol) and 4-piperidone hydrochloride monohydrate (45 g, 0.29 mol) were heated at reflux with dioxane (1L) and hydrochloric acid 12N (100 mL) for 17 hours. After cooling at room temperature, the dioxane was removed by evaporation and ethanol (100 mL) was added. The suspension was cooled in an ice bath and the solid was collected by filtration and washed with ethanol to give a crude product (87.7 g, 118%), which contained ammonium chloride as the impurity, and was used in the next step without further purification. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.44 (s, 1H), 11.63 (s, 1H), 8.13 (s, 1H), 7.70 (dd, 1H, J = 1.6, 8.5 Hz), 7.38 (d, 1H, J = 9.2 Hz), 4.32 (s, 2H), 3.45-3.38 (m, 2H), 3.03 (t, 2H, J = 5.7 Hz).

Step C. 2,3,4,5-Tetrahydro-1*H*-pyrido[4-3b]indole-8-methyl carboxylate



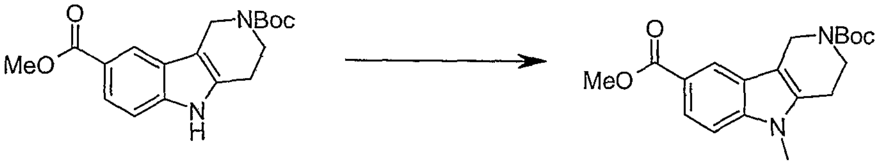
The carboxylic acid (87.7 g) was mixed with methanol in a 3L round bottom flask and cooled in an ice bath. Acetyl chloride (100 mL) was slowly added and the ice bath was removed. The mixture was heated at reflux for 3.5 hours. After cooling at room temperature, the mixture was concentrated by evaporation of methanol and the solid was collected by filtration to provide final product (87.3 g, 111 % for two steps, still containing ammonium chloride). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 9.66 (s, 1H), 8.16 (s, 1H), 7.71 (dd, 1H, J = 1.6, 8.6 Hz), 7.41 (dd, 1H, J = 0.5, 8.5 Hz), 4.33 (s, 2H), 3.82 (s, 3H), 3.43 (s, 2H), 3.03 (t, 2H, J = 5.9 Hz).

Step D. 2-Boc-2,3,4,5-tetrahydro-1*H*-pyrido[4-3b]indole-8-methyl carboxylate



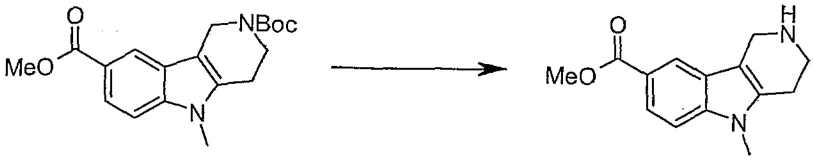
The crude amine (87.3 g) was stirred in methanol (1,5 L) in an ice bath. Then 5N sodium hydroxide solution (60 mL) was slowly added, followed by addition of Boc anhydride (80 g 0.37 mol). The mixture was stirred at room temperature for 2.5 hours. The starting material then disappeared by TLC (AcOEt). The mixture was concentrated by evaporation of methanol and the solid was collected by filtration to give a pink solid (97.3 g, quantitative yield for 3 steps). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.39 (s, 1H), 8.06 (s, 1H), 7.67 (dd, 1H, *J* = 1.7, 8.5 Hz), 7.36 (d, 1H, *J* = 8.5 Hz), 4.55 (s, 2H), 3.81 (s, 3H), 3.69 (t, 2H, *J* = 5.7 Hz), 2.77 (t, 2H, *J* = 5.5Hz), 1.42 (s, 9H).

Step E: 2-*tert*-Butyl 8-methyl 5-methyl-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2,8-dicarboxylate



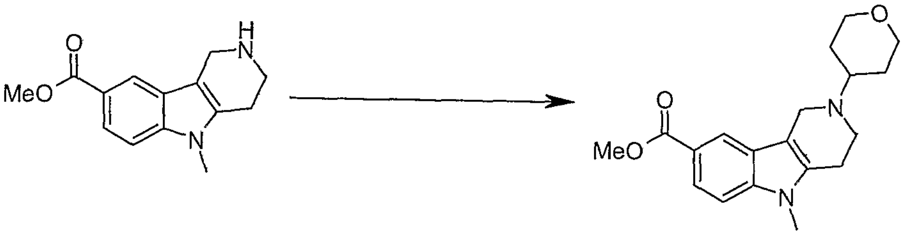
NaH (60% in oil, 6.4 g, 160 mmol) was slowly added into a solution of 2-*tert*-butyl 8-methyl 1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2,8-dicarboxylate(6.3 g, 20 mmol) in DMF at 0°C, followed by addition of iodomethane (10 mL, 160 mmol). After stirred overnight at room temperature, DMF was evaporated and the product was extracted with CH_2Cl_2 and washed with water to obtain the crude product (11 g), which was carried over to the next step. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.49 (s, 9 H) 2.82 (s, 3 H) 3.65 (s, 3 H) 3.84 (s, 3 H) 3.93 (s, 3 H) 7.27 (d, *J*=8.79 Hz, 1 H) 7.89 (d, *J*=8.59 Hz, 1 H) 8.21 (s, 1 H).

Step F: Methyl 5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate



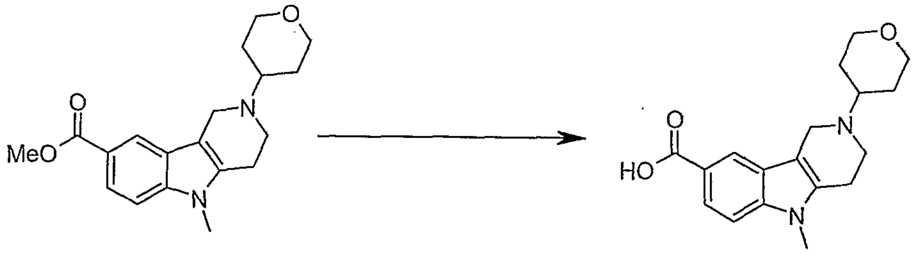
2-*tert*-Butyl 8-methyl 5-methyl-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2,8-dicarboxylate (3.4 g, 10 mmol) was dissolved in (15 mL) CH_2Cl_2, TFA (15 mL) was added and the reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated and lyophilized to yield 3.4 g of crude product as TFA salt, which was carried over to the next step. ^{1}H NMR (400 MHz, METHANOL-D4) δ 3.13 - 3.21 (m, 2 H) 3.66 (t, *J*=6.25 Hz, 2 H) 3.74 (s, 4 H) 3.90 (s, 4 H) 4.48 (dd, 1 H) 7.47 (dd, *J*=8.79, 0.59 Hz, 1 H) 7.89 (dd, *J*=8.69, 1.66 Hz, 1 H) 8.21 (d, *J*=1.56 Hz, 1 H).

Step G: Methyl 5-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate



Methyl 5-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate (1.5 g, 4.2 mmol) was dissolved in a mixture of CH_2Cl_2:MeOH (1:1, 40 mL), triethylamine (1.2 mL, 8.4 mmol) was added, followed by the addition of tetrahydro-4*H*-pyran-4-one (0.8 mL, 8.4 mmol) and $NaBH_3CN$ (528 mg, 8.4 mmol). The reaction mixture was stirred at 50 °C overnight, concentrated and extracted with CH_2Cl_2, washed with $NaHCO_3$ then brine. The crude product (1.7g) was carried over to the next step. MS (APPI) $(M+H)^+$= 329.10.

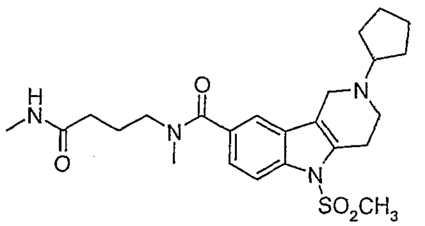
Step H: 5-Methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylic acid



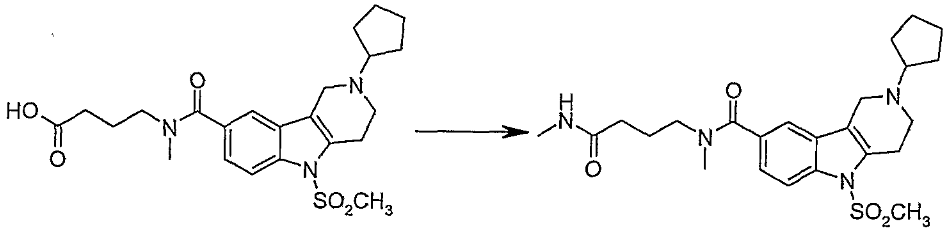
Methyl 5-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate(1.7 g, 5 mmol) was dissolved in a mixture of THF/MeOH/H_2O (1:1:1), KOH (1.4 g, 25 mmol) was added and the reaction was stirred at room temperature for 3 hours. The reaction mixture was neutralized with 5N HCl to pH ~ 5.0, concentrated and used as crude product (1.5 g) for the next step. MS (APPI) $(M+H)^+$=315.11.

Example 2

2-Cyclopentyl-*N*-methyl-*N*-[4-(methylamino)-4-oxobutyl]-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide

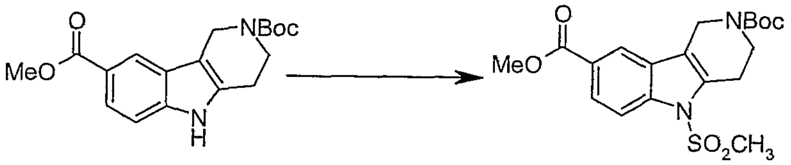


Step A. 2-Cyclopentyl-*N*-methyl-*N*-[4-(methylamino)-4-oxobutyl]-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



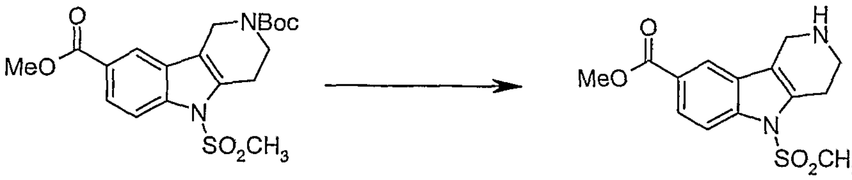
HATU (0.21 g, 0.56 mmol) was added to a solution of 4-[{[2-cyclopentyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid (0.20 g, 0.43 mmol), DIPEA (0.18 mL, 1.0 mmol) and methylamine (2M in THF, 0.25 mL, 0.52 mmol) in DMF (15 mL). The reaction mixture was stirred for 3 hrs. and was then concentrated. The product was purified by preparative reverse-phase HPLC to provide the TFA salt of the title compound as white solid (93 mg, 36 %). ^{1}H NMR (400 MHz, CD_3OD) δ 1.65 - 2.11 (m, 12 H), 2.21 - 2.41 (m, 4 H), 2.44 - 2.56 (m, 1 H), 2.63 - 2.79 (m, 2 H), 2.94 - 3.04 (m, 2 H), 3.09 (s, 1 H), 3.34 - 3.66 (m, 4 H), 3.75 - 3.89 (m, 1 H), 3.90 - 4.06 (m, 1 H), 4.33 - 4.51 (m, 1 H), 4.71 - 4.86 (m, J=13.48, 13.48 Hz, 1 H), 7.43 (dd, J=17.19, 8.79 Hz, 1 H), 7.65 (d, J=18.36 Hz, 1 H), 8.04 (d, J=8.59 Hz, 1 H); MS (ESI) $(M+H)^+$ 475.3.

Step B. 2-Boc-5-methylsulfone-2,3,4,5-tetrahydro-1*H*-pyrido[4-3b]indole-8-methyl carboxylate



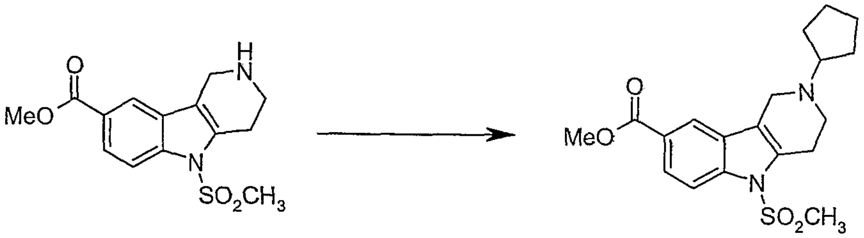
The amine (20 g, 60.5 mmol) was stirred in anhydrous THF (220 mL) with mechanical stirring under a dry nitrogen atmosphere. Sodium hydride (60 %, 6.1 g, 151 mmol, 2.5 eq.) was added to the solution at 0°C. The mixture became thick after warmed to room temperature. Methanesulfonyl chloride (7 mL, 1.5 eq.) was slowly added at 0°C and the mixture was stirred for 1 hour at room temperature. After completion of the reaction by TLC (AcOEt/MeOH 4/6), water (50 mL) was added at 0°C and THF was evaporated. The solid was collected and washed with water to give a yellow powder (27.8 g, with water as the impurity). ^{1}H-NMR (300 MHz, DMSO-d_6) ppm : 8.15 (s, 1H), 7.94 (td, 1H, J = 5.2, 8.8 Hz), 4.57 (s, 2H), 3.87 (s, 3H), 3.70 (t, 2H, J = 5.6Hz), 3.44 (s, 3H), 3.00 (t, 2H, J = 5.4Hz), 1.43 (s, 9H).

Step C. 5-Methylsulfone-2,3,4,5-tetrahydro-1*H*-pyrido[4-3b]indole-8-methyl carboxylate



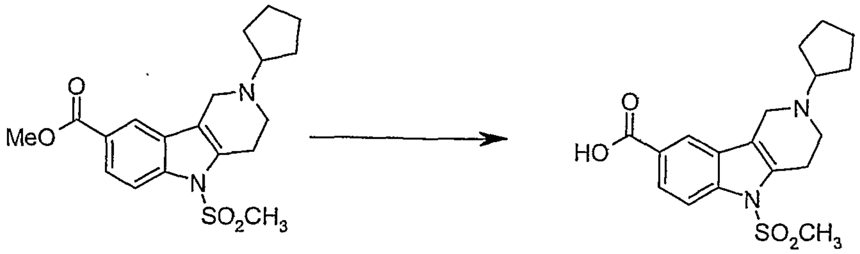
The protected amine (24.7 g, 60.5 mmol) was heated at reflux for 1 hour in methanol (300 mL) and 5N hydrochloric acid in isopropanol (15 mL). After completion of the reaction (TLC MeOH/AcOEt 4/6), the mixture was concentrated by evaporation of methanol and the solid was collected by filtration to give the desired product as its hydrochloride salt (17.7 g, 85 % for 2 steps). The HCl was neutralized by stirring the salt in MeOH and triethylamine and evaporating the solution to dryness. The crude product was used for the next step without any further purification.

Step D. 2-(4-Tetrahydropyranyl)-5-methylsulfone-2,3,4,5-tetrahydro-1*H*-pyrido[4-3b]indole-8-methyl carboxylate



Sodium triacetoxyborohydride (13.5 g, 63.5 mmol, 1.1 eq.) was added into a mixture of cyclopentanone (5.6 mL, 64.5 mmol, 1.1 eq.) and crude methylsulfone-2,3,4,5-tetrahydro-1*H*-pyrido[4-3b]indole-8-methyl carboxylate (17.7 g) in THF (400 mL), followed by addition of acetic acid (6.6 mL, 115.4 mmol, 2 eq.). The mixture was stirred for 16 hours at room temperature. More cyclopentanone (0.5 mL, 0.1 eq.) and sodium triacetoxyborohydride (1.2 g, 0.1 eq.) were then added and the mixture was stirred for an additional 5 hours. After completion of the reaction, saturated sodium carbonate solution (300 mL) was added and THF was evaporated by vacuum. Then the product precipitated as a thick gum. The aqueous phase was decanted and the crude product was used for the next step without any further purification.

Step E. 2-(4-Tetrahydropyranyl)-5-methylsulfone-2,3,4,5-tetrahydro-1*H*-pyrido[4-3b]indole-8-carboxylic acid



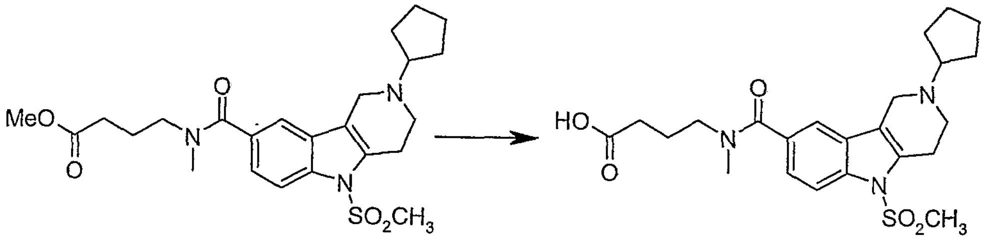
The crude methyl ester was diluted in hot denatured ethanol (350 mL) and 1,2 M lithium hydroxide solution (60 mL) was added. The mixture was heated at reflux for 4 hours. After cooling to room temperature, ethanol was evaporated and water (60 mL) was added. Acetic acid was slowly added to obtain a pH of 5-6. Then the product precipitated as a thick solid that gave to the mixture a creamy texture. After filtration under vacuum, the final product was obtained as a beige solid (free amine). To release the oil coming from NaH (used in the synthesis of an intermediate), the solid was triturated twice with pentane and the product was transformed into the hydrochloric salt by trituration in methanol and HCl/isopropanol 5N. After filtration of the suspension and drying under vacuum, the final product was obtained as a beige powder (12.7 g, 55 %). ^{1}H-NMR (300 MHz, DMSO-d_6) ppm : 8.20 (s, 1H), 7.96-7.89 (m, 2H), 4.05 (s, 2H), 3.41 (s, 3H), 3.15 (s, 5H), 2.05-1.95 (m, 2H), 1.70-1.54 (m, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6) ppm : 168.10, 138.51, 127.89, 126.66, 126.03, 113.95, 66.49, 49.08, 47.54, 41.94, 29.80, 24.25.

Step F. Methyl 4-[{[2-cyclopentyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoate

2-Cyclopentyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylic acid (3.0 g, 7.5 mmol) and $SOCl_2$ (20 mL) were mixed together and heated to 85°C for 3 hrs. The reaction mixture was evaporated to dryness and the solid residue was added to a solution of the HCl salt of methyl 4-(methylamino)butanoate (3.8 g, 22 mmol) and DIPEA (13 mL, 75 mmol) in DCM (280 mL) at 0°C. The reaction mixture was stirred for 2 hrs. and the solvent was concentrated. The product was purified by normal-phase MPLC using 2% Et_3N, 5% MeOH and 10% acetone in DCM to provide the title compound as a yellow solid (2.59 g, 72 %). ^{1}H NMR (400 MHz, CD_3OD) δ 1.46 - 1.71 (m, 4 H), 1.72 - 1.92 (m, 3 H), 1.93 - 2.14 (m, 3 H), 2.14 - 2.23 (m, *J*=6.64, 6.64 Hz, 1 H), 2.41 - 2.52 (m, 1 H), 2.84 - 2.94 (m, *J*=8.11, 8.11 Hz, 1 H), 2.94 - 3.03 (m, 4 H), 3.03 - 3.14 (m, 4 H), 3.16 (s, 3 H), 3.34 - 3.41 (m, 1

H), 3.56 - 3.63 (m, J=6.45, 6.45 Hz, 1 H), 3.68 (s, 2 H), 3.73 - 3.83 (m, 2 H), 7.24 - 7.43 (m, J=9.37, 9.37 Hz, 1 H), 7.49 - 7.62 (m, J=8.20 Hz, 1 H), 8.02 (d, J=8.59 Hz, 1 H); MS (ESI) $(M+H)^+$ 476.2.

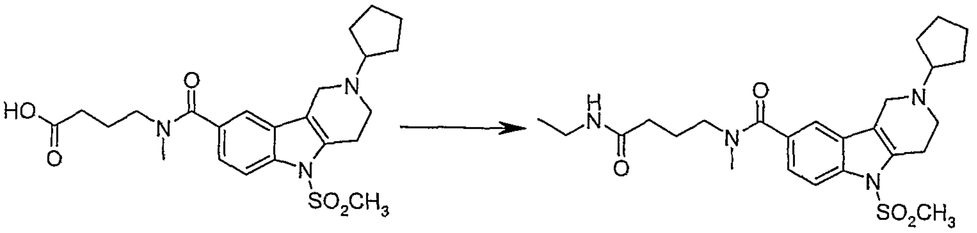
Step G. 4-[{[2-Cyclopentyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid



MeOH (4 mL) was added to a mixture of methyl 4-[{[2-cyclopentyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoate (2.4 g, 5.1 mmol), LiOH 2M (4 mL) and water (40 mL). The reaction mixture was stirred for 5 hrs. and concentrated to 40 mL. The solution was neutralized at 0°C to pH 6 using HCl (2M). The solvent was evaporated to dryness by azeotropic co-evaporation with EtOH to provide the title compound as a white solid, which was used in the next step without further purification. MS (ESI) $(M+H)^+$ 462.2.

Example 3

2-Cyclopentyl-*N*-[4-(ethylamino)-4-oxobutyl]-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide

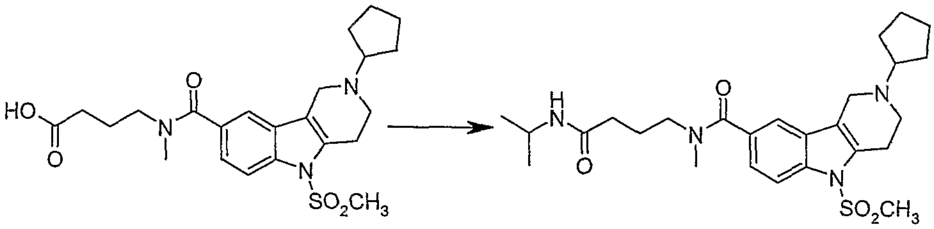


Following the procedure for Step A in Example 2, using ethylamine in THF (2M, 0.25 mL, 0.52 mmol) provided the TFA salt of the title compound as a white solid (77 mg, 29 %). ^1H NMR (400 MHz, CD_3OD) δ 0.94 (t, J=7.13 Hz, 1 H), 1.12 (t, J=7.23 Hz, 1

H), 1.65 - 2.11 (m, 12 H), 2.19 - 2.44 (m, 4 H), 3.00 (s, 3 H), 3.11 (s, 2 H), 3.21 (q, *J*=7.23 Hz, 1 H), 3.35 - 3.67 (m, 4 H), 3.84 (t, *J*=7.91 Hz, 1 H), 3.92 - 4.07 (m, *J*=5.27 Hz, 1 H), 4.33 - 4.50 (m, *J*=18.55 Hz, 1 H), 4.70 - 4.87 (m, 1 H), 7.44 (dd, *J*=17.28, 9.08 Hz, 1 H), 7.66 (d, *J*=18.55 Hz, 1 H), 8.06 (d, *J*=8.59 Hz, 1 H); MS (ESI) (M+H)$^+$ 489.3.

Example 4

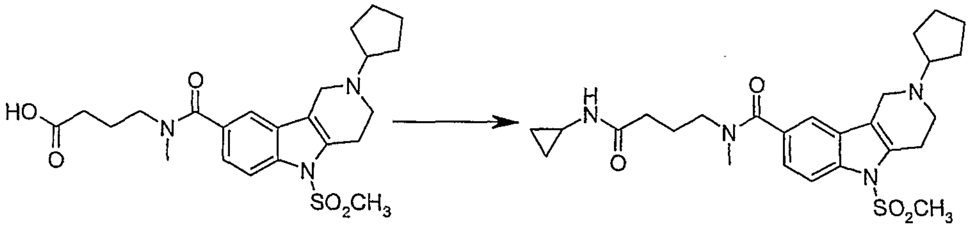
2-Cyclopentyl-*N*-[4-(isopropylamino)-4-oxobutyl]-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



Following the procedure for Step A in Example 2, using isopropylamine (0.03 g, 0.52 mmol) provided the TFA salt of the title compound as a white solid (73 mg, 27 %). ^{1}H NMR (400 MHz, CD$_3$OD) δ 0.95 (d, *J*=6.44 Hz, 3 H), 1.13 (d, *J*=6.45 Hz, 3 H), 1.65 - 2.10 (m, 13 H), 2.15 - 2.44 (m, 4 H), 2.99 (s, 2 H), 3.10 (s, 1 H), 3.34 - 3.64 (m, 4 H), 3.83 (t, *J*=7.81 Hz, 1 H), 3.90 - 4.07 (m, 1 H), 4.32 - 4.51 (m, *J*=9.96, 9.96 Hz, 1 H), 4.71 - 4.85 (m, *J*=13.28, 13.28 Hz, 1 H), 7.43 (dd, *J*=19.82, 8.50 Hz, 1 H), 7.66 (d, *J*=20.12 Hz, 1 H), 8.04 (d, *J*=8.59 Hz, 1 H); MS (ESI) (M+H)$^+$ 503.3.

Example 5

2-Cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide

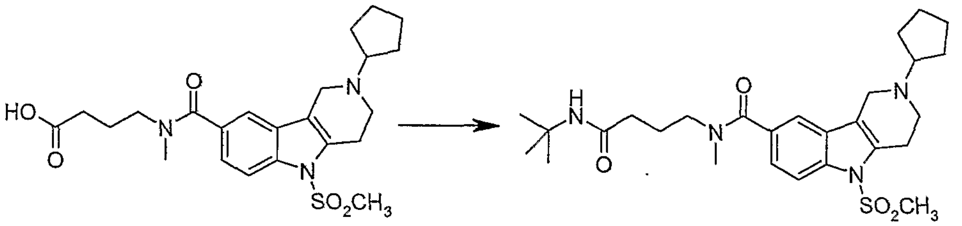


Following the procedure for Step A in Example 2, using cyclopropylamine (0.03 g, 0.52 mmol) provided the TFA salt of the title compound as a white solid (58 mg, 21 %). ^{1}H NMR (400 MHz, CD$_3$OD) δ 0.16 - 0.33 (m, 1 H), 0.42 - 0.54 (m, 1 H), 0.58

(d, J=6.25 Hz, 1 H), 0.71 (d, J=6.84 Hz, 1 H), 1.66 - 2.10 (m, 12 H), 2.19 - 2.39 (m, 4 H), 3.00 (s, 2 H), 3.10 (s, 1 H), 3.30 - 3.34 (m, J=1.17 Hz, 4 H), 3.58 (t, J=6.93 Hz, 1 H), 3.84 (t, J=7.91 Hz, 1 H), 3.92 - 4.07 (m, 1 H), 4.33 - 4.53 (m, 1 H), 4.71 - 4.86 (m, 1 H), 7.44 (dd, J=17.67, 8.89 Hz, 1 H), 7.66 (d, J=18.36 Hz, 1 H), 8.06 (dd, J=8.69, 0.68 Hz, 1 H); MS (ESI) $(M+H)^+$ 501.3.

Example 6

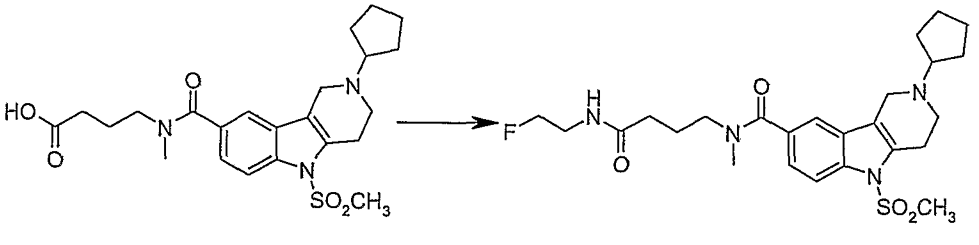
N-[4-(*tert*-Butylamino)-4-oxobutyl]-2-cyclopentyl-N-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



Following the procedure for Step A in Example 2, using *tert*-butylamine (0.04 g, 0.52 mmol) provided the TFA salt of the title compound as a white solid (99 mg, 36 %). ^{1}H NMR (400 MHz, CD_3OD) δ 1.14 (s, 4 H), 1.33 (s, 5 H), 1.67 - 2.05 (m, 12 H), 2.21 (t, J=7.81 Hz, 1 H), 2.26 - 2.42 (m, 3 H), 2.94 - 3.04 (m, 2 H), 3.05 - 3.15 (m, 1 H), 3.33 - 3.66 (m, 4 H), 3.75 - 3.91 (m, 1 H), 3.91 - 4.08 (m, 1 H), 4.33 - 4.53 (m, 1 H), 4.67 - 4.84 (m, 1 H), 7.44 (dd, J=19.53, 8.98 Hz, 1 H), 7.66 (d, J=19.33 Hz, 1 H), 8.05 (d, J=8.79 Hz, 1 H); MS (ESI) $(M+H)^+$ 517.3.

Example 7

2-Cyclopentyl-N-{4-[(2-fluoroethyl)amino]-4-oxobutyl}-N-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide

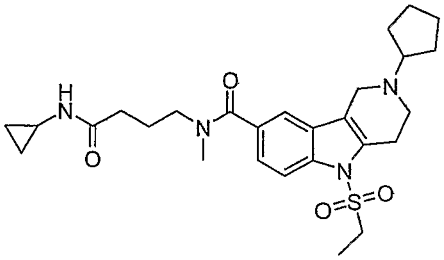


Following the procedure for Step A in Example 2, using 2-fluoroethylamine (0.05 g, 0.52 mmol) provided the TFA salt of the title compound as a white solid (80 mg, 29 %). ^{1}H NMR (400 MHz, CD_3OD) δ 1.63 - 2.19 (m, 12 H), 2.22 - 2.47 (m, 4 H), 3.01

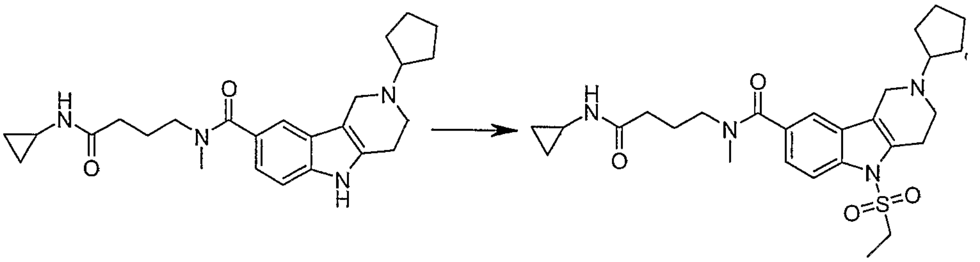
(s, 2 H), 3.11 (s, 1 H), 3.35 - 3.69 (m, 8 H), 3.84 (t, *J*=7.62 Hz, 1 H), 4.14 - 4.36 (m, 1 H), 4.36 - 4.57 (m, 1 H), 4.72 - 4.87 (m, 1 H), 7.44 (dd, *J*=16.99, 9.18 Hz, 1 H), 7.67 (d, *J*=16.80 Hz, 1 H), 8.06 (d, *J*=8.40 Hz, 1 H); MS (ESI) $(M+H)^+$ 507.3.

Example 8

2-Cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-5-(ethylsulfonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



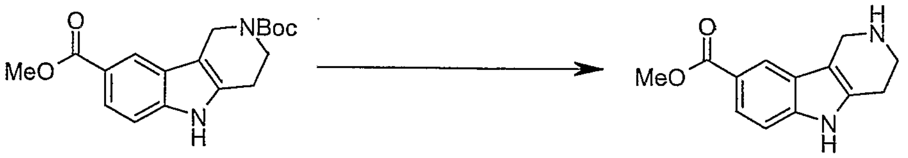
Step A. 2-Cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-5-(ethylsulfonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



NaH (0.18 g, 4.7 mmol) was added to a solution of cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-*N*-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide (0.20 g, 0.47 mmol) in DMF (20 mL) under nitrogen atmosphere. The reaction mixture was stirred for 3 hrs. Ethyl sulfonyl chloride (0.44 mL, 4.7 mmol) was added and the reaction mixture was stirred for 2 hrs. The reaction mixture was slowly added to a mixture of $NaHCO_3$ (0.40 g, 4.8 mmol) and MeOH (80 mL) at -78°C. The resulting mixture was allowed to warm to ambient temperature and the solvent was concentrated. CH_2Cl_2 (20 mL) was added and the precipitated salts were filtered. The filtrate was concentrated and the product was purified by preparative reverse-phase HPLC to provide the TFA salt of the title compound as a white solid (60 mg, 20 %). ^1H NMR (400 MHz, CD_3OD) δ 0.17 - 0.52 (m, *J*=89.06 Hz, 2 H), 0.53 - 0.78 (m, 2 H), 1.23 (t, *J*=6.84 Hz, 3 H), 1.64 - 2.10 (m, 12 H), 2.16 -

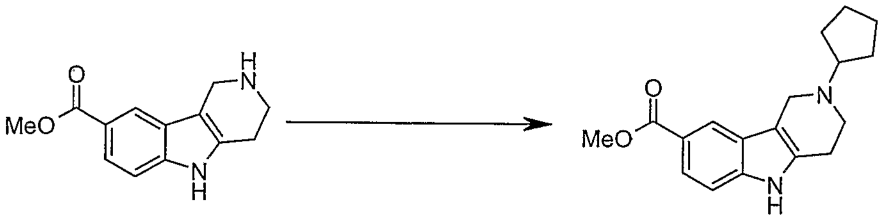
2.43 (m, 4 H), 3.00 (s, 2 H), 3.10 (s, 1 H), 3.41 - 3.67 (m, 4 H), 3.74 - 3.90 (m, 1 H), 3.95 - 4.06 (m, J=13.87 Hz, 1 H), 4.33 - 4.54 (m, J=13.38, 13.38 Hz, 1 H), 4.74 - 4.87 (m, 1 H), 7.44 (dd, J=17.87, 9.86 Hz, 1 H), 7.67 (d, J=18.16 Hz, 1 H), 8.05 (d, J=9.37 Hz, 1 H); MS (ESI) $(M+H)^+$ 515.3.

Step B. Methyl 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate



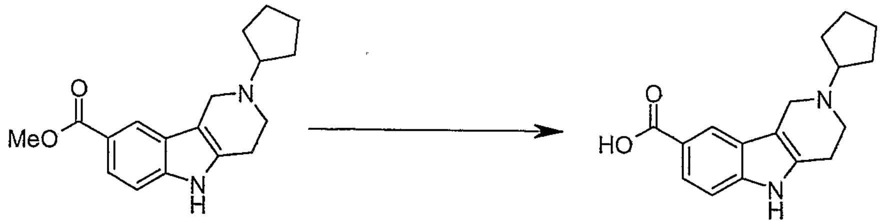
2-*tert*-Butyl 8-methyl 1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indole-2,8-dicarboxylate (5.4 g, 16 mmol) was added to TFA (40 mL) in CH_2Cl_2 (40 mL). The solution was stirred for 1 hr. and concentrated to dryness. The residue was recovered in water (50 mL), stirred at 0°C for 1 hr. and filtered. The solid was thoroughly washed with ether (2 x 150 mL), filtered and dried to provide the pure TFA salt of the title compound as a pink solid (5.6 g, 99 %). MS (ESI) $(M+H)^+$ 231.0.

Step C. Methyl 2-cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate



Cyclopentanone (5.6 mL, 63 mmol) was added to a solution of methyl 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate (5.6 g, 16 mmol) in EtOH (80 mL). The solution was stirred for 1 hr. and $NaBH(OAc)_3$ (5.3 g, 25 mmol) was added. The reaction mixture was stirred for 4 hrs. and the solvent was concentrated. The product was purified by normal-phase MPLC using 2% Et_3N, 5% MeOH and 10% acetone in DCM to provide the title compound as a pale-yellow solid (4.56 g, 94 %). MS (ESI) $(M+H)^+$ 299.1.

Step D. 2-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylic acid

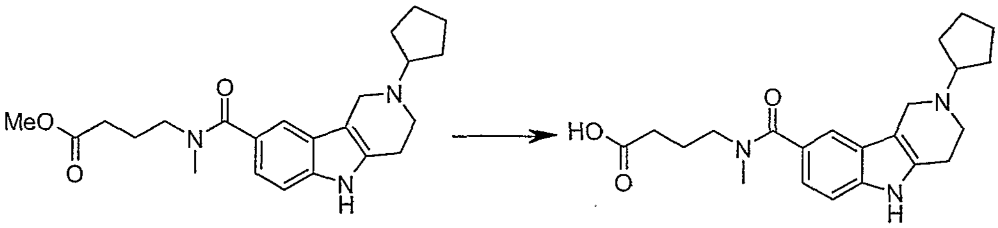


MeOH (15 mL) was added to a mixture of methyl 2-cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylate (4.5 g, 15 mmol) and NaOH 2M (50 mL). The reaction mixture was heated to 85°C upon clear solution obtained and was concentrated to 50 mL. The solution was neutralized with concentrated HCl at 0°C. The precipitate was filtered, washed with ether and dried to provide the pure title compound as a pink solid (4.25 g, 98 %). MS (ESI) $(M+H)^+$ 285.1.

Step E. Methyl 4-[[(2-cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)carbonyl](methyl)amino]butanoate

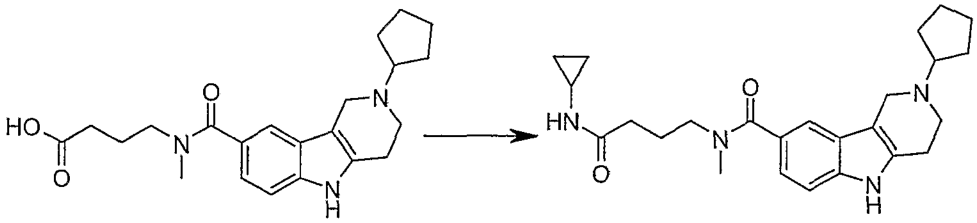
Following the procedure for Step F in Example 2, using 2-cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylic acid (1.0 g, 3.6 mmol) provided the title compound as a colorless oil (0.72 g, 49 %). ^{1}H NMR (400 MHz, CD_3OD) δ 1.48 - 1.70 (m, 5 H), 1.70 - 1.82 (m, 2 H), 1.81 - 2.11 (m, 5 H), 2.84 - 2.94 (m, 3 H), 2.94 - 2.99 (m, *J*=5.37, 5.37 Hz, 2 H), 3.00 - 3.12 (m, 3 H), 3.36 - 3.73 (m, 5 H), 3.76 - 3.84 (m, 2 H), 7.03 - 7.15 (m, *J*=7.03 Hz, 1 H), 7.32 (d, *J*=8.20 Hz, 1 H), 7.42 - 7.52 (m, 1 H); MS (ESI) $(M+H)^+$ 398.2.

Step F. 4-[[(2-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)carbonyl](methyl)amino]butanoic acid



MeOH (4 mL) was added to a mixture of methyl 4-[[(2-cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)carbonyl](methyl)amino]butanoate (0.70 g, 1.7 mmol) and NaOH (2M, 20 mL). The reaction mixture was heated to 60°C upon a clear solution, and was then concentrated to 20 mL. The solution was neutralized with concentrated HCl at 0°C. The precipitate was filtered, washed with ether and dried to provide the pure title compound as a pink solid (0.66 g, 97 %). MS (ESI) $(M+H)^+$ 384.2.

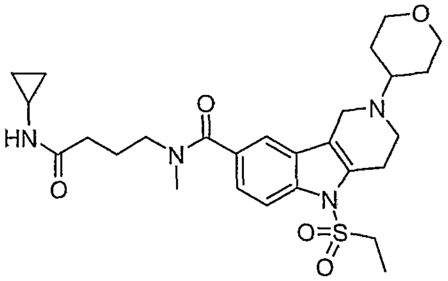
Step G. 2-Cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-*N*-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



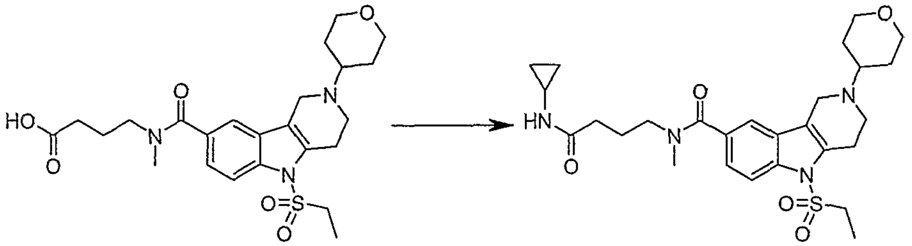
Following the procedure for Step A in Example 2, using 4-[[(2-cyclopentyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl)carbonyl](methyl)amino]butanoic acid (0.65 g, 1.7 mmol) and cyclopropylamine (0.14 g, 2.5 mmol) provided the title compound as a white solid (0.70 g, 97 %). ^{1}H NMR (400 MHz, CD_3OD) δ 0.15 - 0.31 (m, *J*=3.71 Hz, 2 H), 0.42 - 0.53 (m, 2 H), 0.62 - 0.79 (m, *J*=7.52, 7.52 Hz, 2 H), 1.68 - 2.06 (m, 12 H), 2.15 - 2.43 (m, 4 H), 2.97 - 3.13 (m, *J*=19.33 Hz, 2 H), 3.13 - 3.28 (m, 1 H), 3.46 - 3.66 (m, 1 H), 3.75 - 3.88 (m, *J*=7.71, 7.71 Hz, 1 H), 3.89 - 4.02 (m, *J*=13.09 Hz, 1 H), 4.31 - 4.48 (m, 1 H), 4.69 - 4.85 (m, *J*=15.82 Hz, 1 H), 7.16 - 7.29 (m, 1 H), 7.35 - 7.47 (m, *J*=8.40, 0.59 Hz, 1 H), 7.53 - 7.64 (m, 1 H); MS (ESI) $(M+H)^+$ 423.3.

Example 9

N-[4-(Cyclopropylamino)-4-oxobutyl]-5-(ethylsulfonyl)-N-methyl-2-(tetrahydro-2H-pyran-4-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole-8-carboxamide

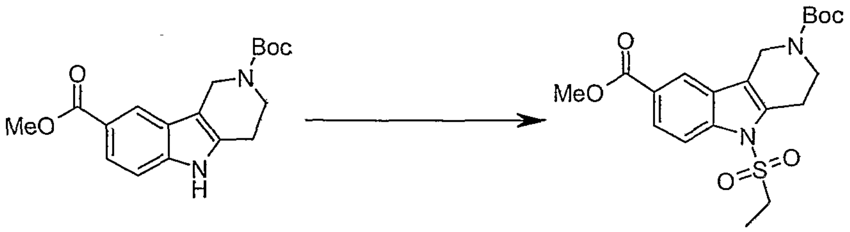


Step A. N-[4-(Cyclopropylamino)-4-oxobutyl]-5-(ethylsulfonyl)-N-methyl-2-(tetrahydro-2H-pyran-4-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole-8-carboxamide



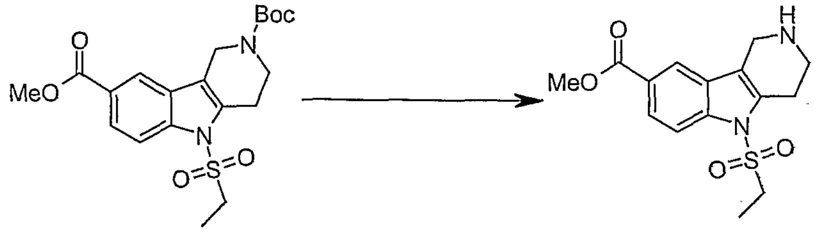
Following the procedure for Step A in Example 2, using 4-[{[5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid hydrochloride (107 mg, 0.20 mmol), cyclopropylamine (23 mg, 0.40 mmol), *N,N*-diisopropylethylamine (77 mg, 104 uL, 0.60 mmol) and HATU (99 mg, 0.26 mmol) in DMF (5 mL). The crude product was purified by reverse-phase HPLC using high pH column 20-40% acetonitrile gradient to give the title compound as a white solid (63 mg, 60%). ^{1}H NMR (400 MHz, METHANOL-D4) δ -0.09 - 0.06 (m, 1 H), 0.16 - 0.27 (m, 1 H), 0.28 - 0.36 (m, 1 H), 0.41 - 0.50 (m, 1 H), 0.97 (t, *J*=7.03 Hz, 3 H), 1.55 - 1.79 (m, 5 H), 1.86 - 2.05 (m, 3 H), 2.10 - 2.24 (m, 0.5 H), 2.35 - 2.44 (m, 0.5 H), 2.75 (s, 1.5 H), 2.84 (s, 1.5 H), 3.12 - 3.38 (m, 10 H), 3.41 - 3.55 (m, 1 H), 3.66 - 3.82 (m, 1 H), 3.88 (dd, *J*=11.52, 4.30 Hz, 2 H), 4.14 - 4.57 (m, 2 H), 7.19 (m, 1 H), 7.38 (s, 0.5 H), 7.43 (s, 0.5 H), 7.79 (d, *J*=8.79 Hz, 1 H); MS (APPI) $(M+H)^+$=531.2.

Step B. 2-*tert*-Butyl-8-methyl-5-(ethylsulfonyl)-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2,8(5*H*)-dicarboxylate



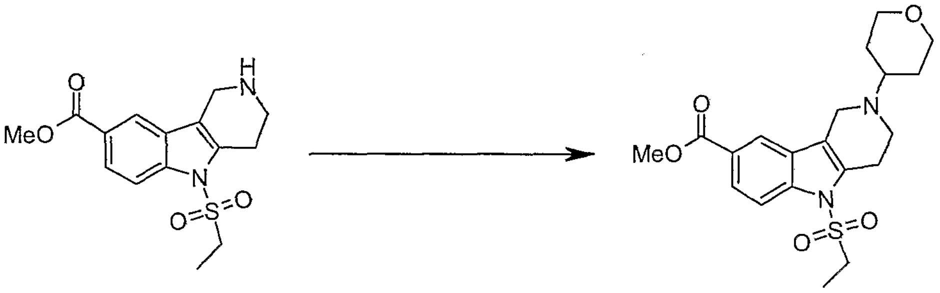
In a three-neck round bottom flask, equipped with a mechanical stirrer and under a nitrogen atmosphere, the indole (40.0 g, 121mmol) was dissolved in dry THF (400 mL). The solution was cooled at 0 °C and NaH (7.03 g, 145 mmol) was added portionwise over 20 minutes. The ice bath was then removed and the mixture was stirred at room temperature for 30 minutes. After 30 minutes, the mixture was cooled at 0 °C and ethanesulfonyl chloride (17 mL, 179 mmol) was added slowly. The mixture was then stirred for one hour at 0 °C and then at room temperature for 3 hours. The solution was cooled at 0 °C and water was slowly added to quench excess of sodium hydride. THF was removed under reduced pressure. Water (200 mL) and ethyl acetate (300 mL) was added to the residue. A solid precipitated out, was removed by filtration and set aside. The phases were separated. The organic phase was washed with $NaHCO_3$ (5%), brine, dried over Na_2SO_4 and then concentrated to give a beige solid. The solid collected previously by filtration contained salts. It was dissolved in a mixture of EtOAc (800 mL) and water (200 mL). The phases were separated. The organic portion was washed with brine, dried over Na_2SO_4 and concentrated to give a white solid. Both solids were reunited and triturated in ether, recovered by filtration and dried under vacuum to yield the titled compound (35.5 g, 70%).

Step C. Methyl 5-(ethylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole-8-carboxylate



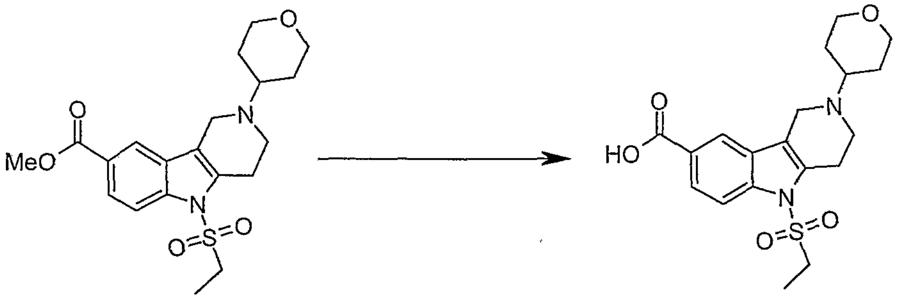
The protected amine (18.8 g, 44.6 mmol) was suspended in methanol and a solution of 5M HCl in isopropanol (15 mL) was added. The mixture was heated at reflux for one hour. The mixture was cooled down to room temperature and a solid precipitated. Half of the methanol was removed under reduced pressure and ether (500 mL) was added to the suspension. The mixture was cooled at 0 °C and stirred for 15 minutes. The solid was collected by filtration, washed with cold ether and dried under vacuum to yield the amine as its hydrochloride salt (16.0 g, 99 %).

Step D. Methyl 5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole-8-carboxylate



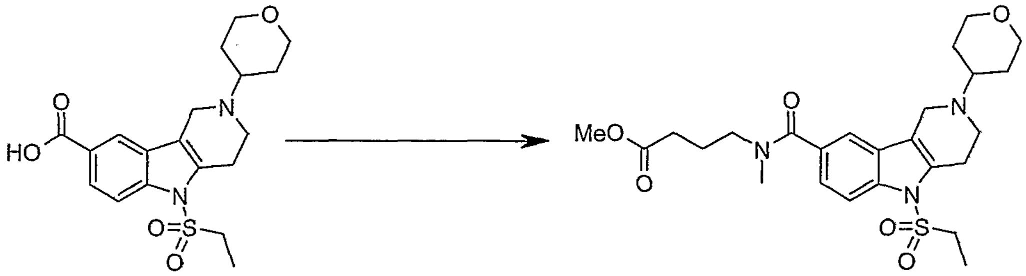
The amine (16.0 g, 44.6 mmol) was suspended in THF (400 mL). Triethylamine (7.0 mL, 50 mmol) was added and the mixture was stirred for 10 minutes at room temperature. Ketone (5.0 mL, 54 mmol), NaBH(OAc)$_3$ (10.4 g, 49.0 mmol) and acetic acid (3.0 mL, 52 mmol) were then added. The mixture was stirred overnight at room temperature. After 16 hours, TLC (95/5/0.1 CH_2Cl_2/MeOH/NH_4OH) showed some starting material left. The ketone (1 mL) and NaBH(OAc)$_3$ (1.02 g) were added and the mixture was stirred at room temperature for 8 hours. After that time, there was still some starting material left. The ketone (0.5 mL), NaBH(OAc)$_3$ (1.9 g), Et_3N (0.7 mL) and AcOH (2.5 mL) were added and the mixture was stirred overnight. The solid was then filtered off and discarded and the solvent was evaporated. The residue was taken up in dichloromethane and the organic phase was washed with a saturated solution of Na_2CO_3, dried over Na_2SO_4 and concentrated to give the titled compound which was used without any further purification for the next step (19.1 g).

Step E. 5-(Ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole-8-carboxylic acid



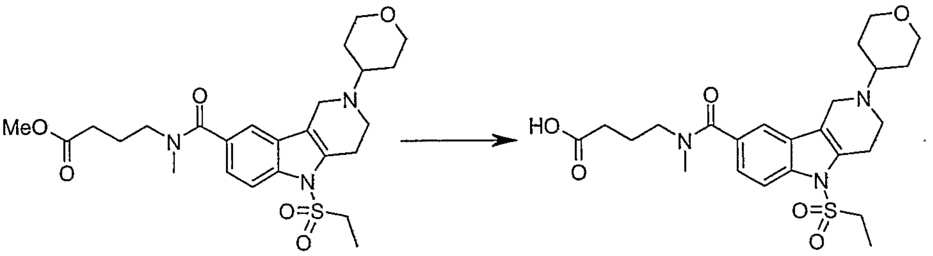
The methyl ester (18.1 g , a wet solid, 44 mmol) was dissolved in a mixture of THF (70 mL) and methanol (40 mL). An aqueous solution of NaOH (20 mL, 5N, 100 mmol) was added and the mixture was stirred at room temperature overnight. The solvents were then concentrated under reduced pressure. The remaining aqueous solution was diluted with water and acetic acid was added until the pH reached 5. The mixture was cooled at 0 °C and the material came out as a sticky gum. Water was decanted and set aside. The gum was triturated in methanol and a solid formed. This solid was recovered by filtration. The aqueous solution was concentrated under vacuum until a solid came out. This solid was recovered by filtration and added to the solid previously isolated. The beige solid was then suspended in methanol and a solution of 5M HCl in isopropanol was added until all the material went into solution. The solution was stirred for 10 minutes and cooled down at 0 °C and a precipitate formed. This precipitate was collected by filtration. The solid was triturated in ether and dried under vacuum to yield the titled compound (10.4 g, 55 %).

Step F. Methyl 4-[{[5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoate



Following the procedure for Step F in Example 2, using 5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxylic acid hydrochloride (4.29 g, 10 mmol), methyl 4-(methylamino)butanoate (1.97 g, 15 mmol), *N,N*-diisopropylethylamine (3.88 g, 5.23 mL, 30 mmol) and HATU (4.94 g, 13 mmol) in DMF (40 mL). The crude product was purified by MPLC on silica gel using CH_2Cl_2/MeOH (20:1) to give the title compound as a white solid (1.91 g, 38 %). ^1H NMR (400 MHz, METHANOL-D4) δ 1.21 (t, *J*=7.32 Hz, 3 H), 1.83 - 2.03 (m, 4 H), 2.10 - 2.23 (m, 4 H), 2.44 (t, *J*=6.93 Hz, 1 H), 2.99 (s, 1.5 H), 3.08 (s, 1.5 H), 3.31 - 3.39 (m, 1 H), 3.42 - 3.55 (m, 7 H), 3.60 (t, *J*=7.23 Hz, 2 H), 3.65 - 3.77 (m, 3 H), 4.12 (dd, *J*=11.72, 4.10 Hz, 2 H), 4.36 - 4.83 (m, 2 H), 7.37 - 7.48 (m, 1 H), 7.66 (s, 1 H), 8.03 (d, *J*=8.79 Hz, 1 H); MS (APPI) $(M+H)^+$= 506.2.

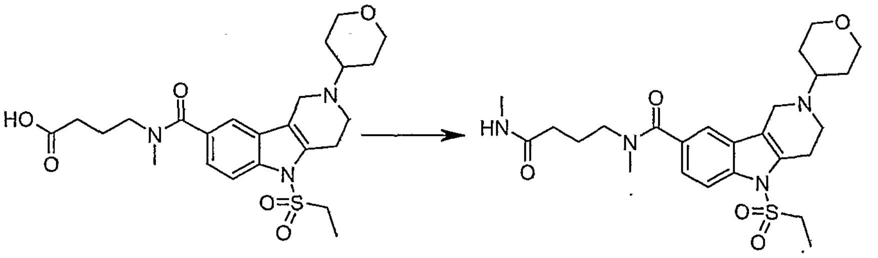
Step G. 4-[{[5-(Ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid



Lithium hydroxide (0.18 g, 7.55 mmol) was added to a solution of methyl 4-[{[5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoate (1.91 g, 3.78 mmol) in 70 mL of THF-H_2O (7:3). Stirring for 1.5 h at room temperature, the reaction mixture was neutralized by 2*N* HCl until pH= 5-6. After concentration and dried *in vacuo*, a white solid was obtained as a hydrochloride salt (2.01 g, 99%). The crude product was used directly for the next step without further purification. MS (APPI) $(M+H)^+$=492.3.

Example 10

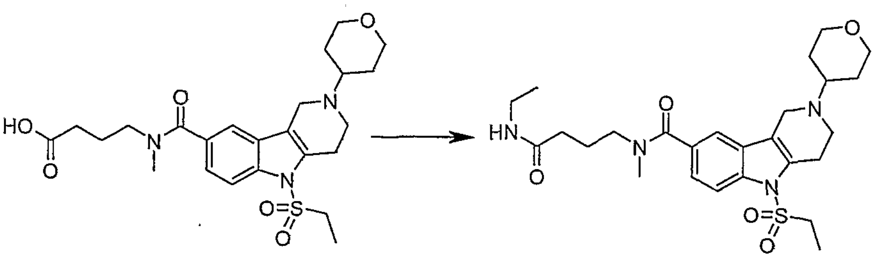
5-(Ethylsulfonyl)-*N*-methyl-*N*-[4-(methylamino)-4-oxobutyl]-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



Following the procedure for Step A in Example 2, using 4-[{[5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid hydrochloride (107 mg, 0.20 mmol), methylamine in THF (2.0 *M*, 0.2 mL, 0.40 mmol), *N*,*N*-diisopropylethylamine (77 mg, 104 uL, 0.60 mmol) and HATU (99 mg, 0.26 mmol) in DMF (5 mL). The crude product was purified by reverse-phase HPLC using high pH column 20-40% acetonitrile gradient to give the title compound as white solid (50 mg, 50 %). ^{1}H NMR (400 MHz, METHANOL-D4) δ 1.19 (t, *J*=7.42 Hz, 3 H), 1.81 - 2.05 (m, 6 H), 2.10 - 2.21 (m, 2 H), 2.26 (t, *J*=6.84 Hz, 1 H), 2.48 (s, 1.5 H), 2.69 (s, 1.5 H), 2.97 (s, 1.5 H), 3.07 (s, 1.5 H), 3.48 (m, 6 H), 3.53 - 3.62 (m, 2 H), 3.64 - 3.76 (m, 2 H), 3.89 - 4.05 (m, 1 H), 4.10 (dd, *J*=11.33, 4.49 Hz, 2 H), 4.41 - 4.80 (m, 2 H), 7.36 - 7.46 (m, 1 H), 7.60 (s, 0.5 H), 7.65 (s, 0.5 H), 8.01 (d, *J*=8.79 Hz, 1 H); MS (APPI) $(M+H)^+$= 505.3.

Example 11

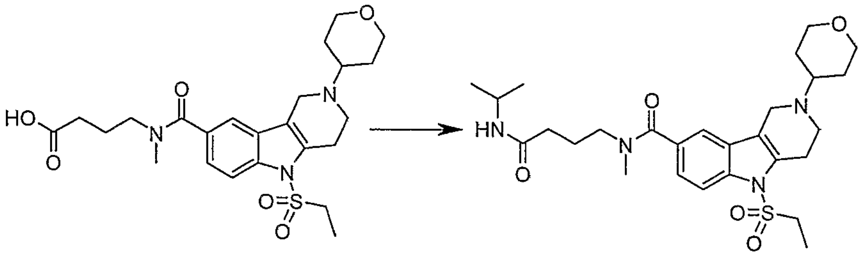
N-[4-(Ethylamino)-4-oxobutyl]-5-(ethylsulfonyl)-*N*-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



Following the procedure for Step A in Example 2, using 4-[{[5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid hydrochloride(107 mg, 0.20 mmol), ethylamine in THF (2.0 *M*, 0.2 mL, 0.40 mmol), *N*,*N*-diisopropylethylamine (77 mg, 104 uL, 0.60 mmol) and HATU (99 mg, 0.26 mmol) in DMF (5 mL). The crude product was purified by reverse-phase HPLC using high pH column 20-40% acetonitrile gradient to give the title compound as white solid (57 mg, 55 %). ^{1}H NMR (400 MHz, METHANOL-D4) δ 0.91 (t, *J*=7.32 Hz, 1.5 H), 1.09 (t, *J*=7.23 Hz, 1.5 H), 1.19 (t, *J*=7.23 Hz, 3 H), 1.79 - 2.06 (m, 6 H), 2.10 - 2.19 (m, 2 H), 2.21 - 2.30 (m, 1 H), 2.90 - 2.97 (m, 1 H), 2.97 (s, 1.5 H), 3.07 (s, 1.5 H), 3.13 - 3.22 (m, 1 H), 3.37 - 3.52 (m, 6 H), 3.56 (t, *J*=6.54 Hz, 2 H), 3.65 - 3.77 (m, 2 H), 3.88 - 4.05 (m, 1 H), 4.10 (dd, *J*=11.62, 4.00 Hz, 2 H), 4.41 - 4.82 (m, 2 H), 7.35 - 7.48 (m, 1 H), 7.60 (s, 0.5 H), 7.65 (s, 0.5 H), 8.01 (d, *J*=8.59 Hz, 1 H); MS (APPI) $(M+H)^+$= 519.3.

Example 12

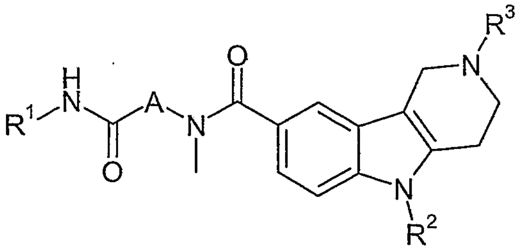
5-(Ethylsulfonyl)-*N*-[4-(isopropylamino)-4-oxobutyl]-*N*-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide



Following the procedure for Step A in Example 2, using 4-[{[5-(ethylsulfonyl)-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-8-yl]carbonyl}(methyl)amino]butanoic acid hydrochloride (107 mg, 0.20 mmol), isopropylamine (24 mg, 0.40 mmol), *N*,*N*-diisopropylethylamine (77 mg, 104 uL, 0.60 mmol) and HATU (99 mg, 0.26 mmol) in DMF (5 mL). The crude product was purified by reverse-phase HPLC using high pH column 20-40% acetonitrile gradient to give the title compound as white solid (65 mg, 55 %). ^{1}H NMR (400 MHz, METHANOL-D4) δ 0.92 (d, J=6.05 Hz, 3 H), 1.10 (d, *J*=6.44 Hz, 3 H), 1.16 - 1.23 (m, 3 H), 1.76 - 2.03 (m, 6 H), 2.09 - 2.19 (m, 2 H), 2.22 (t, *J*=7.03 Hz, 1 H), 2.97 (s, 1.5 H), 3.07 (s, 1.5 H), 3.48 (m, 7 H), 3.55 (t, *J*=6.25 Hz, 2 H), 3.64 - 3.77 (m, 2 H), 3.85 - 4.03 (m, 1 H), 4.10 (dd, *J*=11.13, 4.10 Hz, 2 H), 4.38 - 4.81 (m, 2 H), 7.33 - 7.48 (m, 1 H), 7.61 (s, 0.5 H), 7.65 (s, 0.5 H), 8.01 (d, *J*=8.79 Hz, 1 H); MS (APPI) $(M+H)^+$= 533.3.

What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof, a diastereomer, an enantiomer, or a mixture thereof:



I

wherein

A is $-(CH_2)_n-$ optionally substituted with one or more groups selected from methyl, ethyl, phenyl, benzyl and halogen, wherein n is 2, 3 or 4;

R^1 is selected from C_{1-6}alkyl, halogenated C_{1-6}alkyl and C_{3-6}cycloalkyl;

R^2 is selected from –H, C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)-NR^9R^{10}$, $-S(=O)_2-NR^9R^{10}$, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2-C_{6-10}$aryl, $-S(=O)_2-C_{3-5}$heteroaryl, $-C(=O)-C_{1-6}$alkyl; C_{6-10}aryl-C_{1-4}alkyl; and C_{3-5}heteroaryl-C_{1-4}alkyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2-C_{6-10}$aryl, $-S(=O)_2-C_{3-5}$heteroaryl, $-C(=O)-C_{1-6}$alkyl; C_{6-10}aryl-C_{1-4}alkyl; and C_{3-5}heteroaryl-C_{1-4}alkyl used in defining R^2 is optionally substituted with one or more group selected from -OR, R, $-CO_2H$, $-CO_2-R$; $-SO_2-R$; halogen, $-NO_2$, -OH, $-NH_2$, -NHR, $-C(=O)-NH_2$, and -C(=O)-NHR;

R^3 is selected from C_{3-6}heterocycloalkyl, C_{3-6}heterocycloalkyl-C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl-C_{1-4}alkyl, C_{3-6}heteroaryl-C_{1-4}alkyl, $-C(=O)-C_{1-6}$alkyl, $-C(=O)-C_{3-6}$cycloalkyl and $-C(=NH)-C_{1-6}$alkyl, wherein said C_{3-6}heterocycloalkyl, C_{3-6}heterocycloalkyl-C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl-C_{1-4}alkyl, C_{3-6}heteroaryl-C_{1-4}alkyl, $-C(=O)-C_{1-6}$alkyl, $-C(=O)-C_{3-6}$cycloalkyl and $-C(=NH)-C_{1-6}$alkyl used in defining R^3 is optionally substituted with one or more groups selected from -OR, R, NO_2, $-CO_2H$, $-CO_2-R$; $-SO_2-R$; halogen; -OH; $-NH_2$; -NHR, $-C(=O)-NH_2$, and -C(=O)-NHR;

R is C_{1-6}alkyl; and

R^9 and R^{10} are independently selected from –H, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}aryl-C_{1-4}alkyl, C_{3-6}heterocyclyl, C_{3-6}heterocyclyl-C_{1-4}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, and C_{3-6}cycloalkyl-C_{1-4}alkyl; N,N-di(C_{1-4}alkyl)amido-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl and C_{1-6}alkoxy-C_{1-6}alkyl.

2. A compound as claimed in claim 1, wherein

R^2 is selected from methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, t-butyl, allyl, $-S(=O)_2-CH_3$, $-S(=O)_2-CH_2CH_3$, 2-methoxyethyl, tetrahydropyran-4-yl-methyl, 1-propylsulfonyl, methylsulfonyl, ethylsulfonyl, cyclopropylsulfonyl, phenyl, phenylsulfonyl, 2-(methoxycarbonyl)-phenylsulfonyl; 2-(hydroxycarbonyl)-phenylsulfonyl, 1-methyl-1H-imidazol-4-yl-sulfonyl, 1H-imidazol-1-yl-sulfonyl, furylsulfonyl, (5-methylisoxazol-4-yl)sulfonyl, morpholin-4-ylcarbonyl, 4-amino-phenyl, $-CH_2-C(=O)-N(CH_3)_2$, $-C(=O)-N(CH_3)_2$, $-S(=O)_2-N(CH_3)_2$, $-S(=O)_2-NHCH_2CH_3$, $-C(=O)-CH_2CH_2CH_3$, $-CH_2-C(=O)-OCH_3$, $-CH_2-C(=O)-OCH_2CH_3$, $-CH_2-CO_2H$, benzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-methylsulfonyl-benzyl, 4-methylthio-benzyl, 4-acetylamino-benzyl, 4-methoxy-benzyl, 4-ethoxy-benzyl, 2,6-difluorobenzyl, (6-chloro-1,3-benzodioxol-5-yl)methyl, (5-ethoxycarbonyl)-fur-2-yl-methyl, (2-methyl-1,3-thiazol-4-yl)-methyl, (5-methyl-isoxazol-4-yl)-methyl, pyridin-2-ylmethyl, cyclobutylmethyl, and cyclopropylmethyl;

R^3 is selected from ethyl, isopropyl, propyl, 2-methy-propyl, 1-butyl, 1-pentyl, 1-acetyl-piperidin-4-yl, tetrahydrothien-3-yl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-tetrahydro-2H-pyranyl, tetrahydro-thiopyran-4-yl, 2-pyrimidinyl, 1-iminoethyl, 2-pyridinyl, 3,4,5,6-tetrahydropyrdin-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, 2-pyridinyl-methyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 1-methyl-4-piperidinyl, 4-piperidinyl, (6-methyl-pyridin-2-yl)methyl, (2-ethyl-4-methyl-1H-imidazol-5-yl)methyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-3-ylmethyl, 1-ethyl-1H-pyrazol-4-yl, 1,3-dimethyl-1H-pyrazol-5-yl, (3-methylpyridin-4-yl)methyl, 1,3-oxazol-2-ylmethyl, 1,3-oxazol-5-ylmethyl, 2-(tetrahydro-2H-pyran-4-yl)ethyl, tetrahydro-2H-pyran-4-ylmethyl, 2-phenylethyl, 2-methoxybenzyl, 3,3,3-trifluoropropyl, 2,2-difluoroethyl, 2-hydroxycyclopentyl, (1-ethyl-3-methyl-1H-pyrazol-5-yl)methyl, 2,1,3-benzoxadiazol-5-ylmethyl, 3-thienylmethyl, 2-trifluoromethyl-benzyl, 3-methylbutyl, cyclohex-3-en-1-ylmethyl, 2-fluoro-6-methoxybenzyl, 2-phenyl-propyl, 2-ethyl-butyl, cyclobutylcarbonyl, 2,2-difluoropropanoyl, cyclopentylcarbonyl, tetrahydro-2Hpyran-4-ylcarbonyl, cyclopropylcarbonyl, propylcarbonyl, N-ethylaminocarbonyl, N-isopropylaminocarbonyl, cyclopropylsulfonyl, and ethylsulfonyl.

3. A compound as claimed in claim 1, wherein

R^1 is selected from methyl, ethyl, 2-fluoroethyl, isopropyl, tert-butyl and cyclopropyl;

R^2 is selected from methyl, methylsulfonyl and ethylsulfonyl; and

R^3 is selected from ethyl, isopropyl, propyl, 2-methy-propyl, 1-butyl, 1-pentyl, 1-acetyl-piperidin-4-yl, tetrahydrothien-3-yl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-tetrahydro-2H-pyranyl, tetrahydro-thiopyran-4-yl, 1-iminoethyl, 3,4,5,6-tetrahydropyrdin-2-yl, 3,4-dihydro-2H-pyrrol-5-yl, tetrahydrofuran-3-ylmethyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 1-methyl-4-piperidinyl, 2-(tetrahydro-2H-pyran-4-yl)ethyl, tetrahydro-2H-pyran-4-ylmethyl, 3,3,3-trifluoropropyl, 2,2-difluoroethyl, 2-hydroxycyclopentyl, 3-methylbutyl, cyclohex-3-en-1-ylmethyl, and 2-ethyl-butyl.

4. A compound as claimed in claim 1, wherein A is $-(CH_2)_3-$.

5. A compound as claimed in claim 1, wherein A is $-(CH_2)_2-$.

6. A compound as claimed in claim 1, wherein A is $-(CH_2)_4-$.

7. A compound as claimed in claim 1, wherein A is $-CH_2-CH_2-CH(-Ph)-$.

8. A compound as claimed in claim 1, wherein A is $-CH_2-CH_2-CH(-CH_2Ph)-$.

9. A compound selected from

N-[4-(Cyclopropylamino)-4-oxobutyl]-*N*,5-dimethyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;

2-Cyclopentyl-*N*-methyl-*N*-[4-(methylamino)-4-oxobutyl]-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;

2-Cyclopentyl-*N*-[4-(ethylamino)-4-oxobutyl]-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;

2-Cyclopentyl-*N*-[4-(isopropylamino)-4-oxobutyl]-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
2-Cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
N-[4-(*tert*-Butylamino)-4-oxobutyl]-2-cyclopentyl-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
2-Cyclopentyl-*N*-{4-[(2-fluoroethyl)amino]-4-oxobutyl}-*N*-methyl-5-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
2-Cyclopentyl-*N*-[4-(cyclopropylamino)-4-oxobutyl]-5-(ethylsulfonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
N-[4-(Cyclopropylamino)-4-oxobutyl]-5-(ethylsulfonyl)-*N*-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
5-(Ethylsulfonyl)-*N*-methyl-*N*-[4-(methylamino)-4-oxobutyl]-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
N-[4-(Ethylamino)-4-oxobutyl]-5-(ethylsulfonyl)-*N*-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
5-(Ethylsulfonyl)-*N*-[4-(isopropylamino)-4-oxobutyl]-*N*-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-8-carboxamide;
and pharmaceutically acceptable salts thereof.

10. A compound according to any one of claims 1-9 for use as a medicament.

11. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the therapy of pain.

12. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the treatment of anxiety disorders.

13. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

14. A pharmaceutical composition comprising a compound according to any one of claims 1-9 and a pharmaceutically acceptable carrier.

15. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000822

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: C07D, A61K

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, 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.
A	JP 2005162657 A, TAKEDA CHEMICAL INDUSTRIES LTD, 2005-06-23: (abstract) Retrieved from: EPODOC database --	1-14
A	US 20040023947 A1 (MARTIN ET AL), 5 February 2004 (05.02.2004) --	1-14
P,X	WO 2006101434 A1 (ASTRAZENECA AB), 28 Sept 2006 (28.09.2006) -- --------	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search 19 December 2007	Date of mailing of the international search report 03 -01- 2008
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000822

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 15 relate to a method of treatment of the human or animal body by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search based on the alleged effects of the compounds has been executed for this claim.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International patent classification (IPC)

C07D 471/04 (2006.01)
A61K 31/437 (2006.01)
A61P 1/00 (2006.01)
A61P 25/00 (2006.01)
A61P 35/00 (2006.01)
A61P 9/00 (2006.01)

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- e-tjänster/anförda dokument(service in Swedish).

Use the application number as username.
The password is **PDXBAJMWYH**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/09/2007

International application No.
PCT/SE2007/000822

US	20040023947	A1	05/02/2004	AU	2003243328	A	00/00/0000
				CA	2485909	A	04/12/2003
				EP	1532153	A	25/05/2005
				JP	2005531585	T	20/10/2005
				US	20050054634	A	10/03/2005
				WO	03099821	A	04/12/2003
WO	2006101434	A1	28/09/2006	AR	053699	A	16/05/2007