



Organizacion CSA Ltda



DELEGATURA PROPIEDAD INDUSTRIAL

Division de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

07-62933

54. TITULO

NOVEDOSOS DERIVADOS AZABICICLO NAFTILO SUSTITUIDOS Y SU

USO COMO INHIBIDORES DE RECAPTURA DE NEUROTRANSMISOR MONOAMINA

51. CLASIFICACION INTERNACIONAL

A61K31/46

71. SOLICITANTE

NEUROSEARCH A/S

DOMICILIO

BALLERUP, DINAMARCA.

74. APODERADO

JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

587 1810/08

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062933- -00000-0000

Fecha: 2007-06-21 17:02:05
Tra. 11 PATENTE Y II
Act. 411 PRESENTACION

Dep. 2020 NUECREACIONES
Eve: 378 FASE NACIONAL I
Folios: 90

RECIBO OFICIAL DE CAJA : 07 - 23,444
FECHA : MARZO 21 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	59310980	21/03/2007	16,740,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PETITORIO

AS: 103.558



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062933- -00000-0000

Fecha: 2007-06-21 17:02:05 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 90

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☒ Capítulo I.		☐ Capítulo II.	
2 SOLICITANTE (71)	Nombre: NEUROSEARCH A/S Dirección: 93 Pederstrupvej, DK-2750 Ballerup, Dinamarca Nacionalidad o Domicilio: Dinamarca Lugar de Constitución: Dinamarca Teléfono: Fax: E-mail:		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21 Torre B – Piso 4 Bogota, Colombia Teléfono: 744-2200 Fax: 742-2200 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>80.410.337</u> TP <u>57492</u>
4 INVENTOR (ES) (72)	Nombre: Dan PETERS, Gunnar M. OLSEN, Elsebet Østergaard NIELSEN. Dirección: c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup, DK; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup, DK; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup, DK. (Respectivamente) Nacionalidad o Domicilio: Dinamarca (Respectivamente)		
5 PCT (86) Solicitud Internacional No. <u>PCT/EP2005/056846</u> Fecha <u>16-12-2005</u> Publicación Internacional No. <u>WO 2006/067090 A1</u> Fecha <u>29-06-2006</u>			
6 Título (54): <u>NOVEDOSOS DERIVADOS AZABICICLO NAFTILO SUSTITUIDOS Y SU USO COMO INHIBIDORES DE RECAPTURA DE NEUROTRANSMISOR MONOAMINA</u>			
7 Clasificación Internacional (51) <u>C02D 453/02</u>			
8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	DK	22-12-2004	PA 2004 01984
	US	22-12-2004	60/637,735
9 Comprobante de pago No. <u>07-23,444</u> Fecha <u>20-06-2007</u>			

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$482.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Declaración Publicada bajo la Regla PCT 4.17
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Extracto para Publicación y Tarjeta de Archivo Temático
Tarjeta de propietarios.
Documentos PCT

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO TEMÁTICO

PATENTE DE INVENCION X PCT X MODELO DE UTILIDAD

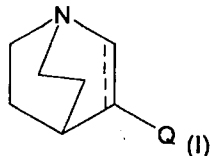
DISEÑO INDUSTRIAL

(21) N° de solicitud:		(22) Fecha de solicitud:	
(51) Clasificación Internacional:			
(71) Solicitante(s): NEUROSEARCH A/S			
(72) Inventor(es): Dan PETERS, Gunnar M. OLSEN, Elsebet Østergaard NIELSEN.			
(74) Agente: JUAN PABLO CADENA SARMIENTO			
(30) Prioridad	(31)	No. Prioridad	(32)
		PA 2004 01984	Fecha
		60/637,735	(33)
			País
			DK
			US
(85) Fecha inicio fase nacional: 22-07-2007		(87) Publicación internacional:	
(86) Datos relativos a la presentación de la solíc. PCT		Fecha: 29-06-2004	
Fecha de presentación de la solicitud: 16-12-2005		No. Publicación: WO 2006/067090 A1	
No. de solicitud: PCT/EP2005/056846			

FIGURA CARACTERISTICA
 6 x 6 cm

(54) Título: NOVEDOSOS DERIVADOS AZABICICLO NAFTILO SUSTITUIDOS Y SU USO COMO INHIBIDORES DE RECAPTURA DE NEUROTRANSMISOR MONOAMINA

(57) Resumen: 1. Un compuesto de la Fórmula I:



CONTINUA AL RESPALDO ...

o cualquiera de sus isómeros o la reivindicación mezcla de sus isómeros,

o su sal farmacéuticamente aceptable, en donde el enlace ----- representa un enlace simple o un doble enlace; y Q representa un grupo naftilo;

el cual grupo naftilo se sustituye con uno o más sustituyentes seleccionados independientemente del grupo conformado por:

halo, trifluorometilo, trifluorometoxi,
ciano, nitro, hidroxilo, alcoxi,
cicloalcoxi, alcoxialquilo,
cicloalcoxialquilo, alquilo,

cicloalquilo, cicloalquilalquilo, alquenilo, alquinilo,
-NR'R", -(C=O)NR'R" o -NR'(C=O)R";

en donde R' y R", independientemente uno de otro, son hidrógeno o alquilo.

10. Una composición farmacéutica, que comprende una cantidad terapéuticamente efectiva de un compuesto de una cualquiera de las reivindicaciones 1-9, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, junto con por lo menos un vehículo, excipiente o diluyente farmacéuticamente aceptable.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
29 June 2006 (29.06.2006)

PCT

(10) International Publication Number
WO 2006/067090 A1(51) International Patent Classification:
C07D 453/02 (2006.01)(21) International Application Number:
PCT/EP2005/056846(22) International Filing Date:
16 December 2005 (16.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2004 01984 22 December 2004 (22.12.2004) DK
60/637,735 22 December 2004 (22.12.2004) US

(71) Applicant (for all designated States except US): NEUROSEARCH A/S [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PETERS, Dan [SE/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). OLSEN, Gunnar, M. [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). NIELSEN, Elsebet, Østergaard [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(74) Common Representative: NeuroSearch A/S; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL NAPHTHYL SUBSTITUTED AZABICYCLO DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS

(57) Abstract: 304-204-WO 19 ABSTRACT NOVEL NAPHTHYL SUBSTITUTED AZABICYCLO DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS This invention relates to novel naphthyl substituted azabicyclo 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.

WO 2006/067090 A1

NOVEL NAPHTHYL SUBSTITUTED AZABICYCLO DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

This invention relates to novel naphthyl substituted azabicyclo 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

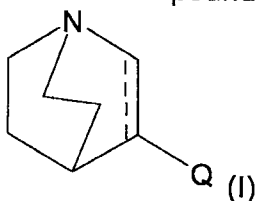
Serotonin Selective Reuptake Inhibitors (SSRIs) currently provide efficacy in the treatment of several CNS disorders, including depression and panic disorder. SSRIs are generally perceived by psychiatrists and primary care physicians as effective, well-tolerated and easily administered. However, they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

WO 02/44176 (NeuroSearch A/S) describes 3-substituted quinuclidines and their use as nicotinic agonists.

SUMMARY OF THE INVENTION

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



or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, wherein the bond ----- represents a single or a double bond; and Q is as defined below.

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

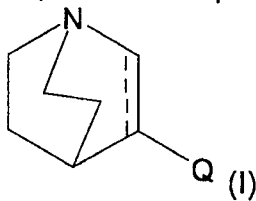
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central 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, or any of its isomers or any mixture of its isomers, 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

Naphthyl substituted azabicyclo derivatives

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



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

the bond ----- represents a single or a double bond; and

Q represents a naphthyl group;

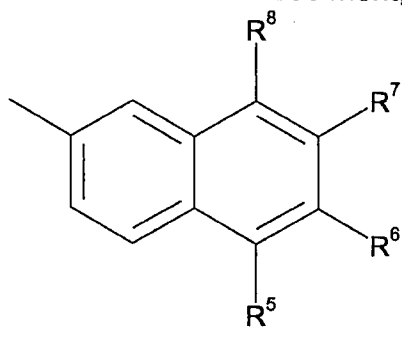
which naphthyl group is substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, $-NR'R''$, $-(C=O)NR'R''$ or $-NR'(C=O)R''$;

wherein R' and R'' independently of each other are hydrogen or alkyl.

In one embodiment, the bond ---- represents a single bond. In a further embodiment, the bond ==== represents a double bond.

In a still further embodiment, Q represents



- 5 wherein each of R^5 , R^6 , R^7 and R^8 independent of each other represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, $-NR'R''$, $-(C=O)NR'R''$ or $-NR'(C=O)R''$;
 wherein R' and R'' independently of each other are hydrogen or alkyl;
 10 with the proviso that at least one of R^5 , R^6 , R^7 and R^8 does not represent hydrogen.

In a special embodiment, each of R^5 , R^6 , R^7 and R^8 independent of each other represent hydrogen, alkyl, alkoxy, cycloalkoxy, alkoxyalkyl or cycloalkoxyalkyl; with the proviso that at least one of R^5 , R^6 , R^7 and R^8 does not represent hydrogen.

- 15 In a further special embodiment, one of R^5 , R^6 , R^7 and R^8 represents alkoxy; and the remaining three of R^5 , R^6 , R^7 and R^8 represent hydrogen. In a still further embodiment, R^6 represents alkoxy and each of R^5 , R^7 and R^8 represents hydrogen.

In a still further embodiment, one of R^5 , R^6 , R^7 and R^8 represents hydroxy; and the remaining three of R^5 , R^6 , R^7 and R^8 represent hydrogen. In a further embodiment,
 20 R^6 represents hydroxy and each of R^5 , R^7 and R^8 represents hydrogen.

In a further embodiment, R^6 represents hydroxy or alkoxy.

In a still further embodiment, Q represents 6-methoxy-naphthalen-2-yl. In a further embodiment, Q represents 6-hydroxy-naphthalen-2-yl.

- 25 In a special embodiment, the chemical compound of the invention is
 3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene;
 6-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-naphthalen-2-ol;
 or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments as described above is
 30 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
5 from one to six carbon atoms (C₁₋₆-alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C₁₋₄-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

10 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 (C₂₋₆-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-
15 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-yne, tri-yne and poly-yne. In a preferred embodiment the alkynyl group of the invention comprises of from two to six
20 carbon atoms (C₂₋₆-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
25 group, preferably containing of from three to seven carbon atoms (C₃₋₇-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 NH₂ or NH-alkyl or N-(alkyl)₂, wherein alkyl is as defined above.

30 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.

35 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 derived, 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 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 contain one or more chiral centers, and that such compounds exist in the form of isomers.

Also, some of the chemical compounds of the invention having a $-C=C-$ double bond may exist in two forms, syn- and anti-form (Z- and E-form), depending on the arrangement of the substituents around the double bond. A chemical compound of the present invention may thus be the syn- or the anti-form, or it may be a mixture hereof.

5 Moreover, the chemical compounds of the present invention may exist as enantiomers in (+) and (-) forms as well as in racemic forms ($\pm$).

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

10 Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the isomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. 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
15 crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) 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
20 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
25 "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

30 The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" 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.

35 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 ^2H (deuterium), ^3H (tritium), ^{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
5 Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS),
Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT),
or combinations thereof.

Methods of Preparation

10 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.

15 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.

20

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
25 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
30 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,
35 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, 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, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, 5 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 10 pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg 15 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 or Gilles de la Tourettes disease. In a 20 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 25 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- 30 micromolar and micromolar range, i.e. of from below 1 to about 100 μ M.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the 35 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.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonic, 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 chemical 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 chemical compound of the present 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 chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical 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.

5 The powders and tablets preferably 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, 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
10 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
15 glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous 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
20 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 chemical compound according to the present invention may thus be formulated
25 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
30 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
35 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,

5 dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical 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

10 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;

15 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

20 single or multi-dose form.

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.

25 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).

30 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

35 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 5 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.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found 10 in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50} , may be determined by standard pharmacological procedures in cell cultures or 15 experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50} . Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

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, 20 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 25 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 30 satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ 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 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

35 **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.

10

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.

15

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

20

Example 1

3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene fumaric acid salt

A mixture of 3-(6-methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]octan-3-ol (0.49 g, 1.72 mmol) and hydrochloric acid (9 ml, 25%) was stirred at 50°C for 15 h. The mixture was cooled on ice and aqueous sodium hydroxide (20 ml, 10 M) was added. The mixture was extracted with dichloromethane (2 X 25 ml). The mixture was dried with magnesium sulfate and evaporated. The crude mixture was purified by silica gel chromatography, using a mixture of dichloromethane : methanol (9:1) and 1% ammonia as eluent. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield: 190 mg (34%). Mp. 226.9°C.

(+/-)-3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]octan-3-ol (Intermediate)

Butyllithium (2.5 M, 1.86 ml, 4.64 mmol) was added to a mixture of 2-bromo-6-methoxynaphthalene (1.0 g, 4.22 mmol) and diethyl ether (10 ml) at 20°C. The temperature was kept below 35°C for 30 min. The mixture was cooled to -70°C and 3-quinuclidinone (0.53 g, 4.22 mmol) was added at -70°C. The mixture was stirred at -70°C for 1 h. The mixture was allowed to reach room temperature. Water (1 ml) was added followed by aqueous sodium hydroxide (1 M, 10 ml). The crystalline product

was filtered and was washed with cold diethyl ether (2 ml). Yield 0.49 g (41%). Mp >330°C.

Example 2

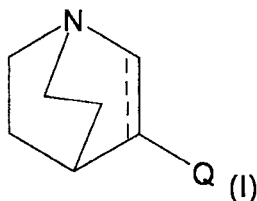
5 **6-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-naphthalen-2-ol hydrochloric acid salt**

A mixture of 3-(6-methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene (0.80 g, 2.10 mmol) and dichloromethane (25 ml) was cooled to -10°C. Borontribromide (10 eq) solved in dichloromethane (21.0 ml, 21.0 mmol) was added dropwise at -10°C. The mixture was allowed to stir for 48 h. Concentrated ammonia (20 ml) was added.

- 10 The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic phase was dried and evaporated. The free base of the title compound was precipitated to the hydrochloric acid salt by addition of hydrogen chloride solved in ethanol. Yield 20 mg (3%). Mp 227-230°C.

CLAIMS

1. A compound the Formula I:



5

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

the bond ----- represents a single or a double bond; and

Q represents a naphthyl group;

10

which naphthyl group is substituted with one or more substituents
independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy,
cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl,
cycloalkylalkyl, alkenyl, alkynyl, -NR'R'', -(C=O)NR'R'' or -
NR'(C=O)R'';

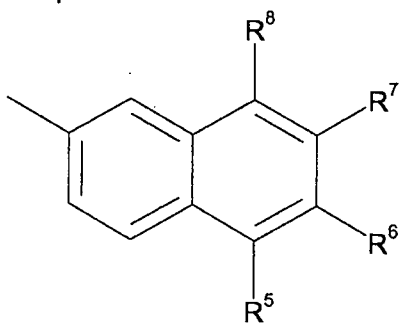
15

wherein R' and R'' independently of each other are hydrogen or
alkyl.

2. The chemical compound of claim 1, wherein
the bond ----- represents a double bond.

20

3. The chemical compound of claims 1 or 2, wherein
Q represents



25

wherein each of R⁵, R⁶, R⁷ and R⁸ independent of each other represent
hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy,
alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl,
cycloalkylalkyl, alkenyl, alkynyl, -NR'R'', -(C=O)NR'R'' or -NR'(C=O)R'';
wherein R' and R'' independently of each other are hydrogen or alkyl.

with the proviso that at least one of R⁵, R⁶, R⁷ and R⁸ does not represent hydrogen.

- 5 4. The chemical compound of claim 3, wherein
wherein each of R⁵, R⁶, R⁷ and R⁸ independent of each other represent
hydrogen, alkyl, alkoxy, cycloalkoxy, alkoxyalkyl or cycloalkoxyalkyl;
with the proviso that at least one of R⁵, R⁶, R⁷ and R⁸ does not represent
hydrogen.
- 10 5. The chemical compound of claim 3, wherein
wherein one of R⁵, R⁶, R⁷ and R⁸ represents alkoxy;
and the remaining three of R⁵, R⁶, R⁷ and R⁸ represent hydrogen.
- 15 6. The chemical compound of claim 3, wherein
wherein one of R⁵, R⁶, R⁷ and R⁸ represents hydroxy;
and the remaining three of R⁵, R⁶, R⁷ and R⁸ represent hydrogen.
- 20 7. The chemical compound of claim 3, wherein
Q represents 6-methoxy-naphthalen-2-yl.
8. The chemical compound of claim 3, wherein
Q represents 6-hydroxy-naphthalen-2-yl.
- 25 9. The chemical compound of claim 1, which is
3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene;
6-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-naphthalen-2-ol;
or a pharmaceutically acceptable salt thereof.
- 30 10. A pharmaceutical composition, comprising a therapeutically effective amount of a
compound of any one of claims 1-9, or any of its isomers or any mixture of its
isomers, or a pharmaceutically acceptable salt thereof, together with at least one
pharmaceutically acceptable carrier, excipient or diluent.
- 35 11. Use of the chemical compound of any of claims 1-9, or any of its isomers or any
mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the
manufacture of a medicament.
-

12. The use according to claim 11, 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.
13. The use according to claim 12, 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, 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, cocaine abuse,
nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, 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, 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 or Gilles de la Tourettes disease.

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
5 such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-9, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.
-

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/056846

A. CLASSIFICATION OF SUBJECT MATTER C07D453/02		
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		
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, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/44176 A (NEUROSEARCH A/S; PETERS, DAN; OLSEN, GUNNAR, M; NIELSEN, ELSEBET, OEST) 6 June 2002 (2002-06-06) Formula I, page 5, lines 35,36; claims 3,8-17; examples 1,2 page 11, line 12 - page 12, line 22	1-14
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1991, STERLING, GERALD H. ET AL: "Quaternary and tertiary quinuclidine derivatives as inhibitors of choline uptake" XP002376783 retrieved from STN Database accession no. 1991:574077 abstract -/--	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 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 12 April 2006		Date of mailing of the International search report 27/04/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Rudolf, M

INTERNATIONAL SEARCH REPORT

International application No PCT/EP2005/056846

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& JOURNAL OF PHARMACEUTICAL SCIENCES , 80(8), 785-9 CODEN: JPMSAE; ISSN: 0022-3549, 1991, -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/056846

Box 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.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2005/056846

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0244176	A	06-06-2002	AU 2051702 A
			EP 1339712 A1
			JP 2004514722 T
			US 2004044026 A1
			11-06-2002
			03-09-2003
			20-05-2004
			04-03-2004

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



(43) Fecha de Publicación Internacional
29 de junio de 2006 (29.06.2006)

(10) Número de Publicación Internacional
WO 2006/067090 A1

PCT

(51) Clasificación Internacional de Patentes:
C07D 453/02 (2006.01)

(21) No. Solicitud Internacional: PCT/EP2005/056846

(22) Fecha de Presentación Internacional:
16 de diciembre de 2005 (16.12.2005)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos relativos a la Prioridad:

PA 2004 01984 22 de diciembre de 2004 (22.12.2004) DK
60/637,735 22 de diciembre de 2004 (22.12.2004) US

(71) Solicitante (para todos los países destinatarios con excepción de US): **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventores, e

(75) Inventores/Solicitantes (para US únicamente):
PETERS, Dan [SE/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **OLSEN, Gunnar, M.** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **NIELSEN, Elsebet, Østergaard** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(74) Agente Representante: **NeuroSearch A/S**; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(81) Países designados (a menos que se indique lo contrario para cada clase de protección disponible):
AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Países designados (a menos que se indique lo contrario para cada clase de protección disponible):
ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo la Regla 4.17:

— en lo que respecta al derecho del solicitante de solicitar y de que se le otorgue una patente, (Regla 4.17(ii))

Publicado:

— con informe internacional de búsqueda
— antes del vencimiento del tiempo límite para modificar las reivindicaciones y para volverse a publicar en el caso de recibo de modificaciones

Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

(54) Título: NOVEDOSOS DERIVADOS AZABICICLO NAFTILO SUSTITUIDOS Y SU USO COMO INHIBIDORES DE RECAPTURA DE NEUROTRANSMISOR MONOAMINA.

(57) Extracto: 304-204-WO 19 EXTRACTO NOVEDOSOS DERIVADOS AZABICICLO NAFTILO SUSTITUIDOS Y SU USO COMO INHIBIDORES DE RECAPTURA DE NEUROTRANSMISOR MONOAMINA. Esta invención se refiere a novedosos derivados azabíciclo naftilo sustituidos, útiles como inhibidores de recaptura de neurotransmisor monoamina. En otros aspectos la invención se relaciona con el uso de estos compuestos en un método para terapia y con composiciones farmacéuticas que contienen los compuestos de la invención.

WO 2006/067090 A1

**NOVEDOSOS DERIVADOS AZABICICLO NAFTILO
SUSTITUIDOS Y SU USO COMO INHIBIDORES DE RECAPTURA
DE NEUROTRANSMISOR MONOAMINA**

CAMPO TÉCNICO

Esta invención se refiere a novedosos derivados azabiciclo naftilo sustituidos útiles como inhibidores de recaptura de neurotransmisor monoamina.

En otros aspectos la invención concierne el uso de estos compuestos en un método para terapia, y a composiciones farmacéuticas que contienen los compuestos de la invención.

ARTE PREVIO

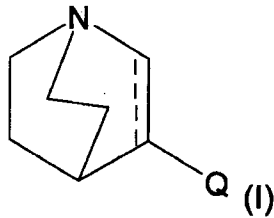
Actualmente los inhibidores selectivos de recaptura de serotonina (ISRS) ofrecen eficacia en el tratamiento de varios trastornos del SNC, incluidos depresión y trastorno pánico. Generalmente los ISRS son considerados por los psiquiatras y médicos de atención primaria como efectivos, bien tolerados y de fácil administración. No obstante, se los asocia con un número de características indeseadas.

Por consiguiente, subsiste aún una marcada necesidad de compuestos con un perfil farmacológico mejorado, en lo que respecta a la actividad sobre la recaptura de los neurotransmisores monoamina serotonina, dopamina y noradrenalina, tal como la relación de la recaptura de serotonina versus la actividad de recaptura de noradrenalina y dopamina.

WO 02/44176 (NeuroSearch A/S) describe quinuclidinas 3-sustituidas y su uso como agonistas nicotínicos.

SUMARIO DE LA INVENCION

En su primer aspecto, la invención provee un compuesto de la Fórmula I:



o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, en donde el enlace - - - - - representa un enlace simple o un enlace doble; y

Q es como se define a continuación.

En su segundo aspecto, la invención provee una composición farmacéutica, que contiene una cantidad terapéuticamente efectiva de un compuesto de la invención, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, junto con por lo menos un vehículo, excipiente o diluyente farmacéuticamente aceptable.

En un aspecto adicional, la invención contempla el uso de un compuesto de la invención, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, para la fabricación de una composición farmacéutica para el tratamiento, prevención o alivio de una enfermedad o trastorno o una afección de un mamífero, incluido un humano, enfermedad o trastorno o afección que responde a la inhibición de recaptura de neurotransmisor monoamina en el sistema nervioso central.

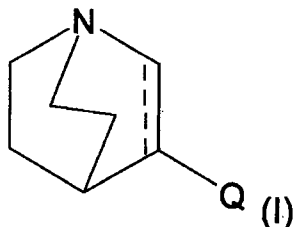
En todavía otro aspecto, la invención se relaciona con un método para tratamiento, prevención o alivio de una enfermedad o trastorno o una afección de un cuerpo animal vivo, incluido un humano, enfermedad o trastorno o afección que responde a la inhibición de recaptura de neurotransmisor monoamina en el sistema nervioso central, método que comprende el paso de administrar a tal cuerpo animal vivo, necesitado de ello, una cantidad terapéuticamente efectiva de un compuesto de la invención, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable.

Otros objetos de la invención serán evidentes a la persona experta en el arte a partir de la siguiente descripción detallada y los ejemplos.

DIVULGACIÓN DETALLADA DE LA INVENCION

Derivados azabicyclo naftilo sustituidos

En su primer aspecto la presente invención provee compuestos de fórmula I:



o cualquiera de sus isómeros o cualquier mezcla de sus isómeros,

o su sal farmacéuticamente aceptable,

en donde

el enlace - - - - representa un enlace simple o un enlace doble; y

Q representa un grupo naftilo;

el cual grupo naftilo se sustituye con uno o más sustituyentes seleccionados del grupo conformado por:

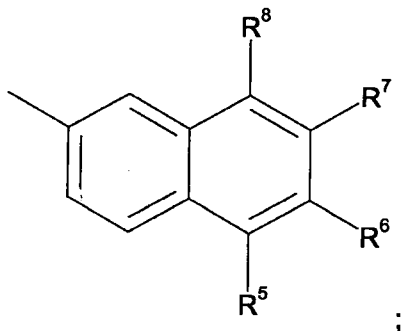
halo, trifluorometilo, trifluorometoxi, ciano, nitro, hidroxilo, alcoxi, cicloalcoxi, alcoxilalquilo, cicloalcoxialquilo, alquilo, cicloalquilo, cicloalquilalquilo, alquenilo, alquinilo, -NR'R'', - (C=O)NR'R'' o -NR'(C=O)R'';

en donde R' y R'', independientemente uno de otro, son hidrógeno o alquilo.

En una incorporación, el enlace - - - - representa un enlace simple.

En una incorporación adicional, el enlace - - - - representa un enlace doble.

En todavía una incorporación adicional, Q representa



en donde cada uno de R^5 , R^6 , R^7 y R^8 , independientes uno de otro, representan

hidrógeno, halo, trifluorometilo, trifluorometoxi, ciano, nitro, hidroxilo, alcoxi, cicloalcoxi, alcoxialquilo, cicloalcoxialquilo, alquilo, cicloalquilo, cicloalquilalquilo, alqueno, alquino, $-NR'R''$, $-(C=O)NR'R''$ o $-NR'(C=O)R''$;

en donde R' y R'' , independientemente uno de otro, son hidrógeno o alquilo; siempre que por lo menos uno de R^5 , R^6 , R^7 y R^8 no represente hidrógeno.

En una incorporación especial, cada uno de R^5 , R^6 , R^7 y R^8 , independientes uno de otro, representa hidrógeno, alquilo, alcoxi, cicloalcoxi, alcoxialquilo o cicloalcoxialquilo; siempre que por lo menos uno de R^5 , R^6 , R^7 y R^8 no represente hidrógeno.

En una incorporación especial adicional, uno de R^5 , R^6 , R^7 y R^8 representa alcoxi; y los tres restantes de R^5 , R^6 , R^7 y R^8 representan hidrógeno. En todavía otra incorporación, R^6 representa alcoxi y cada uno de R^5 , R^7 y R^8 representa hidrógeno.

En todavía otra incorporación, uno de R^5 , R^6 , R^7 y R^8 representa hidroxilo; y los tres restantes de R^5 , R^6 , R^7 y R^8 representan hidrógeno.

En una incorporación adicional, R^6 representa hidroxilo y cada uno de R^5 , R^7 y R^8 representa hidrógeno.

En una incorporación adicional, R^6 representa hidroxilo o alcoxi.

En todavía una incorporación adicional, Q representa 6-metoxinaftalen-2-ilo. En una incorporación adicional, Q representa 6-hidroxinaftalen-2-ilo.

En una incorporación adicional, el compuesto químico de la invención es

3-(6-metoxinaftalen-2-il)-1-aza-biciclo[2.2.2]oct-2-eno;

6-(1-aza-biciclo[2.2.2]oct-2-en-3-il)-naftalen-2-ol;

o su sal farmacéuticamente aceptable.

Se considera dentro del ámbito de la presente invención cualquier combinación de dos o más de las incorporaciones ya descritas.

Definición de Sustituyentes

En el contexto de esta invención halo representa fluoro, cloro, bromo o yodo.

En el contexto de esta invención un grupo alquilo designa una cadena hidrocarburo recto o ramificado, univalente, saturado. La cadena hidrocarburo contiene preferiblemente de uno a seis átomos de carbono (C_{1-6} -alquilo), incluidos pentilo, isopentilo, neopentilo, pentilo terciario, hexilo e isohexilo. En una incorporación preferida alquilo representa un grupo C_{1-4} -alquilo, incluidos butilo, isobutilo, butilo secundario, y butilo terciario. En otra incorporación preferida de esta invención, alquilo representa un grupo C_{1-3} -alquilo, que puede ser en particular metilo, etilo propilo o isopropilo.

En el contexto de esta invención, un grupo alquenilo designa una cadena carbono que contiene uno o más enlaces dobles, incluidos di-enos, tri-enos y poli-enos. En una incorporación preferida el grupo alquenilo de la invención comprende de dos a seis átomos de carbono (C_{2-6} -alquenilo), incluido por lo menos un enlace doble. En una incorporación muy preferida el grupo alquenilo de la invención es etenilo; 1- ó 2-propenilo; 1-, 2- ó 3-butenilo, o 1,3-butadienilo; 1-, 2-, 3-, 4- ó 5-hexenilo, o 1,3-hexadienilo, o 1,3,5-hexatrienilo.

En el contexto de esta invención un grupo alquinilo designa una cadena carbono que contiene uno o más enlaces triples, incluidos di-ínos, tri-ínos y poli-ínos. En una incorporación preferida el grupo alquinilo de la invención comprende de dos a seis átomos de carbono (C_{2-6} -alquinilo), incluido por lo menos un triple enlace. En su incorporación muy preferida el grupo alquinilo de la invención es etinilo; 1-, ó 2-propinilo; 1-, 2-, ó 3-butinilo, o 1,3-butadiinilo; 1-, 2-, 3-, 4-pentinilo, o 1,3-pentadiinilo; 1-, 2-, 3-, 4-, ó 5-hexinilo, o 1,3-hexadiinilo o 1,3,5-hexatriinilo.

En el contexto de esta invención un grupo cicloalquilo designa un grupo alquilo cíclico, que contiene preferiblemente de desde tres a siete átomos de carbono (C_{3-7} -cicloalquilo), incluidos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

Alcoxi es O-alquilo, en donde alquilo es como se define anteriormente.

Cicloalcoxi significa O-cicloalquilo, en donde cicloalquilo es como se define anteriormente.

Cicloalquilalquilo significa cicloalquilo como se define anteriormente y alquilo es como se define anteriormente, significando por ejemplo, ciclopropilmetilo.

Amino es NH_2 o NH -alquilo o N -(alquilo) $_2$, en donde alquilo es como se define anteriormente.

Sales Farmacéuticamente Aceptables

El compuesto químico de la invención puede proveerse en cualquier forma apropiada para la administración prevista. Formas apropiadas incluyen sales farmacéuticamente aceptables (es decir, fisiológicamente), y formas de pre- o profármacos del compuesto químico de la invención.

Ejemplos de sales de adición farmacéuticamente aceptables incluyen, sin limitación, las sales de adición de ácidos orgánicos e inorgánicos no tóxicos, tales como el clorhidrato, el bromuro de hidrógeno, el nitrato, el perclorato, el fosfato, el sulfato, el formiato, el acetato, el aconato, el ascorbato, el bencenosulfonato, el benzoato, el cinnamato, el citrato, el embonato, el enantato, el fumarato, el glutamato, el glicolato, el lactato, el maleato, el malonato, el mandelato, el metanosulfonato, el naftalen-2-sulfonato derivado, el ftalato, el salicilato, el sorbato, el estearato, el succinato, el tartrato, el toluen-p-sulfonato, y similares. Tales sales pueden formarse por procedimientos bien conocidos y descritos en el arte.

Otros ácidos tales como ácido oxálico, que no pueden considerarse farmacéuticamente aceptables, pueden tener utilidad en la preparación de

sales útiles como intermedios en obtener un compuesto químico de la invención y su sal de adición de ácido farmacéuticamente aceptable.

Ejemplos de sales catiónicas farmacéuticamente aceptables de un compuesto químico de la invención incluyen, sin limitación, la sal de sodio, potasio, calcio, magnesio, zinc, aluminio, litio, colina, lisina, y la sal de amonio, y similares, de un compuesto químico de la invención, que contiene un grupo aniónico. Tales sales catiónicas pueden formarse por procedimientos bien conocidos y descritos en el arte.

En el contexto de esta invención las "sales de onio" de compuestos que contienen N están también contempladas como sales farmacéuticamente aceptables. "Sales de onio" preferidas incluyen las sales de alquil-onio, las sales de cicloalquil-onio, y las sales de cicloalquilalquil-onio.

Ejemplos de formas de pre- o profármacos del compuesto químico de la invención incluyen ejemplos de profármacos apropiados de las sustancias de acuerdo con la invención, compuestos modificados en uno o más grupos reactivos o susceptibles de derivación del compuesto original. De interés particular son compuestos modificados en un grupo carboxilo, un grupo hidroxilo, o un grupo amino. Ejemplos de derivados apropiados son ésteres o amidas.

El compuesto químico de la invención puede proveerse en formas solubles o insolubles, junto con un disolvente farmacéuticamente aceptable tal como agua, etanol, y similares. Formas solubles pueden incluir igualmente formas hidratadas tales como el monohidrato, el dihidrato, el hemihidrato, el trihidrato, el tetrahidrato, y similares. En general, las formas solubles se consideran equivalentes a las formas insolubles para los propósitos de esta invención.

Isómeros Estéricos

Se observará por los expertos en el arte que los compuestos de la presente invención pueden contener uno o más centros quirales, y que tales compuestos existen en la forma de isómeros.

Además, algunos de los compuestos químicos de la invención con un doble enlace $-C=C-$ pueden existir en dos formas, forma *sin-* y *anti-* (forma Z- y E-), dependiendo del arreglo de los sustituyentes alrededor del doble enlace. Por consiguiente, un compuesto químico de la presente invención puede ser la forma *sin-* o la forma *anti-*, o puede ser una mezcla de las mismas.

Más aún, los compuestos químicos de la presente invención pueden existir como enantiómeros en formas (+) y (-), así como en formas racémicas ($\pm$).

La invención incluye la totalidad de tales isómeros y cualesquiera mezclas de los mismos, incluidas mezclas racémicas.

Formas racémicas pueden resolverse en los antípodas ópticos por métodos y técnicas conocidos. Un modo de separar las sales isoméricas es mediante el uso de un ácido ópticamente activo, y liberar el compuesto amina ópticamente activa por tratamiento con una base. Otro método para resolver racematos en los antípodas ópticos se basa en cromatografía en una matriz activa óptica. Por consiguiente, los compuestos racémicos de la presente invención pueden resolverse en sus antípodas ópticos, por ejemplo, por cristalización fraccionaria de sales d- o l- (tartratos, mandelatos, o sulfonato de alcanfor), por ejemplo.

Los compuestos químicos de la presente invención pueden resolverse asimismo por la formación de amidas diastereoméricas mediante reacción de los compuestos químicos de la presente invención con un ácido carboxílico activado, ópticamente activo, tal como los derivados de (+) o (-) fenilalanina, (+) o (-) fenilglicina, ácido (+) o (-) canfánico o por la formación de carbamatos diastereoméricos por reacción del compuesto químico de la presente invención con un cloroformiato ópticamente activo, o similar.

Métodos adicionales para resolver los isómeros ópticos son conocidos en el arte. Tales métodos incluyen los descritos por *Jaques J, Collet A, & Wilen S* en "Enantiomers. Racemates, and Resolutions", John Wiley and Sons, New York (1981).



Compuestos activos ópticos pueden prepararse también de materiales de partida activos ópticos.

Compuestos Marcados

Los compuestos de la invención pueden usarse en su forma marcada o no marcada. En el contexto de esta invención el compuesto marcado tiene uno o más átomos sustituidos por un átomo con una masa atómica o número de masa diferente de la masa atómica o número de masa usualmente hallados en la naturaleza. La marcación permitirá una fácil detección cuantitativa de dicho compuesto.

Los compuestos marcados de la invención pueden ser útiles como herramientas diagnósticas, radio-trazadores, o agentes de monitoreo en varios métodos diagnósticos, y para diagnóstico por imágenes de receptores *in vivo* ("*in vivo receptor imaging*").

Preferiblemente el isómero marcado de la invención contiene por lo menos un radionúclido como marca. Radionúclidos que emiten positrones son todos candidatos para utilización. En el contexto de esta invención el radionúclido se selecciona preferiblemente de ^2H (deuterio), ^3H (tritio), ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I , y ^{18}F .

El método físico para detectar el isómero marcado de la presente invención puede seleccionarse de Tomografía con Emisión de Positrones (PET), Tomografía Computarizada de Emisión de Fotón (SPECT - *Single Photon Emission Computed Tomography*), Espectroscopia por Resonancia Magnética (MRS), Exploración de Resonancia Magnética (MRI), y Tomografía Axial Computarizada (CAT), o sus combinaciones.

Métodos de Preparación

Los compuestos químicos de la invención pueden prepararse por métodos convencionales de síntesis química, por ejemplo, los descritos en los ejemplos prácticos. Los materiales de partida para los procesos descritos en la presente solicitud son conocidos o pueden prepararse

fácilmente por métodos convencionales, a partir de productos químicos disponibles en el comercio.

Asimismo un compuesto de la invención puede convertirse en otro compuesto de la invención usando métodos convencionales.

Los productos finales de las reacciones descritas en esta solicitud pueden aislarse por técnicas convencionales, por ejemplo, mediante extracción, cristalización, destilación, cromatografía, etc.

Actividad Biológica

Compuestos de la invención pueden probarse con respecto a su capacidad de inhibir la recaptura de las monoaminas dopamina, noradrenalina y serotonina en sinaptosomas, por ejemplo, tal como se describe en WO 97/30997 (NeuroSearch A/S). Con base en la actividad balanceada observada en estas pruebas, el compuesto de la invención se considera útil para el tratamiento, prevención o alivio de una enfermedad o trastorno o una afección de un mamífero, incluido un humano, enfermedad o trastorno o afección que responde a la inhibición de recaptura de neurotransmisor monoamina en el sistema nervioso central.

En una incorporación especial, los compuestos de la invención se consideran útiles para el tratamiento, prevención o alivio de: trastorno del estado de ánimo, depresión, depresión atípica, depresión secundaria al dolor, trastorno depresivo mayor, trastorno distímico, trastorno bipolar, trastorno bipolar I, trastorno bipolar II, trastorno ciclotímico, trastorno del estado de ánimo debido a enfermedad, trastorno del estado de ánimo inducido por sustancias, pseudodemencia, síndrome de Ganser, trastorno obsesivo-compulsivo, trastorno pánico, trastorno pánico sin agorafobia, trastorno pánico con agorafobia, agorafobia sin historia de trastorno pánico, ataque pánico, fallas de la memoria, pérdida de la memoria, trastorno por deficiencia de atención con hiperactividad, obesidad, ansiedad, trastorno de ansiedad generalizada, trastorno del apetito, enfermedad de Parkinson, parkinsonismo, demencia, demencia del envejecimiento, demencia senil, enfermedad de Alzheimer, complejo síndrome de demencia -

inmunodeficiencia adquirida, disfunción de la memoria por envejecimiento, fobia específica, fobia social, trastorno de ansiedad social, trastorno de estrés pos-traumático, trastorno de estrés agudo, drogadicción, toxicomanía, abuso de cocaína, abuso de nicotina, abuso del tabaco, adicción al alcohol, alcoholismo, cleptomanía, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor de migraña, cefalea tensional, cefalea tensional crónica, dolor asociado con depresión, fibromialgia, artritis, osteoartritis, artritis reumatoide, dolor de espalda, dolor por cáncer, dolor de intestino irritable, síndrome de intestino irritable, dolor pos-operatorio, síndrome de dolor pos-mastectomía (PMPS), dolor pos-infarto, neuropatía inducida por fármacos, neuropatía diabética, dolor mantenido por el sistema nervioso simpático, neuralgia trigémina, dolor de muelas, dolor miofacial, dolor fantasma en un miembro, bulimia, síndrome premenstrual, trastorno disfórico premenstrual, síndrome de fase luteínica tardía, síndrome pos-traumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia urinaria de urgencia, incontinencia urinaria nocturna, disfunción sexual, eyaculación precoz, dificultad de erección, disfunción eréctil, orgasmo femenino precoz, síndrome de piernas inquietas, trastorno de movimientos periódicos de las piernas, trastornos del apetito, anorexia nerviosa, trastornos del sueño, trastorno extensivo del desarrollo, autismo, trastorno de Asperger, trastorno de Rett, trastorno desintegrativo de la niñez, discapacidades del aprendizaje, trastornos de las habilidades motoras, mutismo, tricotilomanía, narcolepsia, depresión pos-infarto, lesión cerebral inducida por infarto, lesión neuronal inducida por infarto o enfermedad de Gilles de la Tourette. En una incorporación preferida, los compuestos se consideran útiles para el tratamiento, prevención o alivio de la depresión.

Actualmente se contempla que una posología apropiada del ingrediente farmacéutico activo (API- *Active Pharmaceutical Ingredient*) está en el rango de desde alrededor de 0.1 a alrededor de 1000 mg API/día, más preferiblemente de desde alrededor de 10 a alrededor de 500 mg API/día, muy preferiblemente de desde alrededor de 30 a alrededor de 100 mg API/día, dependiendo, sin embargo, del modo exacto de administración,

la forma en la cual se administra, la indicación considerada, el sujeto y, en particular, el peso corporal del sujeto involucrado y, además, la preferencia y experiencia del médico o veterinario encargado.

Compuestos preferidos de la invención muestran actividad biológica en el rango sub-micromolar y micromolar, es decir, de desde por debajo de 1 a alrededor de 100 μM .

Composiciones Farmacéuticas

En otro aspecto la invención provee composiciones farmacéuticas novedosas, que contienen una cantidad terapéuticamente efectiva del compuesto químico de la invención.

Aunque un compuesto químico de la invención para uso en terapia puede administrarse en la forma del compuesto químico original, se prefiere introducir el ingrediente activo, opcionalmente en la forma de una sal fisiológicamente aceptable, en una composición farmacéutica junto con uno o más coadyuvantes, excipientes, vehículos, amortiguadores, diluyentes, y/o otros auxiliares farmacéuticos habituales.

En una incorporación preferida, la invención provee composiciones farmacéuticas que contienen el compuesto químico de la invención, o su sal farmacéuticamente aceptable o su derivado, junto con uno o más vehículos farmacéuticamente aceptables y, de manera opcional, otros ingredientes terapéuticos y/o profilácticos, conocidos y utilizados en el arte. El vehículo(s) tiene que ser "aceptable" en el sentido de ser compatible con los demás ingredientes de la formulación y no nocivo al beneficiario del mismo.

Composiciones farmacéuticas de la invención puede ser aquellas apropiadas para administración oral, rectal, bronquial, nasal, pulmonar, tópica (incluida bucal y sub-lingual), transdérmica, vaginal o parenteral (incluida inyección cutánea, subcutánea, intramuscular, intraperitoneal, intravenosa, intra-arterial, intracerebral, intraocular o infusión), o aquella en una forma apropiada para administración por inhalación o insuflación, incluida administración de aerosoles de polvos o líquidos, o por sistemas de

liberación sostenida. Ejemplos apropiados de sistemas de liberación sostenida incluyen matrices semipermeables de polímeros hidrófobos sólidos, que contienen el compuesto de la invención, matrices que pueden estar en la forma de artículos moldeados, por ejemplo, películas o microcápsulas.

Por consiguiente, el compuesto químico de la invención, junto con un coadyuvante, vehículo, o diluyente convencional, puede depositarse en la forma de composiciones farmacéuticas y sus dosis unitarias. Tales formas incluyen sólidos y, en particular, tabletas, cápsulas rellenas, formas en polvo y granuladas, y líquidos, en particular soluciones acuosas y no acuosas, suspensiones, emulsiones, elixires, y cápsulas rellenas de las mismas, todas para uso oral, supositorios para administración rectal, y soluciones inyectables estériles, para uso parenteral. Tales composiciones farmacéuticas y sus presentaciones farmacéuticas unitarias pueden contener ingredientes convencionales en proporciones convencionales, con o sin compuestos o principios activos adicionales, y tales presentaciones farmacéuticas unitarias pueden contener cualquier cantidad efectiva apropiada del ingrediente activo, proporcional con el rango de dosificación diario previsto, que se va a emplear.

El compuesto químico de la presente invención puede administrarse en una amplia variedad de formas farmacéuticas orales y parenterales. Será obvio a aquellas personas expertas en el arte que las siguientes formas farmacéuticas pueden contener, como el componente activo, un compuesto químico de la invención o una sal farmacéuticamente aceptable de un compuesto químico de la invención.

Para preparar composiciones farmacéuticas de un compuesto químico de la presente invención, los vehículos farmacéuticamente aceptables pueden ser sólidos o líquidos. Preparaciones en forma sólida incluyen polvos, tabletas, píldoras, cápsulas, cápsulas amiláceas, supositorios, y gránulos dispersables. Un vehículo sólido puede ser una o más sustancias, que pueden actuar igualmente como diluyentes, agentes saborizantes,

solubilizantes, lubricantes, agentes de suspensión, aglutinantes, preservantes, agentes desagregantes de tabletas, o un material encapsulante.

En polvos, el vehículo es un sólido finamente dividido, que está en una mezcla con el componente activo finamente dividido.

En tabletas, el componente activo se mezcla con el vehículo, con la capacidad aglutinante necesaria, en proporciones apropiadas y se compacta en la forma y tamaño deseados.

Los polvos y tabletas contienen preferiblemente desde 5 o 10 a alrededor de 70% del compuesto activo. Vehículos apropiados son carbonato de magnesio, estearato de magnesio, talco, azúcar, lactosa, pectina, dextrina, almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa sódica, una cera con bajo punto de fusión, manteca de cacao, y similares. El término "preparación" tiene como finalidad incluir la formulación de compuesto activo con material encapsulante como vehículo, proporcionando una cápsula en la cual el componente activo, con o sin vehículos, está rodeado por un vehículo, que queda así en asociación con él. Análogamente, se incluyen cápsulas amiláceas y pastillas para chupar. Tablet, polvos, cápsulas, píldoras, cápsulas amiláceas, y pastillas para chupar pueden usarse como formas sólidas apropiadas para administración oral.

Para preparar supositorios, se funde primeramente una cera con bajo punto de fusión, tal como una mezcla de glicérido de ácido graso o manteca de cacao, y el componente activo se dispersa homogéneamente en ella, mediante, por ejemplo, agitación. La mezcla homogénea fundida se vierte entonces en moldes de tamaño conveniente, se deja enfriar y, con ello, se solidifica.

Composiciones apropiadas para administración vaginal pueden presentarse como pesarios, tampones, cremas, geles, pastas, espumas o aerosoles que contengan, además del ingrediente activo, vehículos tales como los conocidos en el arte por su idoneidad.

Preparaciones líquidas incluyen soluciones, suspensiones, y emulsiones, por ejemplo, soluciones en agua o agua-propilen glicol. Por

ejemplo, preparaciones líquidas para inyección parenteral pueden formularse como soluciones en solución acuosa de polietilen glicol.

En consecuencia, el compuesto químico de acuerdo con la presente invención puede formularse para administración parenteral (por ejemplo, mediante inyección, por ejemplo inyección intravenosa rápida o infusión continua) y puede presentarse en forma farmacéutica en ampollas, jeringas pre-ensadas, infusión de pequeños volúmenes o en envases multi-dosis, con adición de un preservante. Las composiciones pueden adoptar formas tales como suspensiones, soluciones, o emulsiones en vehículos aceitosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizantes y/o dispersantes. Alternativamente, el ingrediente activo puede estar en forma de polvo, obtenido por aislamiento aséptico de un sólido estéril o por liofilización de una solución, para reconstitución con un vehículo apropiado, por ejemplo, agua esterilizada, libre de pirógenos, antes del empleo.

Soluciones acuosas adecuadas para uso oral pueden prepararse disolviendo el componente activo en agua y agregando colorantes, sabores, agentes estabilizantes y espesantes apropiados, según se desee.

Suspensiones acuosas apropiadas para uso oral pueden elaborarse dispersando el componente activo finamente dividido en agua con un material viscoso, tal como gomas naturales o sintéticas, resinas, metilcelulosa, carboximetilcelulosa sódica, u otros agentes de suspensión bien conocidos.

Se incluyen también preparaciones en forma sólida, destinadas para conversión, poco antes del uso, en preparaciones en forma líquida para administración oral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones. Además del componente activo, tales preparaciones pueden contener colorantes, sabores, estabilizantes, amortiguadores, edulcorantes naturales y artificiales, dispersantes, espesantes, agentes solubilizantes y similares.

Para administración tópica a la epidermis, el compuesto químico de la invención puede formularse en forma de ungüentos, cremas o lociones, o

como parche transdérmico. Por ejemplo, los ungüentos y cremas pueden formularse con una base acuosa o aceitosa con la adición de agentes gelificantes o espesantes apropiados. Las lociones pueden formularse con una base acuosa o aceitosa y, en general, contendrán asimismo uno o más agentes emulsionantes, agentes estabilizantes, agentes dispersantes, agentes de suspensión, agentes espesantes, o agentes colorantes.

Composiciones apropiadas para administración tópica en la boca incluyen pastillas para chupar, que contienen el agente activo en una base saborizada, usualmente sacarosa, y acacia o tragacanto; pastillas que contienen el ingrediente activo en una base inerte tal como gelatina y glicerina o sacarosa y acacia; y enjuagues bucales que contienen el ingrediente activo en un vehículo líquido adecuado.

Las soluciones o suspensiones se aplican directamente a la cavidad nasal por medios convencionales, por ejemplo con un cuentagotas, pipeta o aerosol. Las composiciones pueden proveerse en forma de dosis única o dosis múltiples.

La administración al tracto respiratorio puede lograrse asimismo mediante una formulación en aerosol, en la cual el ingrediente activo se provee en un envase a presión con un propulsor apropiado, tal como un clorofluorocarbono (CFC), por ejemplo diclorodifluorometano, triclorofluorometano, o diclorotetrafluoroetano, dióxido de carbono, u otro gas adecuado. Convenientemente, el aerosol puede contener además un tensioactivo tal como lecitina. La dosis de medicamento puede controlarse mediante la provisión de una válvula graduada.

Alternativamente, los ingredientes activos pueden proveerse en la forma de un polvo seco, por ejemplo una mezcla de polvo del compuesto en una base de polvo apropiada tal como lactosa, almidón, derivados de almidón tales como hidroxipropilmetilcelulosa y polivinilpirrolidona (PVP). Convenientemente el vehículo en polvo formará un gel en la cavidad nasal. La composición en polvo puede presentarse en forma farmacéutica unitaria, por ejemplo en cápsulas o cartuchos de gelatina, empaques blíster, desde los cuales puede administrarse el polvo mediante un inhalador.

Por lo general, en composiciones destinadas para administración al tracto respiratorio, incluidas las composiciones intranasales, el compuesto tendrá un tamaño de partícula pequeño, por ejemplo del orden de 5 micrones, o menos. Tal tamaño de partícula puede obtenerse por medios conocidos en el arte, por ejemplo por micronización.

Si se desea, pueden emplearse composiciones adaptadas para permitir una liberación sostenida del ingrediente activo.

Preferiblemente, las preparaciones farmacéuticas se proveen en presentaciones farmacéuticas unitarias. En tal presentación, la preparación se subdivide en dosis unitarias que contienen cantidades apropiadas del componente activo. La presentación farmacéutica unitaria puede ser una preparación empacada, conteniendo el empaque cantidades discretas de la preparación, tales como tabletas empacadas, cápsulas y polvos en frasquitos o ampollas. Asimismo, la presentación farmacéutica unitaria puede ser una cápsula, tableta, cápsula amilácea, o pastilla para chupar, o puede ser el número apropiado de cualquiera de éstas, en forma empacada.

Las composiciones preferidas son tabletas o cápsulas para administración oral y líquidos para administración intravenosa e infusión continua.

Mayores detalles sobre técnicas de formulación y administración pueden encontrarse en la última edición del Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

Una dosis terapéuticamente efectiva se refiere a aquella cantidad de ingrediente activo que alivia los síntomas o enfermedad. La eficacia terapéutica y la toxicidad, verbigracia ED_{50} y LD_{50} , pueden determinarse por procedimientos farmacológicos estándar en cultivos de células o animales experimentales. La proporción de dosis entre efectos terapéuticos y tóxicos es el índice terapéutico y puede expresarse por la proporción LD_{50}/ED_{50} . Se prefieren composiciones farmacéuticas que exhiban índices terapéuticos superiores.

Naturalmente, la dosis administrada tiene que ajustarse cuidadosamente a la edad, peso y condición del individuo que se está

tratando, así como a la vía de administración, presentación farmacéutica y régimen y, por supuesto, el resultado deseado y la posología exacta deben determinarse por el médico.

La posología efectiva depende de la naturaleza y gravedad de la enfermedad que se está tratando, y queda a discreción del médico, y puede variarse mediante ajuste de la dosis a las circunstancias particulares de esta invención, para producir el efecto terapéutico deseado. No obstante, actualmente se contempla que son apropiadas para tratamientos terapéuticos las composiciones farmacéuticas que contienen de desde alrededor de 0.1 a alrededor de 500 mg de ingrediente activo por dosis individual, preferiblemente de desde alrededor de 1 a alrededor de 100 mg, muy preferiblemente de desde alrededor de 1 a alrededor de 10 mg.

El ingrediente activo puede administrarse en una o varias dosis al día. En ciertos casos puede obtenerse un resultado satisfactorio con una dosificación tan baja como 0.1 $\mu\text{g/kg}$ i.v. y 1 $\mu\text{g/kg}$ p.o. Actualmente se considera que el límite superior del rango posológico es de alrededor de 10 mg/kg i.v. y 100 mg/kg p.o. Rangos preferidos van desde alrededor de 0.1 $\mu\text{g/kg}$ a alrededor de 10 mg/kg/día i.v., y desde alrededor de 1 $\mu\text{g/kg}$ a alrededor de 100 mg/kg/día p.o.

Métodos de Terapia

En otro aspecto la invención provee un método para el tratamiento, prevención o alivio de una enfermedad o trastorno o una afección de un cuerpo animal vivo, incluido un humano, enfermedad o trastorno o afección que responde a la inhibición de recaptura de neurotransmisor monoamina en el sistema nervioso central, y método que comprende administrar a tal cuerpo animal vivo, incluido un humano, necesitado de ello, una cantidad efectiva de un compuesto químico de la invención.

Actualmente se contempla que los rangos de dosificación apropiados son de 0.1 a 1.000 miligramos diarios, 10-500 miligramos diarios y, especialmente 30-100 miligramos diarios, dependiendo, como es habitual, del modo exacto de administración, la forma en la cual se administra, la

indicación a la cual se dirige la administración, el sujeto involucrado y el peso corporal del sujeto involucrado y, además, la preferencia y experiencia del médico o veterinario encargado.

EJEMPLOS

La invención se ilustra más pormenorizadamente con referencia a los siguientes ejemplos, los cuales no pretenden ser de ningún modo limitantes del ámbito de la invención, como ésta se reivindica.

General: Todas las reacciones que incluían reactivos sensibles al aire o intermedios se realizaron bajo nitrógeno y en disolventes anhidros. Se utilizó sulfato de magnesio como agente secante en los procedimientos de desarrollo y los disolventes se evaporaron bajo presión reducida.

Ejemplo 1

3-(6-Metoxi-naftalen-2-il)-1-aza-biciclo[2.2.2]oct-2-eno sal de ácido fumárico

Una mezcla de 3-(6-metoxi-naftalen-2-il)-1-aza-biciclo[2.2.2]octan-3-ol (0.49 g, 1.72 mmol) y ácido clorhídrico (9 ml, 25%) se agitó a 50°C durante 15 horas. La mezcla se enfrió en hielo y se agregó hidróxido de sodio acuoso (20 ml, 10 M). La mezcla se extrajo con diclorometano (2 X 25 ml). La mezcla se secó con sulfato de magnesio y se evaporó. La mezcla cruda se purificó por cromatografía en gel de sílice, usando una mezcla de diclorometano : metanol (9:1) y 1% de amoníaco como eluyente. La sal correspondiente se obtuvo por la adición de una mezcla de éter dietílico y metanol (9:1), saturada con ácido fumárico. Rendimiento: 190 mg (34%). Mp. 226.9°C.

(+/-)-3-(6-Metoxi-naftalen-2-il)-1-aza-biciclo[2.2.2]octan-3-ol (Intermedio)

Butil litio (2.5 M, 1.86 ml, 4.64 mmol) se agregó a una mezcla de 2-bromo-6-metoxinaftaleno (1.0 g, 4.22 mmol) y éter dietílico (10 ml) a 20°C. La temperatura se mantuvo por debajo de 35°C durante 30 minutos. La mezcla se enfrió a -70°C y se agregó 3-quinuclidinona (0.53 g, 4.22 mmol) a -70°C. La mezcla se agitó a -70°C durante 1 hora. Se dejó que la mezcla alcanzara la temperatura de la sala. Se agregó agua (1 ml), seguida por hidróxido de sodio acuoso (1 M, 10 ml). El producto cristalino se filtró y se lavó con éter dietílico frío (2 ml). Rendimiento 0.49 g (41%). Mp >330°C.

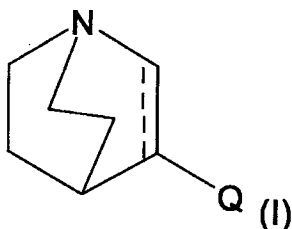
Ejemplo 2

6-(1-Aza-biciclo[2.2.2]oct-2-en-3-il)-naftalen-2-ol sal de ácido clorhídrico

Una mezcla de 3-(6-metoxi-naftalen-2-il)-1-aza-biciclo[2.2.2]oct-2-eno (0.80 g, 2.10 mmol) y diclorometano (25 ml) se enfrió a -10°C. Se agregó gota a gota tribromuro de bromo (10 equivalentes) disuelto en diclorometano (21.0 ml, 21.0 mmol) a -10°C. La mezcla se dejó agitar durante 48 horas. Se agregó amoníaco concentrado (20 ml). Se separaron las fases y la fase acuosa se extrajo con diclorometano (2 x 20 ml). La fase orgánica combinada se secó y se evaporó. La base libre del compuesto del título se precipitó a la sal de ácido clorhídrico mediante la adición de cloruro de hidrógeno disuelto en etanol. Rendimiento 20 mg (3%). Mp 227-230°C.

REIVINDICACIONES

1. Un compuesto de la Fórmula I:



o cualquiera de sus isómeros o la reivindicación mezcla de sus isómeros,
o su sal farmacéuticamente aceptable, en donde
el enlace - - - - representa un enlace simple o un doble enlace; y

Q representa un grupo naftilo;

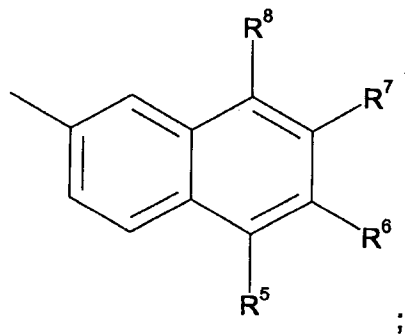
el cual grupo naftilo se sustituye con uno o más sustituyentes
seleccionados independientemente del grupo conformado por:

halo, trifluorometilo, trifluorometoxi, ciano, nitro, hidroxilo,
alcoxi, cicloalcoxi, alcoxialquilo, cicloalcoxialquilo, alquilo,
cicloalquilo, cicloalquilalquilo, alqueno, alquino, -NR'R'', -
(C=O)NR'R'' o -NR'(C=O)R'';

en donde R' y R'', independientemente uno de otro, son
hidrógeno o alquilo.

2. El compuesto químico de la reivindicación 1, en donde
el enlace - - - - representa un enlace doble.

3. El compuesto químico de las reivindicaciones 1 ó 2, en donde
Q representa



en donde cada uno de R^5 , R^6 , R^7 y R^8 , independientes uno de otro, representan

hidrógeno, halo, trifluorometilo, trifluorometoxi, ciano, nitro, hidroxilo, alcoxi, cicloalcoxi, alcoxialquilo, cicloalcoxialquilo, alquilo, cicloalquilo, cicloalquilalquilo, alqueno, alquino, $-NR'R''$, $-(C=O)NR'R''$ o $-NR'(C=O)R''$;

en donde R' y R'' independientemente uno de otro son hidrógeno o alquilo; siempre que por lo menos uno de R^5 , R^6 , R^7 y R^8 no represente hidrógeno.

4. El compuesto químico de la reivindicación 3, en donde cada uno de R^5 , R^6 , R^7 y R^8 , independientes uno de otro, representa hidrógeno, alquilo, alcoxi, cicloalcoxi, alcoxialquilo o cicloalcoxialquilo; siempre que por lo menos uno de R^5 , R^6 , R^7 y R^8 no representen hidrógeno.
5. El compuesto químico de la reivindicación 3, en donde uno de R^5 , R^6 , R^7 y R^8 representa alcoxi; y los tres restantes de R^5 , R^6 , R^7 y R^8 representan hidrógeno.
6. El compuesto químico de la reivindicación 3, en donde uno de R^5 , R^6 , R^7 y R^8 representa hidroxilo; y los tres restantes de R^5 , R^6 , R^7 y R^8 representan hidrógeno.
7. El compuesto químico de la reivindicación 3, en donde Q representa 6-metoxi-naftalen-2-ilo.
8. El compuesto químico de la reivindicación 3, en donde Q representa 6-hidrox-naftalen-2-ilo.
9. El compuesto químico de la reivindicación 1, el cual es 3-(6-metoxi-naftalen-2-il)-1-aza-biciclo[2.2.2]oct-2-eno;

6-(1-aza-biciclo[2.2.2]oct-2-en-3-il)-naftalen-2-ol;
o su sal farmacéuticamente aceptable.

10. Una composición farmacéutica, que comprende una cantidad terapéuticamente efectiva de un compuesto de una cualquiera de las reivindicaciones 1-9, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, junto con por lo menos un vehículo, excipiente o diluyente farmacéuticamente aceptable.
11. Uso del compuesto químico de cualquiera de las reivindicaciones 1-9, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, para la fabricación de un medicamento.
12. El uso de acuerdo con la reivindicación 11, para la fabricación de una composición farmacéutica para el tratamiento, prevención o alivio de una enfermedad o un trastorno o una afección de un mamífero, incluido un humano, enfermedad, trastorno o afección que es susceptible a la inhibición de la recaptura del neurotransmisor monoamina en el sistema nervioso central.
13. El uso de acuerdo con la reivindicación 12, en donde la enfermedad, trastorno o afección es trastorno del estado de ánimo, depresión, depresión atípica, depresión secundaria al dolor, trastorno depresivo mayor, trastorno distímico, trastorno bipolar, trastorno bipolar I, trastorno bipolar II, trastorno ciclotímico, trastorno del estado de ánimo debido a enfermedad, trastorno del estado de ánimo inducido por sustancias, seudodemencia, síndrome de Ganser, trastorno obsesivo-compulsivo, trastorno pánico, trastorno pánico sin agorafobia, trastorno pánico con agorafobia, agorafobia sin historia de trastorno pánico, ataque pánico, fallas de la memoria, pérdida de

la memoria, trastorno por deficiencia de atención con hiperactividad, obesidad, ansiedad, trastorno de ansiedad generalizada, trastorno del apetito, enfermedad de Parkinson, parkinsonismo, demencia, demencia del envejecimiento, demencia senil, enfermedad de Alzheimer, complejo síndrome de demencia - inmunodeficiencia adquirida, disfunción de la memoria por envejecimiento, fobia específica, fobia social, trastorno de ansiedad social, trastorno de estrés pos-traumático, trastorno de estrés agudo, drogadicción, toxicomanía, abuso de cocaína, abuso de nicotina, abuso del tabaco, adicción al alcohol, alcoholismo, cleptomanía, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor de migraña, cefalea tensional, cefalea tensional crónica, dolor asociado con depresión, fibromialgia, artritis, osteoartritis, artritis reumatoide, dolor de espalda, dolor por cáncer, dolor de intestino irritable, síndrome de intestino irritable, dolor pos-operatorio, síndrome de dolor pos-mastectomía (PMPS), dolor pos-infarto, neuropatía inducida por fármacos, neuropatía diabética, dolor mantenido por el sistema nervioso simpático, neuralgia trigémina, dolor de muelas, dolor miofacial, dolor fantasma en un miembro, bulimia, síndrome premenstrual, trastorno disfórico premenstrual, síndrome de fase luteínica tardía, síndrome pos-traumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia urinaria de urgencia, incontinencia urinaria nocturna, disfunción sexual, eyaculación precoz, dificultad de erección, disfunción eréctil, orgasmo femenino precoz, síndrome de piernas inquietas, trastorno de movimientos periódicos de las piernas, trastornos del apetito, anorexia nerviosa, trastornos del sueño, trastorno extensivo del desarrollo, autismo, trastorno de Asperger, trastorno de Rett, trastorno desintegrativo de la niñez, discapacidades del aprendizaje, trastornos de las habilidades motoras, mutismo, tricotilomanía, narcolepsia, depresión pos-infarto, lesión cerebral inducida por

infarto, lesión neuronal inducida por infarto o enfermedad de Gilles de la Tourette.

14. Un método para tratamiento, prevención o alivio de una enfermedad o un trastorno o una afección del cuerpo de un animal vivo, incluido un humano, enfermedad o trastorno o afección que es susceptible a la inhibición de la recaptura del neurotransmisor monoamina en el sistema nervioso central, método que comprende el paso de administrar a tal cuerpo de un animal vivo, necesitado de ello, una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-9, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable.

PATENT COOPERATION TREATY

FRIST

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing **27/04/2006**
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

304-204-WO

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2005/056846

International filing date (day/month/year)
16.12.2005

Priority date (day/month/year)
22.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07D453/02

Applicant
NEUROSEARCH AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Rudolf, M

Telephone No. +49 89 2399-8604



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/056846

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/056846

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 14 with respect to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 14 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | ☐ has not been furnished |
| | ☐ does not comply with the standard |
| the computer readable form | ☐ has not been furnished |
| | ☐ does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**


International application No.
PCT/EP2005/056846

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-14
Industrial applicability (IA)	Yes: Claims	1-13
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

- 1 Reference is made to the following document:

(D1 : WO 02/44176 A (NEUROSEARCH A/S; PETERS, DAN; OLSEN, GUNNAR, M;
NIELSEN, ELSEBET, OEST) 6 June 2002 (2002-06-06)

- 2 The prior art does not disclose 3-naphthylquinuclidines wherein the naphthalene ring is substituted as set out in claim 1. The claimed subject matter therefore is novel.

Document D1 is considered to represent the closest prior art. This document discloses (unsubstituted) 3-naphthylquinuclidines, and the use thereof for treatment of essentially the same diseases as for the present compounds.

The present invention is considered as a selection from the compounds suggested in D1, the selection residing in the choice of 3-naphthylquinuclidines which are substituted in the naphthalene ring. Such compounds are suggested in D1, page 4 lines 1-11.

It is not at present apparent that the presently claimed compounds exhibit any unexpected or non-obvious features vis-à-vis the compounds of the closest prior art. The presently claimed compounds and compositions, and the use thereof for the treatment of diseases as recited in the claims therefore are obvious in view of document D1.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**


International application No.

PCT/EP2005/056846

- 3 For the assessment of the present claims: 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PCT REQUEST

Print Out (Original in Electronic Form)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT Online Filing Version 3.50 (Build 0001.169)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	304-204-WO
I	Title of Invention	NOVEL NAPHTHYL SUBSTITUTED AZABICYCLO DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	NeuroSearch A/S
II-5	Address	93 Pederstrupvej 2750 Ballerup Denmark
II-6	State of nationality	DK
II-7	State of residence	DK
II-8	Telephone No.	+45 4460 8000
II-9	Facsimile No.	+45 4460 8080
II-11	Applicant's registration No. with the Office	0.0

PCT REQUEST

Print Out (Original in Electronic Form)

III-1	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	PETERS, Dan
III-1-5	Address	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-1-6	State of nationality	SE
III-1-7	State of residence	DK
III-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	OLSEN, Gunnar, M.
III-2-5	Address	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-2-6	State of nationality	DK
III-2-7	State of residence	DK
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	NIELSEN, Elsebet, Østergaard
III-3-5	Address	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-3-6	State of nationality	DK
III-3-7	State of residence	DK

PCT REQUEST

Print Out (Original in Electronic Form)

44

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	NeuroSearch A/S
IV-1-2	Address	Patent Department 93 Pederstrupvej 2750 Ballerup Denmark
IV-1-3	Telephone No.	+45 4460 8000
IV-1-4	Facsimile No.	+45 4460 8084
IV-1-5	e-mail	patents@neurosearch.dk
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	22 December 2004 (22.12.2004)
VI-1-2	Number	PA 2004 01984
VI-1-3	Country	DK
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	22 December 2004 (22.12.2004)
VI-2-2	Number	60/637,735
VI-2-3	Country	US
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

61

PCT REQUEST

Print Out (Original in Electronic Form)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	



PCT REQUEST

Print Out (Original in Electronic Form)

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application NeuroSearch A/S is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i)		NeuroSearch A/S is entitled as employer of the inventor, PETERS, Dan
VIII-2-1(i)		NeuroSearch A/S is entitled as employer of the inventor, OLSEN, Gunnar, M.
VIII-2-1(i)		NeuroSearch A/S is entitled as employer of the inventor, NIELSEN, Elsebet, Østergaard
VIII-2-1(x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

PCT REQUEST

Print Out (Original in Electronic Form)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	14	✓
IX-3	Claims	4	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	25	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-17	PCT-SAFE physical media	-	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	(PKCS7 Digital Signature)	
X-1-1	Name (LAST, First)	Michael Abildgren	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

PCT (ANNEX - FEE CALCULATION SHEET)

Print Out (Original in Electronic Form)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet			
0-4-1	Prepared Using	PCT Online Filing Version 3.50 (Build 0001.169)		
0-9	Applicant's or agent's file reference	304-204-WO		
2	Applicant	NEUROSEARCH A/S		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (EUR)	
12-1	Transmittal fee T	⇒	100	
12-2-1	Search fee S	⇒	1550	
12-2-2	International search to be carried out by	EP		
12-3	International filing fee (first 30 sheets) i1	902		
12-4	Remaining sheets	0		
12-5	Additional amount (X)	0		
12-6	Total additional amount i2	0		
12-7	i1 + i2 = i	902		
12-12	Electronic Filing reduction (Image) R	-129		
12-13	Total International filing fee (i-R) I	⇒	773	
12-14	Fee for priority document Number of priority documents requested	0		
12-15	Fee per document (X)	30		
12-16	Total priority document fee: P	⇒		
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	2423	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office	European Patent Office (EPO) (RO/EP)		
12-20-1	Authorization to charge the total fees indicated above	✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓		
12-20-3	Authorization to charge the fee for priority document	✓		
12-21	Deposit account No.	28030031		
12-22	Date	16 December 2005 (16.12.2005)		
12-23	Name and signature	MICHAEL ABILDGREN, /Michael Abildgren/		

61

NOVEL NAPHTHYL SUBSTITUTED AZABICYCLO DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

5

This invention relates to novel naphthyl substituted azabicyclo 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
10 the invention.

BACKGROUND ART

Serotonin Selective Reuptake Inhibitors (SSRIs) currently provide efficacy in the
15 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.

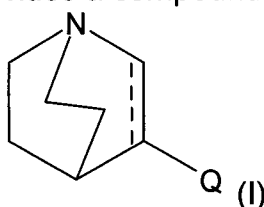
Thus, there is still a strong need for compounds with an optimised
20 pharmacological profile as regards the activity on reuptake of the monoamine neurotransmitters serotonin, dopamine and noradrenaline, such as the ratio of the serotonin reuptake versus the noradrenaline and dopamine reuptake activity.

WO 02/44176 (NeuroSearch A/S) describes 3-substituted quinuclidines and their use as nicotinic agonists.

25

SUMMARY OF THE INVENTION

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



30 or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, wherein the bond ----- represents a single or a double bond; and Q is as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or any
35 of its isomers or any mixture of its isomers, 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, or any of its isomers or any mixture of its isomers, 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, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

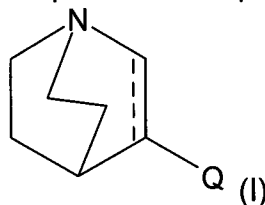
Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

20

DETAILED DISCLOSURE OF THE INVENTION

Naphthyl substituted azabicyclo derivatives

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



or any of its isomers or any mixture of its isomers,
or a pharmaceutically acceptable salt thereof,

wherein

the bond ----- represents a single or a double bond; and

Q represents a naphthyl group;

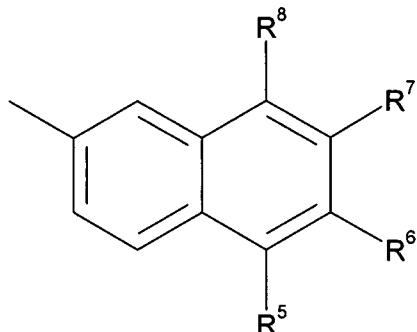
which naphthyl group is substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, -NR'R'', -(C=O)NR'R'' or -NR'(C=O)R'';

wherein R' and R'' independently of each other are hydrogen or alkyl.

In one embodiment, the bond ----- represents a single bond. In a further embodiment, the bond = represents a double bond.

In a still further embodiment, Q represents



- 5 wherein each of R^5 , R^6 , R^7 and R^8 independent of each other represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, $-\text{NR}'\text{R}''$, $-(\text{C}=\text{O})\text{NR}'\text{R}''$ or $-\text{NR}'(\text{C}=\text{O})\text{R}''$;

wherein R' and R'' independently of each other are hydrogen or alkyl;

- 10 with the proviso that at least one of R^5 , R^6 , R^7 and R^8 does not represent hydrogen.

In a special embodiment, each of R^5 , R^6 , R^7 and R^8 independent of each other represent hydrogen, alkyl, alkoxy, cycloalkoxy, alkoxyalkyl or cycloalkoxyalkyl; with the proviso that at least one of R^5 , R^6 , R^7 and R^8 does not represent hydrogen.

- 15 In a further special embodiment, one of R^5 , R^6 , R^7 and R^8 represents alkoxy; and the remaining three of R^5 , R^6 , R^7 and R^8 represent hydrogen. In a still further embodiment, R^6 represents alkoxy and each of R^5 , R^7 and R^8 represents hydrogen.

- In a still further embodiment, one of R^5 , R^6 , R^7 and R^8 represents hydroxy; and the remaining three of R^5 , R^6 , R^7 and R^8 represent hydrogen. In a further embodiment, 20 R^6 represents hydroxy and each of R^5 , R^7 and R^8 represents hydrogen.

In a further embodiment, R^6 represents hydroxy or alkoxy.

In a still further embodiment, Q represents 6-methoxy-naphthalen-2-yl. In a further embodiment, Q represents 6-hydroxy-naphthalen-2-yl.

- 25 In a special embodiment, the chemical compound of the invention is 3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene; 6-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-naphthalen-2-ol; or a pharmaceutically acceptable salt thereof.

- Any combination of two or more of the embodiments as described above is 30 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
5 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.

10 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-
15 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
20 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
25 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.

30 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.

35 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 derived, 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 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 contain one or more chiral centers, and that such compounds exist in the form of isomers.

Also, some of the chemical compounds of the invention having a -C=C- double bond may exist in two forms, syn- and anti-form (Z- and E-form), depending on the arrangement of the substituents around the double bond. A chemical compound of the present invention may thus be the syn- or the anti-form, or it may be a mixture hereof.

5 Moreover, the chemical compounds of the present invention may exist as enantiomers in (+) and (-) forms as well as in racemic forms ($\pm$).

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
10 and techniques. One way of separating the isomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. 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
15 crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) 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
20 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
25 "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

30 The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" 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.

35 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 ^2H (deuterium), ^3H (tritium), ^{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
5 Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS),
Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT),
or combinations thereof.

Methods of Preparation

10 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.

15 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.

20

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
25 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
30 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,
35 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, 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, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, 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, myofascial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, 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 or Gilles de la Tourette's disease. 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 μ M.

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.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonic, 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 chemical 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 chemical compound of the present 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 chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical 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.

5 The powders and tablets preferably 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, 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
10 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.

15 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,
20 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.

25 The chemical 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
30 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
35 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
5 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 chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.
10 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.

15 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.

20 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.

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
25 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,
30 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
35 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.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

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).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50} , may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50} . Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

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 $\mu\text{g}/\text{kg}$ i.v. and 1 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g}/\text{kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

61

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 mono-amine neurotransmitter re-uptake in the central nervous system, and which method
5 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
10 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.

15

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.

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

25 Example 1

3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene fumaric acid salt

A mixture of 3-(6-methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]octan-3-ol (0.49 g, 1.72 mmol) and hydrochloric acid (9 ml, 25%) was stirred at 50°C for 15 h. The mixture was cooled on ice and aqueous sodium hydroxide (20 ml, 10 M) was added.
30 The mixture was extracted with dichloromethane (2 X 25 ml). The mixture was dried with magnesium sulfate and evaporated. The crude mixture was purified by silica gel chromatography, using a mixture of dichloromethane : methanol (9:1) and 1% ammonia as eluent. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield: 190 mg (34%). Mp.
35 226.9°C.

(+/-)-3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]octan-3-ol (Intermediate)

Butyllithium (2.5 M, 1.86 ml, 4.64 mmol) was added to a mixture of 2-bromo-6-methoxynaphthalene (1.0 g, 4.22 mmol) and diethyl ether (10 ml) at 20°C. The



temperature was kept below 35°C for 30 min. The mixture was cooled to -70°C and 3-quinuclidinone (0.53 g, 4.22 mmol) was added at -70°C. The mixture was stirred at -70°C for 1 h. The mixture was allowed to reach room temperature. Water (1 ml) was added followed by aqueous sodium hydroxide (1 M, 10 ml). The crystalline product
5 was filtered and was washed with cold diethyl ether (2 ml). Yield 0.49 g (41%). Mp >330°C.

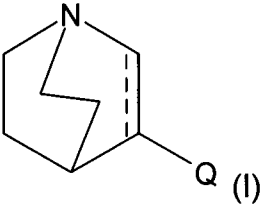
Example 2

6-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-naphthalen-2-ol hydrochloric acid salt

10 A mixture of 3-(6-methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene (0.80 g, 2.10 mmol) and dichloromethane (25 ml) was cooled to -10°C. Borontribromide (10 eq) solved in dichloromethane (21.0 ml, 21.0 mmol) was added dropwise at -10°C. The mixture was allowed to stir for 48 h. Concentrated ammonia (20 ml) was added. The phases were separated and the aqueous phase was extracted with dichloromethane
15 (2 x 20 ml). The combined organic phase was dried and evaporated. The free base of the title compound was precipitated to the hydrochloric acid salt by addition of hydrogen chloride solved in ethanol. Yield 20 mg (3%). Mp 227-230°C.

CLAIMS

1. A compound the Formula I:

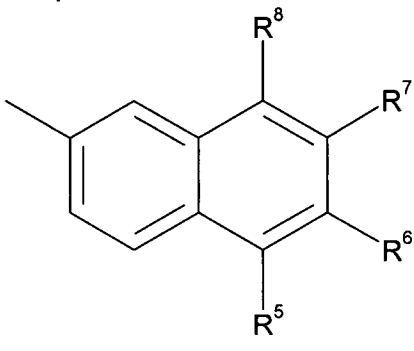


or any of its isomers or any mixture of its isomers,
or a pharmaceutically acceptable salt thereof,
wherein
the bond ----- represents a single or a double bond; and
Q represents a naphthyl group;

which naphthyl group is substituted with one or more substituents
independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy,
cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl,
cycloalkylalkyl, alkenyl, alkynyl, -NR'R'', -(C=O)NR'R'' or -NR'(C=O)R'';
wherein R' and R'' independently of each other are hydrogen or
alkyl.

2. The chemical compound of claim 1, wherein
the bond ----- represents a double bond.

3. The chemical compound of claims 1 or 2, wherein
Q represents



wherein each of R⁵, R⁶, R⁷ and R⁸ independent of each other represent
hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy,
alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkoxyalkyl, alkyl, cycloalkyl,
cycloalkylalkyl, alkenyl, alkynyl, -NR'R'', -(C=O)NR'R'' or -NR'(C=O)R'';
wherein R' and R'' independently of each other are hydrogen or alkyl.



with the proviso that at least one of R⁵, R⁶, R⁷ and R⁸ does not represent hydrogen.

4. The chemical compound of claim 3, wherein
5 wherein each of R⁵, R⁶, R⁷ and R⁸ independent of each other represent hydrogen, alkyl, alkoxy, cycloalkoxy, alkoxyalkyl or cycloalkoxyalkyl; with the proviso that at least one of R⁵, R⁶, R⁷ and R⁸ does not represent hydrogen.
- 10 5. The chemical compound of claim 3, wherein wherein one of R⁵, R⁶, R⁷ and R⁸ represents alkoxy; and the remaining three of R⁵, R⁶, R⁷ and R⁸ represent hydrogen.
6. The chemical compound of claim 3, wherein
15 wherein one of R⁵, R⁶, R⁷ and R⁸ represents hydroxy; and the remaining three of R⁵, R⁶, R⁷ and R⁸ represent hydrogen.
7. The chemical compound of claim 3, wherein
20 Q represents 6-methoxy-naphthalen-2-yl.
8. The chemical compound of claim 3, wherein
Q represents 6-hydroxy-naphthalen-2-yl.
9. The chemical compound of claim 1, which is
25 3-(6-Methoxy-naphthalen-2-yl)-1-aza-bicyclo[2.2.2]oct-2-ene;
6-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-naphthalen-2-ol;
or a pharmaceutically acceptable salt thereof.
10. A pharmaceutical composition, comprising a therapeutically effective amount of a
30 compound of any one of claims 1-9, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.
11. Use of the chemical compound of any of claims 1-9, or any of its isomers or any
35 mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.
12. The use according to claim 11, 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.

- 5 13. The use according to claim 12, 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, 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, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, 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, 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 or Gilles de la Tourettes disease.
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



5

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 1-9, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

**ABSTRACT****NOVEL NAPHTHYL SUBSTITUTED AZABICYCLO DERIVATIVES AND THEIR USE
AS MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS**

This invention relates to novel naphthyl substituted azabicyclo 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.



Brigard & Castro

BOGOTA - COLOMBIA

AS: 96467

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) NeuroSearch A/S

domiciliado(s) en

domiciled in 93 Pederstrupvej
DK-2750 Ballerup, Denmark

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO** y/o **CARLOS H. PALACIO EASTMAN** y/o **HECTOR GOMEZ MEJIA**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, enovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO** and/or **CARLOS H. PALACIO EASTMAN** and/or **HECTOR GOMEZ MEJIA**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions; derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO** y/o **CARLOS H. PALACIO EASTMAN** y/o **HECTOR GOMEZ MEJIA**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO** and/or **CARLOS H. PALACIO EASTMAN** and/or **HECTOR GOMEZ MEJIA**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Otorgado y firmado en

hoy de de

Firma

Nombre
Cargo

and signed in

day of 200



Peder Velling
Peder Velling
Head of Patents

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Hoy de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él



LEGALIZACION POR APOSTILLA ES REQUERIDA.

On this 14th day of April of 2005 personally appeared before me

Peder Velling
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
Head of patent department
of

Neurosearch A/S

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Denmark
under date of 14th April 2005

and that he (she) who grants the present power of attorney is its Representative.

Public Notary (Seal)

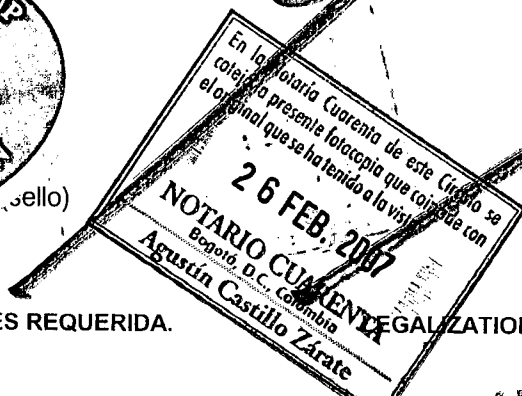
HENNING BROMAN
Reassessor
**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this 14th day of April of 2005 personally appeared before me

Peder Velling
who is (are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grants the document for the uses and purposes therein expressed.

Notary Public (Seal)

HENNING BROMAN
Reassessor



LEGALIZATION BY APOSTILLE IS REQUIRED.

The City Court of Ballerup
Blegdamsvej 6
2200 Copenhagen
Denmark



THE TRUE SIGNATURE OF
Henning Broman

IS HEREBY CERTIFIED.

COPENHAGEN, 17 APR. 2005

FOR THE MINISTER FOR FOREIGN AFFAIRS.

B.A.

Henning Broman

BIRGITTE THORELL

RECEIVED
DENMARK
COLOMBIA

EL CONSUL AD-HONOREM DE COLOMBIA EN
COPENHAGUE, DINAMARCA

Feca. 18 APR. 2005 No: 222

Previa la confrontación correspondiente DA
FE de que la firma que aparece en este docu-
mento es similar a la REGISTRADA aquí por

este

Ole Waage Pedersen
CONSUL AD-HONOREM

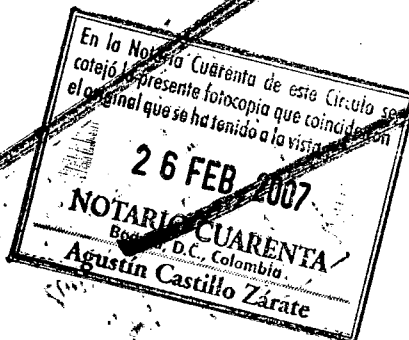
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 ABR 27 A 10:14

us
DE LEGALIZACIONES
BOMBA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

355440
Ole Waage
CON LA FIRMA APARECE EN EL
DOCUMENTO DE EMPLEO
LAS FUNCIONES INDICADAS



769
TRADUCCION OFICIAL NO.364/2005-

TRADUCCIÓN DE LOS SELLOS QUE APARECEN EN EL PODER GENERAL OTORGADO POR **NEUROSEARCH A/S.** SOCIEDAD DOMICILIADA EN 93 pederstrupvej DK-2750 BALLERUP, DINAMARCA, A LOS DOCTORES JUAN PABLO CADENA SARMIENTO Y/O BEATRIZ JARAMILLO Y/O CARLOS H. PALACIO EASTMAN Y/O HECTOR GOMEZ MEJIA.

FIRMADO: PEDER VELLING, DIRECTOR DE PATENTES

CERTIFICADO NOTARIAL (SOCIEDAD)

HOY 1° DE ABRIL DE 2005 PERSONALMENTE COMPARECIÓ ANTE MI **PEDER VELLING**, A QUIEN CONOZCO Y DE QUIEN ME CONSTA QUE FIRMO EL ANTERIOR DOCUMENTO, Y QUIEN DEBIDAMENTE JURAMENTADO DECLARO Y DIJO QUE ÉL ES EL DIRECTOR DEL DEPARTAMENTO DE **PATENTES DE NEUROSEARCH A/S.**, SOCIEDAD LEGALMENTE CONSTITUIDA PARA UN PERIODO DE DURACIÓN QUE AUN NO HA TERMINADO; QUE EL DECLARANTE ESTA AUTORIZADO POR DICHA COMPAÑÍA PARA CONFERIR ESTE PODER; QUE EL SELLO ESTAMPADO POR ÉL AL PIE DE TAL PODER, EN NOMBRE Y REPRESENTACIÓN DE LA EXPRESADA COMPAÑÍA, ES EL SELLO OFICIAL DE ELLA; Y QUE EL OBJETO PARA EL CUAL SE CONFIERE ESTE INSTRUMENTO ESTA COMPRENDIDO DENTRO DEL DE LA SOCIEDAD. EL SUSCRITO NOTARIO HACE CONSTAR QUE TUVO A LA VISTA LAS PRUEBAS DE LA EXISTENCIA DE LA SOCIEDAD.

DINAMARCA, FECHADO EL 1° DE ABRIL DE 2005.

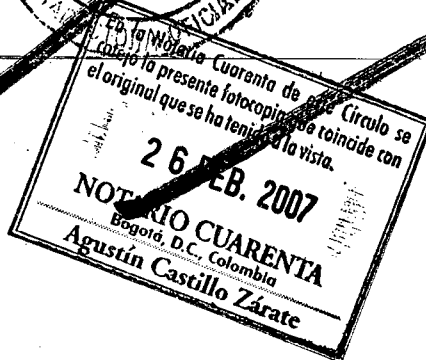
Y QUE QUIEN CONFIERE EL PRESENTE PODER ES SU REPRESENTANTE.

FIRMADO: HENNING BROMAN, NOTARIO.

HAY SELLO EN RELIEVE DEL NOTARIO.

CERTIFICADO NOTARIAL (PERSONA NATURAL)

Hoy 1° DE ABRIL DE 2004, COMPARECIÓ ANTE MI PEDER VELLING, A QUIEN CONOZCO Y ME CONSTA QUE ES LA PERSONA FIRMANTE DEL



TRADUCCION OFICIAL NO.364/2005-.

DOCUMENTO QUE PRECEDE Y QUIEN DECLARA QUE OTORGA EL MISMO PARA LOS FINES Y PROPÓSITOS QUE EN EL SE EXPRESAN.

FIRMADO: HENNING BROMAN, NOTARIO.

HAY SELLO EN RELIEVE DEL NOTARIO.

CORTE DE LA CIUDAD DE BALLERUP

BLEGDAMSVEL 6

2200 COPENHAGUEN, DINAMARCA

MINISTERIO DE RELACIONES EXTERIORES

SE CERTIFICA LA AUTENTICIDAD DE LA FIRMA DE HENNING BROMAN COPENHAGUE, 1° DE ABRIL DE 2005

POR EL MINISTERIO DE RELACIONES EXTERIORES

FIRMADO: BIRGITTE THORELL. HAY SELLO DEL MINISTERIO DE RELACIONES EXTERIORES.

SIGUE AUTENTICACIÓN DE LA FIRMA QUE PRECEDE EFECTUADA POR EL CONSULADO AD-HONOREM DE COLOMBIA EN COPENHAGUE, DINAMARCA BAJO EL NO. 222 DEL 18 DE ABRIL DE 2005.

FIRMADO: OLE WAAGE PEDERSEN, CÓNSUL AD-HONOREM

SIGUE AUTENTICACIÓN DE LA FIRMA DE OLE WAAGE, CÓNSUL AD-HONOREM DE COLOMBIA EN DINAMARCA, EFECTUADA POR EL MINISTERIO DE RELACIONES EXTERIORES EN BOGOTA BAJO EL NO. 355460 DEL 27 DE ABRIL DE 2005.

LA TRADUCTORA OFICIAL

HELENA URIBÉ DE LEMOINE





No. 07-062933- -00000-0000

Fecha: 2007-06-21 17:02:05 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 90

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION



MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Descripción de la invención []
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Fdo B
Firma Responsable

Fecha 21 JUN. 2007

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia