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(54) Title: PIPERAZINYL-ALKYL-BENZOIMIDAZOL-2-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

(57) Abstract: The present application discloses novel piperazinyl-alkyl-benzoimidazol-2-one derivatives useful as monoamine neurotransmitter re-uptake inhibitors. In other aspects the invention discloses the use of these compounds in a method for therapy, and pharmaceutical compositions comprising the compounds of the invention.

PIPERAZINYL-ALKYL-BENZOIMIDAZOL-2-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

This invention relates to novel piperazinyl-alkyl-benzoimidazol-2-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, such as a rapid onset of action combined with a long-term effect of the compound.

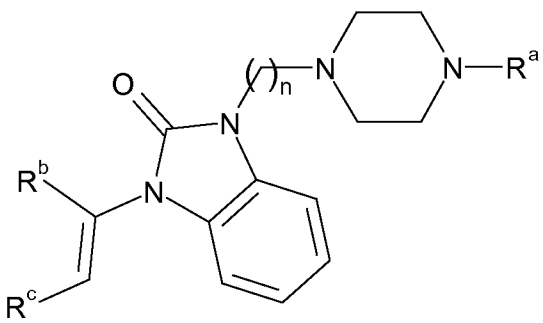
Rémond G. *et al.* (*Eur J Med Chem* (1997) 32, 843-868) describe the pharmacological profile of a series benzimidazolone derivatives being NK1 antagonists.

SUMMARY OF THE INVENTION

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

A further object of the invention is the provision of compounds which - in addition to the re-uptake inhibitor activity - show activity as NK1 and/or NK2 modulators, in particular activity as NK1 antagonists.

In one 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 n, R^a, R^b and R^c are as defined below.

In another aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula I, any of its steroisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In another aspect, the invention provides the use of a compound of formula (I), 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.

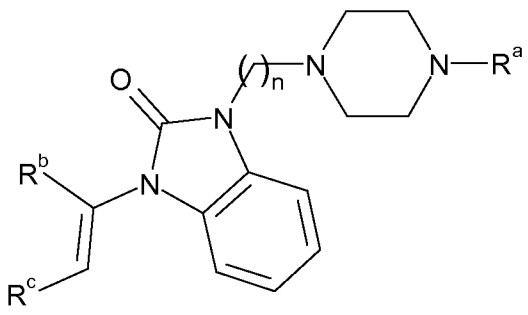
In another aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to inhibition of monoamine neurotransmitter re-uptake in 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 formula (I), any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is the provision of compounds with optimal pharmacodynamic and/or pharmacokinetic properties such as kinetic behaviour, bioavailability, solubility, efficacy and/or adverse effects.

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

In one 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

n is 1, 2 or 3;

R^a represents an indole group; which indole group is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, -NR'R'', -(C=O)NR'R'' or -NR'(C=O)R''; wherein R' and R'' independent of each other are hydrogen or C_{1-6}-alkyl; and

R^b and R^c independent of each other represent hydrogen or C_{1-6}-alkyl; which C_{1-6}-alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{3-7}-cycloalkoxy, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; or

R^b and R^c together form -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH=CH-CH_2- or -CH=CH-CH_2-CH_2-.

In one embodiment of the invention, in formula (I), n is 2. In another embodiment n is 1. In another embodiment n is 3.

In another embodiment of the invention, in formula (I), R^a represents an indole group, which indole group is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, cyano and C_{1-6}-alkoxy. In another embodiment, R^a represents an indole group which is optionally substituted with C_{1-6}-alkyl. In another embodiment, R^a represents an indole group. In another embodiment, R^a represents an indole group substituted with C_{1-6}-alkyl.

In another embodiment of the invention, in formula (I), R^b represents C_{1-6}-alkyl. In another embodiment, R^b represents methyl.

In another embodiment of the invention, in formula (I), R^c represents hydrogen.

In another embodiment of the invention, in formula (I), R^b and R^c together form -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH=CH-CH_2- or -CH=CH-CH_2-CH_2-. In another embodiment, R^b and R^c together form -CH_2-CH_2-, -CH_2-CH_2-CH_2- or -CH_2-CH_2-CH_2-CH_2-. In another embodiment, R^b and R^c together form -CH_2-CH_2-CH_2-CH_2-.

In another embodiment the compound of the invention is:

1-Isopropenyl-3-{2-[4-(1-methyl-1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;

1-Cyclohex-1-enyl-3-{2-[4-(1-methyl-1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;

1-Cyclohex-1-enyl-3-{2-[4-(1-methyl-1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;

1-Isopropenyl-3-{2-[4-(1-methyl-1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;

1-{2-[4-(1H-Indol-6-yl)-piperazin-1-yl]-ethyl}-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one;

1-Cyclohex-1-enyl-3-{2-[4-(1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;

1-Cyclohex-1-enyl-3-{2-[4-(1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;

1-{2-[4-(1H-Indol-5-yl)-piperazin-1-yl]-ethyl}-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one;

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

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

Definition of Substituents

As used throughout the present specification and appended claims, the following terms have the indicated meaning:

The term "C_{1-6}-alkyl" as used herein means a saturated, branched or straight hydrocarbon group having from 1-6 carbon atoms, e.g. C_{1-3}-alkyl, C_{1-4}-alkyl, C_{1-6}-alkyl, C_{2-6}-alkyl, C_{3-6}-alkyl, and the like. Representative examples are methyl, ethyl, propyl (e.g. prop-1-yl, prop-2-yl (or *iso*-propyl)), butyl (e.g. 2-methylprop-2-yl (or *tert*-butyl), but-1-yl, but-2-yl), pentyl (e.g. pent-1-yl, pent-2-yl, pent-3-yl), 2-methylbut-1-yl, 3-methylbut-1-yl, hexyl (e.g. hex-1-yl), and the like.

The term "C_{2-6}-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond, e.g. C_{2-6}-alkenyl, C_{3-6}-alkenyl, and the like. Representative examples are ethenyl (or vinyl), propenyl (e.g. prop-1-enyl, prop-2-enyl), butadienyl (e.g. buta-1,3-dienyl), butenyl (e.g. but-1-en-1-yl, but-2-en-1-yl), pentenyl (e.g. pent-1-en-1-yl, pent-2-en-2-yl), hexenyl (e.g. hex-1-en-2-yl, hex-2-en-1-yl), 1-ethylprop-2-enyl, 1,1-(dimethyl)prop-2-enyl, 1-ethylbut-3-enyl, 1,1-(dimethyl)but-2-enyl, and the like.

The term "C_{2-6}-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Representative examples are ethynyl, propynyl (e.g. prop-1-ynyl, prop-2-ynyl), butynyl (e.g. but-1-ynyl, but-2-ynyl), pentynyl (e.g. pent-1-ynyl, pent-2-ynyl), hexynyl (e.g. hex-1-ynyl, hex-2-ynyl), 1-ethylprop-2-ynyl, 1,1-(dimethyl)prop-2-ynyl, 1-ethylbut-3-ynyl, 1,1-(dimethyl)but-2-ynyl, and the like.

The term "halo" or "halogen" shall mean fluorine, chlorine, bromine or iodine.

The term "hydroxy" shall mean the radical -OH.

The term "cyano" shall mean the radical -CN.

The term "nitro" shall mean the radical $-NO_2$.

The term “amino” shall mean the radical -NH_2.

The term “trihalomethyl” shall mean trifluoromethyl, trichloromethyl, and similar trihalo-substituted methyl groups.

The term “trihalomethoxy” shall mean trifluoromethoxy, trichloromethoxy, and similar trihalo-substituted methoxy groups.

The term “C_{1-6}-alkoxy” as used herein refers to the radical C_{1-6}-alkyl-O-. Representative examples are methoxy, ethoxy, propoxy (e.g. 1-propoxy, 2-propoxy), butoxy (e.g. 1-butoxy, 2-butoxy, 2-methyl-2-propoxy), pentoxy (1-pentoxy, 2-pentoxy), hexoxy (1-hexoxy, 3-hexoxy), and the like.

The term “C_{3-7}-cycloalkyl” as used herein represents a saturated monocyclic carbocyclic ring having from 3 to 7 carbon atoms, e.g. C_{3-6}-alkyl, C_{3-4}-alkyl, C_{3-5}-alkyl C_{3-7}-alkyl, and the like. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term “C_{3-7}-cycloalkoxy” as used herein represents a C_{3-7}-cycloalkyl group as defined above attached through an oxygen bridge. Representative examples are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, and the like.

Certain of the defined terms may occur in combinations, and it is to be understood that the first mentioned radical is a substituent on the subsequently mentioned radical, where the point of substitution, i.e. the point of attachment to another part of the molecule, is on the last mentioned of the radicals. Such combinations of terms include for example:

“C_{1-6}-alkoxy-C_{1-6}-alkyl”; representative examples are methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxyprop-1-yl, and the like.

“C_{3-7}-cycloalkyl-C_{1-6}-alkyl”; representative examples are cyclopropylmethyl, 2-cyclohexylethyl, 3-cyclopentylprop-1-yl, 1-cyclohexylethyl, adamantylmethyl, and the like.

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 hydrochloride, 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.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

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 including 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.

The invention includes all such stereoisomers 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 or intermediates.

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 radio-nuclide 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) or WO 97/16451 (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 one 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 disorders, anorexia nervosa, bulimia, 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, chronic 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. In another embodiment, the compounds 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 or substance-induced mood disorder. In another embodiment, the compounds are considered useful for the treatment of depression.

In another embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of pain, chronic pain, inflammatory pain, neuropathic pain, diabetic 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, 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, 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.

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.

NK1 and NK2 Modulator Activity

Compounds of the invention may be tested for their ability to modulate the G-protein coupled receptors NK1 and NK2 - the affinity and antagonistic potency - such as described in Rémond G et al. (*Eur J Med Chem* (1997) 32, 843-868).

Pharmaceutical Compositions

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

While a 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 one embodiment, the invention provides pharmaceutical compositions comprising the 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.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The compound of the invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from a compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also

act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets may contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, cellulose, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

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

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or

cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

In one embodiment, the invention provides tablets or capsules for oral administration.

In another embodiment, the invention provides liquids for intravenous administration and continuous infusion.

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 dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

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. 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 following examples and general procedures refer to intermediate compounds and final products for general formula (I) identified in the specification. The preparation of the compounds of general formula (I) of the present invention is described in detail using the following examples. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognized by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, which is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials.

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

The abbreviations as used in the examples have the following meaning:
DCM: Dichloromethane
DMF: N,N-dimethylformamide

General method A

1-Isopropenyl-3-{2-[4-(1-methyl-1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one fumaric acid salt (Compound A1)

A mixture of 1-methyl-5-piperazin-1-yl-1H-indole (0.135 g, 0.41 mmol), 1-(2-chloro-ethyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one (0.163 g, 0.69 mmol) (prepared according to Rémond G. et al. *Eur J Med Chem* (1997) 32, 843-868), N,N-diisopropylethylamine (0.122 g, 0.94 mmol) and DMF (4 ml) was stirred at 60 °C for 96 h. The mixture was allowed to reach room-temperature. Aqueous sodium bicarbonate was added followed by extraction with ethylacetate. The organic phase was washed three times with brine. Chromatography on silica gel with dichloromethane, 10 % methanol and 0.5% aqueous ammonia as solvent gave a crude product. Yield 40 mg. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 25 mg (11 %).
LC-ESI-HRMS of [M+H]+ shows 416.2469 Da. Calc. 416.245035 Da, dev. 4.5 ppm.

1-Cyclohex-1-enyl-3-{2-[4-(1-methyl-1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one fumaric acid salt (Compound A2)

Was prepared according to the general method A from 1-methyl-5-piperazin- 1-yl-1H-indole and 1-(2-chloro-ethyl)-3-cyclohex-1-enyl-1,3-dihydro-benzoimidazol-2-one.
LC-ESI-HRMS of [M+H]+ shows 456.2783 Da. Calc. 456.276335 Da, dev. 4.3 ppm.

1-Cyclohex-1-enyl-3-{2-[4-(1-methyl-1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one fumaric acid salt (Compound A3)

Was prepared according to the general method A from 1-methyl-6-piperazin-1-yl-1H-indole and 1-(2-chloro-ethyl)-3-cyclohex-1-enyl-1,3-dihydro-benzoimidazol-2-one.
LC-ESI-HRMS of [M+H]+ shows 456.2787 Da. Calc. 456.276335 Da, dev. 5.2 ppm.

1-Isopropenyl-3-{2-[4-(1-methyl-1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one fumaric acid salt (Compound A4)

Was prepared according to the general method A from 1-methyl-6-piperazin-1-yl-1H-indole and 1-(2-chloro-ethyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one.
LC-ESI-HRMS of [M+H]+ shows 416.2448 Da. Calc. 416.245035 Da, dev. -0.6 ppm.

1-{2-[4-(1H-Indol-6-yl)-piperazin-1-yl]-ethyl}-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one free base (Compound A5)

Was prepared according to the general method A from 6-piperazin-1-yl-1H-indole and 1-(2-chloro-ethyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one. Mp 195-197 °C.
LC-ESI-HRMS of [M+H]+ shows 402.2299 Da. Calc. 402.22884 Da, dev. 2.6 ppm.

1-Cyclohex-1-enyl-3-{2-[4-(1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one free base (Compound A6)

Was prepared according to the general method A from 6-piperazin-1-yl-1H-indole and 1-(2-chloro-ethyl)-3-cyclohex-1-enyl-1,3-dihydro-benzoimidazol-2-one. Mp 171-173 °C.

LC-ESI-HRMS of [M+H]+ shows 442.2615 Da. Calc. 442.26014 Da, dev. 3.1 ppm.

1-Cyclohex-1-enyl-3-{2-[4-(1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one fumaric acid salt (Compound A7)

Was prepared according to the general method A from 5-piperazin-1-yl-1H-indole and 1-(2-chloro-ethyl)-3-cyclohex-1-enyl-1,3-dihydro-benzoimidazol-2-one. Mp 92-94 °C.

LC-ESI-HRMS of [M+H]+ shows 442.2617 Da. Calc. 442.26014 Da, dev. 3.5 ppm.

1-{2-[4-(1H-Indol-5-yl)-piperazin-1-yl]-ethyl}-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one fumaric acid salt (Compound A8)

Was prepared according to the general method A from 5-piperazin-1-yl-1H-indole and 1-(2-chloro-ethyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one. Mp 112-114 °C.

LC-ESI-HRMS of [M+H]+ shows 402.2297 Da. Calc. 402.22884 Da, dev. 2.1 ppm.

In vitro inhibition activity

Compounds were tested for their ability to inhibit the reuptake of the monoamine neurotransmitters dopamine (DA) noradrenaline (NA) and serotonine (5-HT) in synaptosomes as described in WO 97/16451 (NeuroSearch A/S).

The test values are given as IC_{50} (the concentration (μM) of the test substance which inhibits the specific binding of ^{3}H-DA, ^{3}H-NA, or ^{3}H-5-HT by 50%).

Test results obtained by testing compounds of the present invention appear from the below table:

Table 1

Test compound	5-HT-uptake IC_{50}(μM)	DA-uptake IC_{50}(μM)	NA-uptake IC_{50}(μM)
A1	0.014	>1.0	0.61
A2	0.0081	1.1	3.0
A3	0.0033	1.7	1.1
A4	0.0048	1.3	0.062
A5	0.0039	1.3	0.11

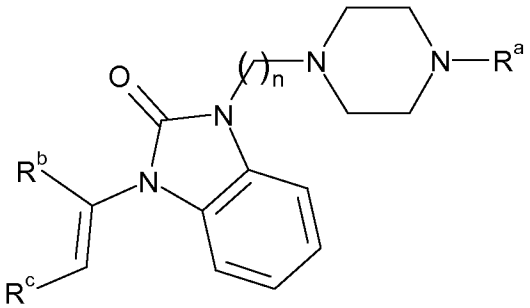
A6	0.0044	0.027	0.16
A7	0.19	2.3	1.2
A8	0.34	>1.0	0.29

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not to be limited as by the appended claims.

The features disclosed in the foregoing description, in the claims and/or in the accompanying drawings, may both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

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

n is 1, 2 or 3;

R^a represents an indole group; which indole group is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, -NR'R'', -(C=O)NR'R'' or -NR'(C=O)R''; wherein R' and R'' independent of each other are hydrogen or C_{1-6}-alkyl; and

R^b and R^c independent of each other represent hydrogen or C_{1-6}-alkyl; which C_{1-6}-alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{3-7}-cycloalkoxy, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; or

R^b and R^c together form -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH=CH-CH_2- or -CH=CH-CH_2-CH_2-.

2. The compound according to claim 1, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein n is 2.

3. The compound according to claims 1 or 2, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R^a represents an indole group, which indole group is optionally substituted with C_{1-6}-alkyl.

4. The compound according to any one of the claims 1-3, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R^b represents C_{1-6}-alkyl.

5. The compound according to any one of the claims 1-4, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R^c represents hydrogen.

6. The compound according to any one of the claims 1-3, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R^b and R^c together form $-CH_2-CH_2-CH_2-CH_2-$.

7. A compound according to claim 1 which is:
1-Isopropenyl-3-{2-[4-(1-methyl-1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;
1-Cyclohex-1-enyl-3-{2-[4-(1-methyl-1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;
1-Cyclohex-1-enyl-3-{2-[4-(1-methyl-1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;
1-Isopropenyl-3-{2-[4-(1-methyl-1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;
1-{2-[4-(1H-Indol-6-yl)-piperazin-1-yl]-ethyl}-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one;
1-Cyclohex-1-enyl-3-{2-[4-(1H-indol-6-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;
1-Cyclohex-1-enyl-3-{2-[4-(1H-indol-5-yl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzoimidazol-2-one;
1-{2-[4-(1H-Indol-5-yl)-piperazin-1-yl]-ethyl}-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one;
any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition, comprising a therapeutically effective amount of a compound according to any one of the claims 1-7, 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.

9. Use of the chemical compound according to any of the 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.

10. The use according to claim 9, 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.

11. The use according to claim 10, 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 or substance-induced mood disorder.

12. A compound according to any one of claims 1-7, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, for use as a medicament.

13. A compound according to any one of the claims 1-7, any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, for use in 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.

14. 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 1-7, or any of its stereoisomers or any mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/063357

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 A61K31/496 A61P25/00
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REMOND G ET AL: "Pharmacological profile of a novel series of NK1 antagonists. In vitro and in vivo potency of benzimidazolone derivatives" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR LNKD- DOI:10.1016/S0223-5234(97)82771-7, vol. 32, no. 11, 1 November 1997 (1997-11-01), pages 843-868, XP004100669 ISSN: 0223-5234 cited in the application the whole document	1,10
A	WO 02/24661 A2 (BOEHRINGER INGELHEIM PHARMA [DE]; CEREDA ENZO [IT]; MAIOCCHI LUCIANO [) 28 March 2002 (2002-03-28) the whole document	1

☐ 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 document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2010	25/10/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/063357

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0224661 A2	28-03-2002	AU 2352802 A	02-04-2002
		CA 2417081 A1	28-03-2002
		JP 2004509872 T	02-04-2004
		MX PA03002370 A	15-10-2003