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(54) Title: NOVEL PHENOXAZIN-3-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

(57) Abstract: This invention relates to novel phenoxazin-3-one derivatives useful as monoamine neurotransmitter re-uptake inhibitors. In other aspects the invention relates to the use of these compounds in a method for therapy and to pharmaceutical compositions comprising the compounds of the invention.

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NOVEL PHENOXAZIN-3-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

This invention relates to novel phenoxazin-3-one derivatives useful as monoamine neurotransmitter re-uptake inhibitors.

In other aspects the invention relates to the use of these compounds in a method for therapy and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

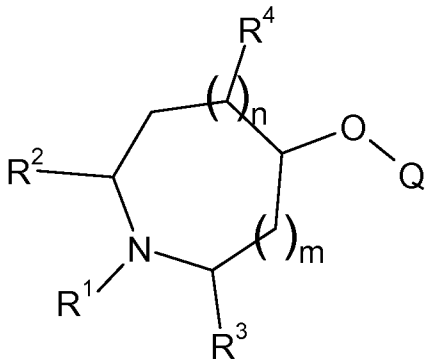
Serotonin Selective Reuptake Inhibitors (SSRIs) currently provide efficacy in the treatment of several CNS disorders, including depression and panic disorder. SSRIs are generally perceived by psychiatrists and primary care physicians as effective, well-tolerated and easily administered. However, they are associated with a number of undesirable features.

Thus, there is still a strong need for compounds with an optimised pharmacological profile as regards the activity on reuptake of the monoamine neurotransmitters serotonin, dopamine and noradrenaline, such as the ratio of the serotonin reuptake versus the noradrenaline and dopamine reuptake activity.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds which show activity as monoamine neurotransmitter re-uptake inhibitors.

In its first aspect, the invention provides a compound of Formula I:



(I)

any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R^1, R^2, R^3, R^4, m, n and Q are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable

salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

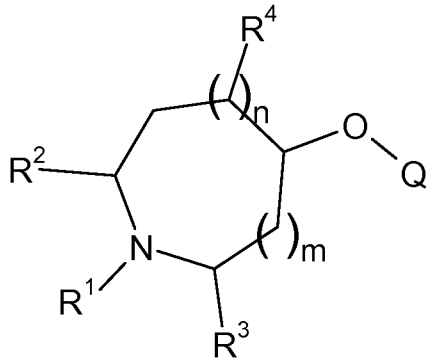
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Phenoxazin-3-one derivatives

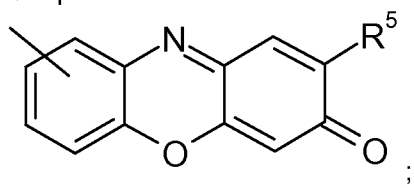
In its first aspect the present invention provides compounds of Formula I:



(I)

any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, wherein

Q represents



;

wherein R^5 represents hydrogen or halo; and **either**

m is 1;

n is 0;

R^1 represents hydrogen or alkyl; which alkyl is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, amino, nitro, hydroxy, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl; and

R^2 and R^3 together form $–CH_2–CH_2–$;

or

m is 0;

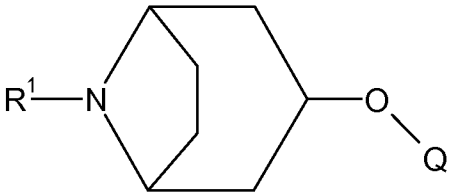
n is 1;

R^1 and R^4 together form $–CH_2–CH_2–$;

R^2 represents hydrogen; and

R^3 represents hydrogen.

In one embodiment, the invention provides compounds of Formula II:

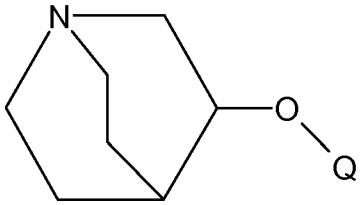


(II);

wherein R^1 and Q are as defined above.

In a special embodiment of the compound of Formula II, R^1 represents hydrogen. In a further embodiment, R1 represents alkyl, such as methyl.

In a further embodiment, the invention provides compounds of Formula III:



(III);

wherein Q is as defined in claim 1.

In a further embodiment of the compounds of Formula I, II and III, R^5 represents hydrogen.

In a still further embodiment, Q represents phenoxazin-3-one-7-yl.

In a special embodiment, the compound of the invention is

7-((1R,3S,5S)-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenoxazin-3-one;

7-((1R,3S,5S)-8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenoxazin-3-one;

(+/-)-7-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-phenoxazin-3-one;

or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments as described above is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contains of from one to six carbon atoms (C_{1-6}-alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, or 1,3-butadienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexadienyl, or 1,3,5-hexatrienyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butadiynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentadiynyl; 1-, 2-, 3-, 4-, or 5-hexynyl, or 1,3-hexadiynyl or 1,3,5-hexatriynyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Cycloalkoxy means O-cycloalkyl, wherein cycloalkyl is as defined above.

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydro-

chloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysinium, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

In the context of this invention the “onium salts” of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred “onium salts” include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

Examples of pre- or prodrug forms of the chemical compound of the invention include examples of suitable prodrugs of the substances according to the invention include compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Steric Isomers

It will be appreciated by those skilled in the art that the compounds of the present invention may exist in different stereoisomeric forms - including enantiomers, diastereomers or cis-trans-isomers.

For example, the group -O-Q of Formula I may in particular be in the exo or endo configuration relative to the azabicyclic ring.

The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the enantiomeric compounds (including enantiomeric intermediates) is - in the case the compound being a chiral acid - by use of an optically active amine, and liberating the diastereomeric, resolved salt by treatment with an acid. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of D- or L- (tartrates, mandelates, or camphor-sulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Labelled Compounds

The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention the labelled compound has one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. The labelling will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{131}I, ^{125}I, ^{123}I, and ^{18}F.

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

Compounds of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes e.g. such as described in WO 97/30997 (NeuroSearch A/S). Based on the balanced activity observed in these tests the compound of the invention is considered useful for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a special embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of: mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, Down's syndrome, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, social anxiety disorder, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, drug abuse liability, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, withdrawal symptoms caused by termination of use of addictive substances, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel

syndrome, post-operative pain, post-mastectomy pain syndrome (PMPS), post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, persistent vegetative state, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg syndrome, periodic limb movement disorder, eating disorders, anorexia nervosa, sleep disorders, pervasive developmental disorders, autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, learning disabilities, motor skills disorders, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, Gilles de la Tourettes disease, tinnitus, tic disorders, body dysmorphic disorders, oppositional defiant disorder or post-stroke disabilities. In a preferred embodiment, the compounds are considered useful for the treatment, prevention or alleviation of depression.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Preferred compounds of the invention show a biological activity in the sub-micromolar and micromolar range, i.e. of from below 1 to about 100 μM.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and

used in the art. The carrier(s) must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington’s Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a chemical compound of the invention.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject

involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Preparatory Examples

All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

endo-Benzoic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester

Benzoylchloride (84.3 g, 600 mmol) was added during 30 min at <30 °C to a mixture of tropine (70.6 g, 500 mmol), potassium *tert*-butoxide (67.3 g, 600 mmol) and THF (500 ml). The mixture was stirred at room temperature for 2 h. Water (1 L) was added followed by extraction with diethylether (2 x 500 ml). The organic phase was washed twice with water (2 x 200 ml) followed by a solution of saturated aqueous sodium chloride (200 ml). The ether phase was dried and hydrochloric acid in ethanol (170 ml, 3 M) was added. The precipitated hydrochloride was filtered and washed with diethyl-ether. The free base was obtained by adding an excess of aqueous ammonia followed by extraction with a mixture of ethylacetate and diethylether. Yield 66.8 g (54%).

endo-Benzoic acid 8-aza-bicyclo[3.2.1]oct-3-yl ester

2,2,2-Trichloroethylchloroformate (75.0 ml, 544 mmol) was added dropwise to a mixture of *endo*-benzoic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (66.8 g, 272 mmol) and dry toluene (500 ml). The mixture was allowed to stir for 1 h at room temperature, followed by 15 h at 100°C. Water (250 ml) was added followed by stirring 1h. The phases were separated and the organic phase was washed twice with water (2 x 200 ml). The mixture of the intermediate 3-benzoyloxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid trichloromethyl ester, was dried and evaporated. Acetic acid (350 ml) was added followed by addition of zinc (53.4 g, 817 mmol) over 3 h time period. Water (100 ml) was added, cooled by adding ice and made alkaline by adding concentrated aqueous ammonia (ca: 400 ml) and the mixture was extracted with dichloromethane (2 X 300 ml). Yield 44.5 g (61%).

endo-3-Benzoyloxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid _tert_-butyl ester
Di-_tert_-butyl-dicarbonate (39.9 g, 183 mmol) solved in THF (100 ml) was added to a stirred mixture of _endo_-benzoic acid 8-aza-bicyclo[3.2.1]oct-3-yl ester (44.5 g, 166.4 mmol), triethylamine (67.4 g, 666 mmol) and THF (250 ml) during 0.5 h at room temperature, followed by stirring for 1 h. Water (1 L) was added and the mixture was extracted with diethylether (2 x 300 ml). The collected ether phase was washed twice with water (2 x 200 ml), dried and evaporated. Yield 60.1 g (100%).

endo-3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid _tert_-butyl ester
A mixture of _endo_-3-benzoyloxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid _tert_-butyl ester (55.0 g, 166 mmol), potassium hydroxide (11.2 g 199 mmol) and ethanol (99%, 400 ml) was stirred for 3 days at room temperature. Potassium benzoate was separated by filtration and the filtrate was evaporated. Diethylether (200 ml) was added and remaining potassium benzoate was separated by filtration and the filtrate was evaporated. The product was triturated with petroleum. Yield 30.0 g (80%). Mp 139.5-140.8°C.

Method A

7-((1R,3S,5S)--8-Aza-bicyclo[3.2.1]oct-3-yloxy)-phenoxazin-3-one hydrochloric acid salt Diethylazodicarboxylate, 40% in toluene (0.885 g, 5.08 mmol) was added to a cold mixture (10 °C) of triphenylphosphine (1.33 g, 5.08 mmol) and dioxane (20 ml). The temperature was kept below 15 °C during the addition. The cooling was removed and
endo-3-hydroxy-8-aza-bicyclo[3.2.1] octane-8-carboxylic acid _tert_-butyl ester (0.888 g, 3.91 mmol) and resofurin (7-hydroxy-phenoxazin-3-one) (1.00 g, 4.69 mmol) was added to the mixture at room-temperature and was allowed to stir for 15 h. The intermediate (1R,3S,5S)-3-(7-oxo-7_H_-phenoxazin-3-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid _tert_-butyl ester was not isolated. Water (15 ml) was added followed by acidification by aqueous hydrochloric acid (4 M). The crude mixture was washed with diethylether. The mixture was made alkaline by adding aqueous sodium hydroxide (4 M). The organic phase was extracted with dichloromethane, dried and evaporated. The free base was converted to the hydrochloric acid salt by adding hydrogen chloride in acetic acid (20 ml, 1 M). Yield 500 mg (36%). LC-ESI-HRMS of [M+H]+ shows 323.1385 Da. Calc. 323.139568 Da, dev. -3.3 ppm.

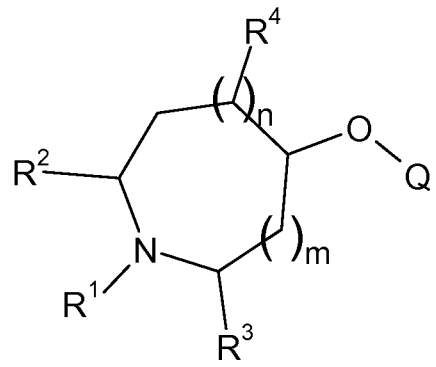
7-((1R,3S,5S)-8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenoxazin-3-one free base
Was prepared according to method A from tropine as reactant.

(+/-)-7-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-phenoxazin-3-one free base

Was prepared according to method A from 3-quinuclidinol as reactant.

CLAIMS

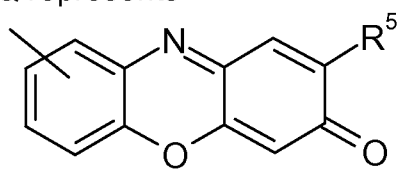
1. A compound of Formula I:



(I)

any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, wherein

Q represents



;

wherein R^5 represents hydrogen or halo; and **either**

m is 1;

n is 0;

R^1 represents hydrogen or alkyl; which alkyl is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, amino, nitro, hydroxy, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl; and

R^2 and R^3 together form $–CH_2–CH_2–$;

or

m is 0;

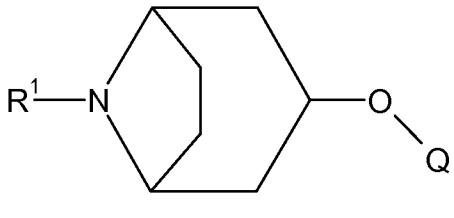
n is 1;

R^1 and R^4 together form $–CH_2–CH_2–$;

R^2 represents hydrogen; and

R^3 represents hydrogen.

2. The compound according to claim 1 of Formula II:

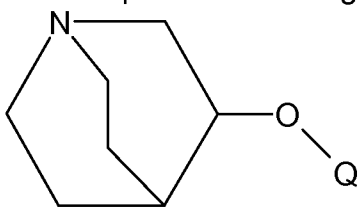


(II);

wherein R^1 and Q are as defined in claim 1.

3. The compound according to claim 2, wherein R^1 represents hydrogen.

4. The compound according to claim 1 of Formula III:



(III);

wherein Q is as defined in claim 1.

5. The compound according to any one of claims 1-4, wherein R^5 represents hydrogen.

6. The compound according to claim 1, which is
7-((1R,3S,5S)-8-Aza-bicyclo[3.2.1]oct-3-yloxy)-phenoxazin-3-one;
7-((1R,3S,5S)-8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenoxazin-3-one;
(+/-)-7-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-phenoxazin-3-one;
or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-6, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

8. Use of the chemical compound of any of claims 1-7, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.

9. The use according to claim 8, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or

condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

10. The use according to claim 9, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, Down's syndrome, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, social anxiety disorder, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, drug abuse liability, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, withdrawal symptoms caused by termination of use of addictive substances, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-mastectomy pain syndrome (PMPS), post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, persistent vegetative state, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg syndrome, periodic limb movement disorder, eating disorders, anorexia nervosa, sleep disorders, pervasive developmental disorders, autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, learning disabilities, motor skills disorders, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, Gilles de la Tourettes disease, tinnitus, tic disorders, body dysmorphic disorders, oppositional defiant disorder or post-stroke disabilities.

11. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or

condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-6, or any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/061835

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 A61K31/535 A61P25/00

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, 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.
Y	WO 2006/035034 A (NEUROSEARCH AS [DK]; PETERS DAN [DK]; OLSEN GUNNAR M [DK]; SCHEEL-KRUE) 6 April 2006 (2006-04-06) claim 1	1-11
Y	WO 97/30997 A (NEUROSEARCH AS [DK]; SCHEEL KRUEGER JOERGEN [DK]; MOLDT PETER [DK]; WA) 28 August 1997 (1997-08-28) cited in the application claim 1	1-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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"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
20 January 2009	03/02/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/061835

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