

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

21-



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División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

06-119265

54 TITULO DERIVADOS NOVEDOSOS DE PIPERAZINA SUSTITUIDA CON ALQUILO Y SU USO COMO
INHIBIDORES DE LA REABSORCION DEL NEUROTRANSMISOR DE MONOAMINA

51 CLASIFICACION INTERNACIONAL _____

71 SOLICITANTE NEUROSEARCH A/S

DOMICILIO BALLERUP, DINAMARCA

74 APODERADO JUAN PABLO CADENA SARMIENTO

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PETITORIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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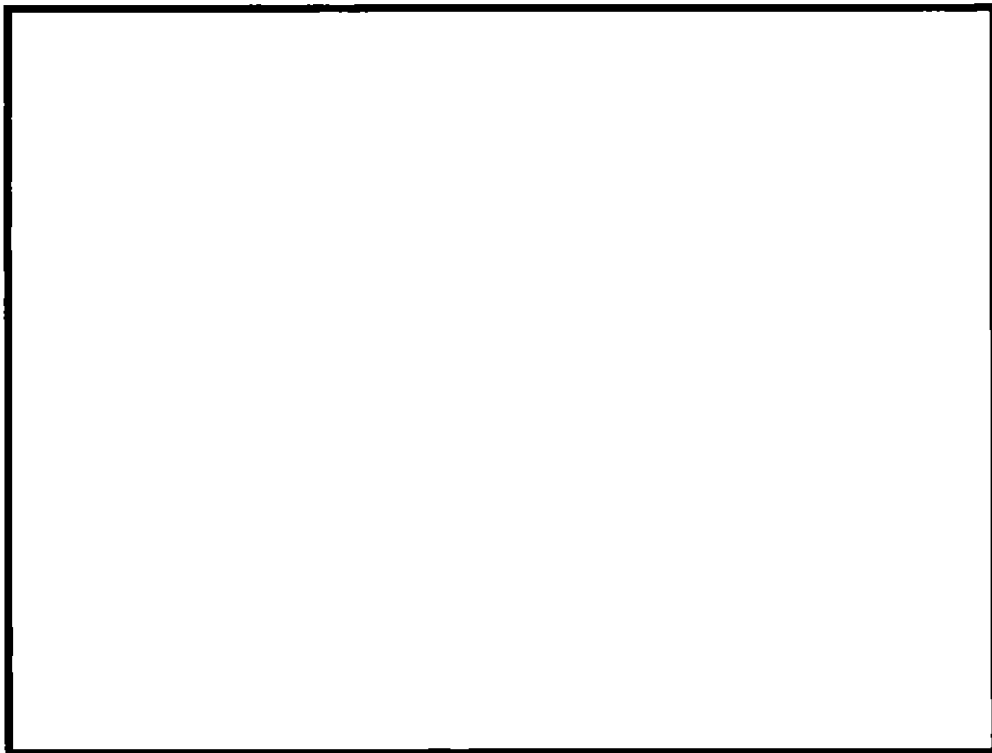
① SOLICITUD DE			
☒ Patente de Invención		☐ Patente de Modelo de Utilidad	
☒ Capítulo I		☐ Capítulo II	
② SOLICITANTE (71)	Nombre NEUROSEARCH A/S Dirección 93 Pederstrupvej, DK-2750 Ballerup, Dinamarca Nacionalidad o Domicilio Dinamarca Lugar de Constitución Dinamarca Teléfono _____ Fax _____ E-mail _____	IDENTIFICACION CC ☐ NIT ☐ CE ☐ Otro ☐ Cuál _____ Número _____	
③ REPRESENTANTE O APODERADO	Nombre JUAN PABLO CADENA SARMIENTO Dirección Carrera 7 No 71-21 Torre B-Piso 4 Teléfono 7442200 Fax 7422200 E-mail bnrcas@bc.com.co	IDENTIFICACION CC ☒ NIT ☐ CE ☐ Otro ☐ Cuál _____ N° 80417337 Usaquén TP 57482	
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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$483.000
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso Copia auténtica.
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ 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 Tarjeta de Propietarios
Documentos PCT

11 FIGURA CARACTERÍSTICA.



Solicito la concesión de la patente,

NOMBRE JUAN PABLO CADENA SARMIENTO

FIRMA

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

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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PCT/EP2005/052732

PATENTE

X

MODELO DE UTILIDAD

DISEÑO INDUSTRIAL

NEUROSEARCH A/S

SOLICITANTE/S RAZON SOCIAL O APELLIDOS Y NOMBRES

DOMICILIO BALLERUP, DINAMARCA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO DERIVADOS NOVEDOSOS DE PÍPERAZINA SUSTITUIDA CON ALQUILIO Y SU USO COMO INHIBIDORES DE LA REABSORCIÓN

CLASIFICACION

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HASTA

PRORROGA

CAMBIO DE NOMBRE

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INVENTOR (ES) DAN PETERS, GUNNAR M OLSEN, ELSEBET OSTERGAARD NIELSEN, JORGEN SCHEEL-KRUGER

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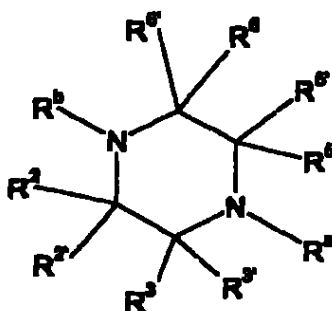
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(54) Title: NOVEL ALKYL SUBSTITUTED PIPERAZINE DERIVATIVES AND THEIR USE AS MONOAMINE NEURO
TRANSMITTER RE-UP TAKE INHIBITORS



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

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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.

NOVEL ALKYL SUBSTITUTED PIPERAZINE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS

TECHNICAL FIELD

This invention relates to novel alkyl substituted piperazine 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

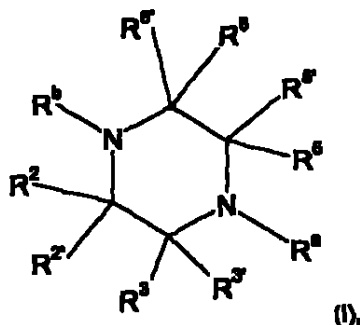
BACKGROUND ART

WO 97/30997 (NeuroSearch A/S) describes tropane derivatives active as neurotransmitter re-uptake inhibitors

However, 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 noreadrenaline, such as the ratio of the serotonin reuptake versus the noreadrenaline and dopamine reuptake activity

SUMMARY OF THE INVENTION

In its first aspect, the invention provides a piperazine derivative of the Formula I



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

wherein R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h and R^i are as defined below

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, 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, 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

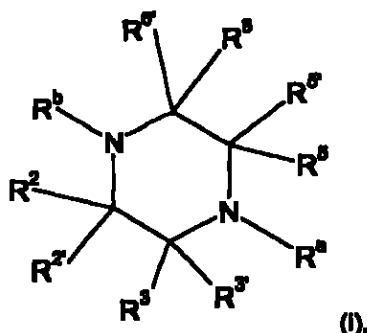
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to response to inhibition of monoamine neurotransmitter re-uptake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

20 Alkyl substituted piperazine derivatives

In its first aspect the present invention provides piperazine derivatives of formula I



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

R^a represents hydrogen or alkyl,

which alkyl is optionally substituted with one or more substituents independently selected from the group consisting of

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

R^b represents an aryl or a heteroaryl group,

which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl, each of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 independently of each other represents hydrogen or alkyl, with the proviso that at least one of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 represents alkyl

In one embodiment, R^a represents hydrogen or alkyl. In a special embodiment, R^a represents hydrogen. In a further embodiment, R^a represents alkyl, such as methyl. In a still further embodiment, R^b represents an optionally substituted aryl, such as an optionally substituted phenyl.

In a further embodiment, R^b represents a phenyl group, which phenyl group is optionally substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy.

In a still further embodiment, R^b represents a phenyl group, which phenyl group is optionally substituted twice with halo. In a special embodiment, R^b represents dichloro-phenyl, such as 3,4-dichloro-phenyl or 2,4-dichlorophenyl.

In a further embodiment, R^b represents a phenyl group, which phenyl group is substituted once with halo. In a special embodiment, R^b represents chloro-phenyl, such as 4-chloro-phenyl. In a further embodiment, R^b represents bromo-phenyl, such as 4-bromo-phenyl. In a still further embodiment, R^b represents iodo-phenyl, such as 4-iodo-phenyl.

In a still further embodiment, R^b represents a phenyl group, which phenyl group is substituted once with trifluoromethyl or trifluoromethoxy. In a special embodiment, R^b represents trifluoromethyl-phenyl, such as 4-trifluoromethyl-phenyl. In a further embodiment, R^b represents trifluoromethoxy-phenyl, such as 4-trifluoromethoxy-phenyl.

In a further embodiment, R^b represents a naphthyl group, which naphthyl group is optionally substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy. In a special embodiment, R^b represents naphthyl, such as naphthalen-2-yl. In a further embodiment, R^b represents alkoxynaphthyl, such as methoxynaphthyl, such as 6-methoxy-naphthalen-2-yl.

In a further embodiment, two of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 represent alkyl, and the remaining six of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 represent hydrogen.

In a special embodiment, R^2 and R^8 represent alkyl, such as methyl, and R^3 , R^4 , R^5 , R^6 , R^7 and R^9 represent hydrogen. In a further embodiment, R^3 and R^8 represent alkyl, such as methyl, and R^2 , R^4 , R^5 , R^6 , R^7 and R^9 represent hydrogen. In a still

further embodiment, R² and R⁶ represent alkyl, such as methyl, and R², R³, R⁴, R⁵, R⁶ and R⁷ represent hydrogen. In a still further embodiment, R³ represents alkyl, such as methyl, and R², R⁴, R⁵, R⁶, R⁷ and R⁸ represent hydrogen.

In a special embodiment, the compound of the invention is a *trans*-dialkyl-piperazine derivative, such as a *trans*-dimethyl-piperazine derivative, such as a *trans*-2,5-dimethyl-piperazine derivative. In a further embodiment, the compound of the invention is a *cis*-dialkyl-piperazine derivative, such as a *cis*-dimethyl-piperazine derivative, such as a *cis*-3,5-dimethyl-piperazine derivative or a *cis*-2,6-dimethyl-piperazine derivative.

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In a special embodiment the chemical compound of the invention is

- 1-(3,4-Dichloro-phenyl)-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-3,5-dimethyl-piperazine,
 - 1-(4-Chloro-phenyl)-2,5-dimethyl-piperazine,
 - 15 1-(4-Iodo-phenyl)-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-2,6-dimethyl-piperazine
 - 1-(4-Bromo-phenyl)-2,5-dimethyl-piperazine,
 - 1-(4-Trifluoromethyl-phenyl)-2,5-dimethyl-piperazine,
 - 1-(4-Trifluoromethoxy-phenyl)-2,5-dimethyl-piperazine,
 - 20 1-(2,4-Dichloro-phenyl)-2,5-dimethyl-piperazine,
 - 1-(2,4-Dichloro-phenyl)-3,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-3-methyl-piperazine,
 - 1-(2-Naphthyl)-2,5-dimethyl-piperazine,
 - 1-(6-Methoxy-naphth-2-yl)-2,5-dimethyl-piperazine,
 - 25 1-(3,4-Dichloro-phenyl)-4-methyl-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-4-methyl-3,5-dimethyl-piperazine,
 - 1-(4-Chloro-phenyl)-4-methyl-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-4-methyl-2,6-dimethyl-piperazine,
 - 1-(4-Trifluoromethoxy-phenyl)-4-methyl-2,5-dimethyl-piperazine,
 - 30 1-(2-Naphthyl)-4-methyl-2,5-dimethyl-piperazine,
- any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof

In a special embodiment the chemical compound of the invention is

- (±)-1-(3,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
- 35 1-(3,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
- (±)-1-(4-Chloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
- (±)-1-(4-Iodo-phenyl)-*trans*-2,5-dimethyl-piperazine,
- 1-(3,4-Dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine
- (±)-1-(4-Bromo-phenyl)-*trans*-2,5-dimethyl-piperazine,

- (±)-1-(4-Trifluoromethyl-phenyl)-*trans*-2,5-dimethyl-piperazine,
 (±)-1-(4-Trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine,
 (±)-1-(2,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
 (±)-1-(2,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
 5 (±)-1-(3,4-Dichloro-phenyl)-3-methyl-piperazine,
 (±)-1-(2-Naphthyl)-*trans*-2,5-dimethyl-piperazine,
 (±)-1-(8-Methoxy-naphth-2-yl)-*trans*-2,5-dimethyl-piperazine,
 1-(3,4-Dichloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
 (±)-1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-3,5-dimethyl-piperazine,
 10 (±)-1-(4-Chloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
 1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-2,6-dimethyl-piperazine,
 (±)-1-(4-Trifluoromethoxy-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
 (±)-1-(2-Naphthyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
 or a pharmaceutically acceptable salt thereof

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

Definition of Substituents

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

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contains of from one to six carbon atoms (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.

30 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-butenyl, or 1,3-butadienyl, 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexadienyl, or 1,3,5-hexatrienyl.

35 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 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 group, preferably containing of from three to seven carbon atoms (C₃₋₇-cycloalkyl),

5 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

In the context of this invention an aryl group designates a carbocyclic aromatic ring system such as phenyl, naphthyl (1-naphthyl or 2-naphthyl) or fluorenyl

10 In the context of this invention a heteroaryl group designates an aromatic mono- or bicyclic heterocyclic group, which holds one or more heteroatoms in its ring structure Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S).

Preferred monocyclic heteroaryl groups of the invention include aromatic 5- and 6-membered heterocyclic monocyclic groups, including for example, but not
15 limited to, oxazolyl (oxazol-2-yl, -4-yl, or -5-yl), isoxazolyl (isoxazol-3-yl, -4-yl, or -5-yl), thiazolyl (thiazol-2-yl, -4-yl, or -5-yl), isothiazolyl (isothiazol-3-yl, -4-yl, or -5-yl), 1,2,4-oxadiazolyl (1,2,4-oxadiazol-3-yl or -5-yl), 1,2,4-thiadiazolyl (1,2,4-thiadiazol-3-yl or -5-yl), 1,2,5-oxadiazolyl (1,2,5-oxadiazol-3-yl or -4-yl), 1,2,5-thiadiazolyl (1,2,5-thiadiazol-3-yl or -4-yl), imidazolyl (2-, 4-, or 5-imidazolyl), pyrrolyl (2- or 3-pyrrolyl),
20 furanyl (2- or 3-furanyl), thienyl (2- or 3-thienyl), pyridyl (2-, 3- or 4-pyridyl), pyrimidyl (2-, 4-, 5- or 6-pyrimidyl), or pyridazinyl (3- or 4-pyridazinyl)

Preferred bicyclic heteroaryl groups of the invention include for example, but not limited to, indolizynyl (2-, 5- or 6-indolizynyl), indolyl (2-, 5- or 6-indolyl), isoindolyl (2-, 5- or 6-isoindolyl), indazolyl (1- or 3-indazolyl), benzofuranyl (2-, 5- or 6-
25 benzofuranyl), benzo[b]thienyl (2-, 5- or 6-benzothienyl), benzimidazolyl (2-, 5- or 6-benzimidazolyl), benzoxazolyl (2-, 5- or 6-benzoxazolyl), benzothiazolyl (2-, 5- or 6-benzothiazolyl), benzo[d]isothiazolyl (1,2-benzo[d]isothiazol-3-yl), purinyl (2- or 6-purinyl), quinolinyl (2-, 3-, 6-, 7- or 8-quinolinyl), isoquinolinyl (1-, 3-, 5-, 6- or 7-isoquinolinyl), cinnolinyl (6- or 7-cinnolinyl), phthalazinyl (6- or 7-phthalazinyl),
30 quinoxalinyl (2-, 6- or 7-quinoxalinyl), quinoxalynyl (2- or 6-quinoxalynyl), 1,8-naphthyridinyl (1,8-naphthyridin-2-, 3-, 6- or 7-yl), pteridinyl (2-, 6- or 7-pteridinyl), and indenyl (1-, 2-, 3-, 6- or 5-indenyl)

Pharmaceutically Acceptable Salts

35 The chemical compound of the invention may be provided in any form suitable for the intended administration Suitable forms include pharmaceutically (i e

physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzenesulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, 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 lysine, 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.

10 Stereoisomers

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.

For example, the compounds of the present invention may exist in cis or trans configurations as well as in mixtures thereof. E.g. those of the substituents R^2/R^2 , R^3/R^3 , R^4/R^4 , and R^5/R^5 which represent alkyl may in particular be in cis or trans configuration relative to each other (e.g. R^2 relative to R^5 , or R^3 relative to R^5). Examples include, without limitation, trans-2,5-dimethyl-piperazine and cis-3,5-dimethyl-piperazine derivatives. The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Moreover, the chemical compounds of the present invention may exist as enantiomers in (+) and (-) forms as well as in racemic forms ($\pm$). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

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

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the 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 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 from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphoric 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 *Jacques J, Collet A, & Wilen S* in

5 "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

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

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

The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the
20 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 Positron Emission Tomography (PET), Single Photon Imaging, Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS),
25 Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of Preparation

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

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

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

Biological Activity

Compounds of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes e.g. such as described in WO 97/30997. Based on the balanced activity observed in these tests
 5 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
 10 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,
 15 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
 20 complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis,
 25 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, late luteal phase syndrome, post-
 30 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, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced
 35 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
5 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

10 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
15 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
20 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,
25 bronchial, nasal, pulmonary, 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
30 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
35 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

5 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.

10 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, 15 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.

20 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 25 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 30 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 35 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 for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

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

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

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

For topical administration to the epidermis the 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 aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

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

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane,

trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an

10 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.

15 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

20 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.

25 Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Mack 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.

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

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of

the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments

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

Methods of Therapy

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

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

EXAMPLES

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

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

Method A**(±)-1-(3,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt**

A mixture of *trans*-2,5-dimethylpiperazine (10 g, 88 mmol), 1-bromo-3,4-dichlorobenzene (22 g, 97 mmol), KO^tBu (20 g, 176 mmol), palladacycle (100 mg) and dioxane (100 ml) was stirred at reflux for 1 h. Water (100 ml) was added to the mixture. The mixture was extracted with diethyl ether (2 x 100 ml). Chromatography on silica gel with methanol, dichloromethane and conc. ammonia (10:80:1) gave the title compound. Yield 7.0 g (31 %). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 209-211°C.

1-(3,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from *cis*-3,5-dimethyl-piperazine. Mp 225-227°C.

15 (±)-1-(4-Chloro-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 165-168°C.

(±)-1-(4-Iodo-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 160-166°C.

20 (±)-1-(3,4-Dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from *cis*-3,5-Dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester followed by deprotection of the 1-carboxylic acid *tert*-butyl ester with a mixture of hydrochloric acid and acetic acid. Mp 170-173°C.

25 (±)-1-(4-Bromo-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 168-170°C.

(±)-1-(4-Trifluoromethyl-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

30 Was prepared according to method A. Mp 186-187°C.

(±)-1-(4-Trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 157-160°C.

35 (±)-1-(2,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine hydrochloric acid salt

Was prepared according to method A. Mp 197-200°C.

(1-(2,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from *cis*-3,5-dimethyl-piperazine. Mp >270°C.

40

(±)-1-(3,4-Dichloro-phenyl)-3-methyl-piperazine fumaric acid salt

Was prepared according to method A from (±)-3-methyl-piperazine Mp 190-192°C

(±)-1-(2-Naphthyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

5 Was prepared according to method A. Mp 178-179°C

(±)-1-(6-Methoxy-naphth-2-yl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A Mp 207°C

10 Method B**(±)-1-(3,4-Dichloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine fumaric acid salt**

A mixture of (±)-1-(3,4-dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine (6.0 g, 23 mmol), formic acid (60 ml) and formaldehyde (60 ml) was stirred at 70°C for 15 h. The
15 mixture was evaporated. An aqueous solution of ammonia (100 ml, 1 M) was added followed by extraction with diethyl ether (2 x 100 ml). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 3.0 g (33 %) Mp 166-168°C

20 1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-3,5-dimethyl-piperazine free base

Was prepared according to method B from (±)-1-(3,4-dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine. The product was isolated as an oil.

(±)-1-(4-Chloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine fumaric acid salt

25 Was prepared according to method B from (±)-1-(4-chloro-phenyl)-*trans*-2,5-dimethyl-piperazine. Mp 142-144.5°C

(±)-1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-2,6-dimethyl-piperazine free base

Was prepared according to method B from (±)-1-(3,4-dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine. The product was isolated as an oil.
30

(±)-1-(4-Trifluoromethoxy-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine hydrochloric acid salt

Was prepared according to method B from (±)-1-(4-trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine. Mp 167-170°C.
35

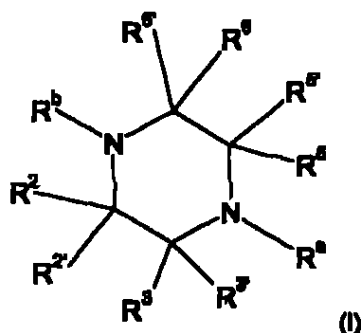
(±)-1-(2-Naphthyl)-4-methyl-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from (±)-1-(2-naphthyl)-*trans*-2,5-dimethyl-piperazine. The product was isolated as an oil.

CLAIMS

1 A piperazine derivative of the Formula I

5



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

10

R^a represents hydrogen or alkyl,

which alkyl is optionally substituted with one or more substituents
independently selected from the group consisting of

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

15

R^b represents an aryl or a heteroaryl group,

which aryl or heteroaryl group is optionally substituted with one or more
substituents independently selected from the group consisting of

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

each of R^2 , R^2 , R^3 , R^5 , R^5 , R^6 , R^6 and R^7 independently of each other represents
hydrogen or alkyl,

with the proviso that at least one of R^2 , R^2 , R^3 , R^5 , R^5 , R^6 , R^6 and R^7 represents
alkyl

20 2 The chemical compound of claim 1, wherein
 R^a represents hydrogen or alkyl

3 The chemical compound of claims 1 or 2, wherein
 R^b represents a phenyl group,

which phenyl group is optionally substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy

- 4 The chemical compound of claims 1 or 2, wherein
5 R^b represents a phenyl group,
which phenyl group is optionally substituted twice with halo
- 5 The chemical compound of any one claims 1-4, wherein
two of $R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^9 represent alkyl, and
the remaining six of $R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^9 represent hydrogen
- 10 6 The chemical compound of claim 1, which is
(±)-1-(3,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
(±)-1-(4-Chloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Iodo-phenyl)-*trans*-2,5-dimethyl-piperazine,
15 1-(3,4-Dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine
(±)-1-(4-Bromo-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Trifluoromethyl-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(2,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
20 (1-(2,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
(±)-1-(3,4-Dichloro-phenyl)-3-methyl-piperazine,
(±)-1-(2-Naphthyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(6-Methoxy-naphth-2-yl)-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
25 (±)-1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-3,5-dimethyl-piperazine,
(±)-1-(4-Chloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-2,6-dimethyl-piperazine,
(±)-1-(4-Trifluoromethoxy-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
(±)-1-(2-Naphthyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
30 or a pharmaceutically acceptable salt thereof
- 7 A pharmaceutical composition, comprising a therapeutically effective amount of a
compound of any one of claims 1-6, any of its isomers or any mixture of its
isomers, or a pharmaceutically acceptable salt thereof, together with at least one
35 pharmaceutically acceptable carrier, excipient or diluent.

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- 8 Use of the chemical compound of any of claims 1-6, any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.
- 5 9 The use according to claim 8, 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
- 10 10 The use according to claim 9, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, 25 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, 30 diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofascial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, 35 erectile dysfunction, premature female orgasm, restless leg syndrome, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourette's disease

- 11 A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-8, any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof
- 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/052732

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/033 A61K31/495 A61P25/00 C07D295/073 C07D295/096

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/46144 A (A CARLSSON RESEARCH AB, SVAN, INGELA, MARIANNE LF, CARLBERG, JENNY LF) 28 June 2001 (2001-06-28) claims and examples 1,2	1-5,7-11
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-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 doubt on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document relating 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 state-of-the-art documents, such combination being obvious to a person skilled in the art
- A document member of the same patent family

Date of the actual completion of the international search

11 October 2005

Date of mailing of the international search report

24/10/2005

Name and mailing address of the ISA
European Patent Office, P.O. Box 5518 Patentstrasse 2
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Authorized officer

Gregoire, A

INTERNATIONAL SEARCH REPORT

International Application No.
PC/EP2005/052732

G.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 247 206 A (YOST WILLIAM LASSITER ET AL) 19 Apr 11 1966 (1966-04-19) examples 3,4	1-5,7,8
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X	BRENNER E ET AL "Nickel-catalysed selective N-arylation or N,N'-diarylation of secondary diamines" August 2002 (2002-08), TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, PAGE(S) 6913-6924, XP004377343 ISSN 0040-4020 products 3 in table 2	1-3,5,7-11
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/052732

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. because they relate to subject matter not required to be searched by this Authority namely
Although claim 11 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 8.4(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/EP2005/052732

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/052732

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(19) Organización Mundial de Propiedad
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PCT

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295/098

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PCT/EP2005/052732

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14 de junio de 2005 (14.06.2005)

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(26) Lenguaje de Publicación

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60/581 363 22 de junio de 2004 (22.06.2004) US

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(81) Estados Designados (a menos que se indique lo
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BG BR BY BZ, CA, CH CN, CO, CR CU CZ,
DE, DK, DM, DZ EC, EE, ES FI GB, GD GE, GH
GM HR HY ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MAMG MG MK,
MN MW MX MZ NO NZ OM PH PL, PT RO
RU SD SE SG SI SK, SL, TJ TM TN TR TT
TZ UAM UG UZ, VN YU ZA ZM ZW

(84) Estados Designados (a menos que se indique lo
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disponible) ARIPO (GH GM KE LS MW MZ SD
SL, SZ TZ, UG, ZM ZW) Euroasiática (AM AZ,
BY KG KZ MD RU TJ TM) Europea (AT BE
BG CH CY CZ, DE DK EE ES FI FR GB GR
IE IT LU MC NL PT SE 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

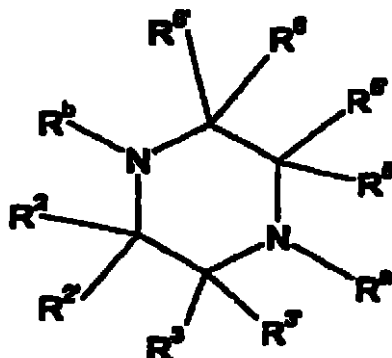
En cuanto al derecho del solicitante de solicitar y
que se le conceda una patente (Regla 4.17 (ii)) para
las siguientes designaciones AE AG AL, AM AT
AU, AZ BA, BB BG BR, BY BZ, CA, CH CN CO,
CR CU CZ DE DK, DM DZ EC EE, ES FI GB
GD GE GH GM HR HY ID IL IN IS JP KE
KG KP KR KZ, LC, LK LR, LS LT, LU LV,
MAMG MG MK MN MW MX MZ, NO NZ OM
PH PL PT RO RU SD SE SG SI SK, SL, TJ
TM TN TR TT TZ UAM UG UZ, VN YU ZA,
ZM, ZW patente ARIPO (GH GM, KE LS MW,
MZ, SD SL, SZ, TZ, UG ZM ZW) Patente
Euroasiática (AM AZ BY KG KZ MD RU TJ
TM) Patente europea (AT BE BG CH CY CZ,
DE DK, EE ES FI FR GB, GR IE, IT LU MC
NL PT SE SK, TR) Patente OAPI (BF BJ CF
CG CI CM GA, GN GQ GW ML MR NE SN
TD TG)

Publicada

Con el informe de búsqueda internacional

[Continúa en la siguiente página]

(54) Título DERIVADOS NOVEDOSOS DE PIPERAZINA SUSTITUIDA CON ALQUILO Y SU USO COMO
INHIBIDORES DE LA REABSORCIÓN DEL NEUROTRANSMISOR DE MONOAMINA



(57) Resumen Esta invención se relaciona con derivados
novedosos de piperazina sustituidos con alquilo útiles como
inhibidores de la reabsorción de los neurotransmisores de
monoamina. En otros aspectos la invención se relaciona con el uso
de estos compuestos en un método para terapia y/o a composiciones
farmacéuticas que comprenden los compuestos de la invención

WO 2005/123707A1



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— antes del vencimiento de la fecha límite para corregir las reivindicaciones y a ser republicado en el evento de recibir las correcciones

Para códigos de dos letras y otras abreviaciones referirse a las "Notas de guía sobre Códigos y Abreviaturas" que aparecen al comienzo de cada edición de la Gaceta del PCT

NUEVOS COMPUESTOS

CAMPO TÉCNICO

La presente invención se refiere a nuevos derivados de piperazina sustituidos por alquilo útiles como inhibidores de la recaptación del neurotransmisor monoamina

En otros aspectos de la invención, se refiere al uso de estos compuestos en un método para terapia y a composiciones farmacéuticas que incluyen a los compuestos de la invención

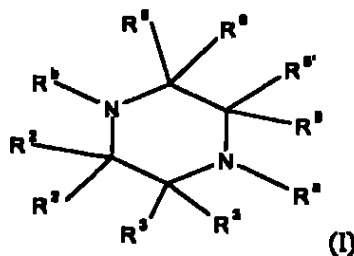
TÉCNICA ANTERIOR

El documento WO 97/30997 (NeuroSearch A/S) describe derivados de tropano activos como inhibidores de la recaptación de neurotransmisores

Sin embargo, aun existe la necesidad de contar con compuestos que presenten un perfil farmacológico óptimo en cuanto a la actividad sobre la recaptación de los neurotransmisores monoamina de la serotonina, dopamina y noradrenalina, como por ejemplo la relación de la recaptación de la serotonina en contraposición con la actividad de la recaptación de la noradrenalina y la dopamina

SÍNTESIS DE LA INVENCION

En un primer aspecto, la invención proporciona un derivado de piperazina de fórmula I



cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos en la que R^a , R^b , R^2 , R^3 , R^4 , R^5 , R^6 , y R^7 son como se definen a continuación

En un segundo aspecto, la invención proporciona una composición farmacéutica, que incluye una cantidad terapéuticamente efectiva de un compuesto de la invención, o cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de la misma, junto con al menos un vehículo, excipiente o diluyente farmacéuticamente aceptable

En aun otro aspecto, la invención proporciona el uso de un compuesto de la invención, de cualquiera de sus isómeros o de cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos, para la preparación de una composición farmacéutica destinada al tratamiento, prevención o alivio de una enfermedad o de un trastorno o de una afección de un mamífero, incluido el ser humano, cuya enfermedad, trastorno o afección responde a la inhibición de la recaptación del neurotransmisor monoamina en el sistema nervioso central

En otro aspecto, la invención se refiere a un método para el tratamiento la prevención o el alivio de una enfermedad o de un trastorno o de una afección de un cuerpo vivo animal con inclusión del ser humano, cuyo trastorno, enfermedad o afección responde a la inhibición de la recaptación del neurotransmisor monoamina en el sistema nervioso central, y dicho método comprende el paso de administrar a un cuerpo animal vivo que necesite una cantidad terapéuticamente efectiva de un compuesto de la invención, de cualquiera de sus isómeros o de

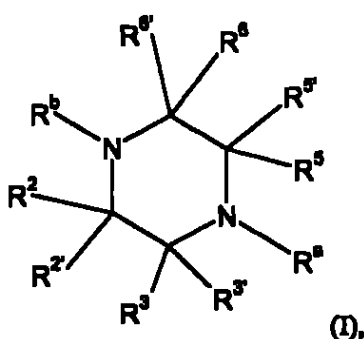
cualquier mezcla de sus isómeros, o de una sal farmacéuticamente aceptable de los mismos

Otros objetos de la invención serán evidentes para un experto en la técnica a partir de la siguiente descripción detallada y de siguientes los ejemplos

DESCRIPCIÓN DETALLADA DE LA INVENCION

Derivados de piperazina sustituidos por alquilo

En un primer aspecto, la presente invención proporciona derivados de piperazina de fórmula I



cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos,

en la que

R^a representa hidrógeno o alquilo,

en donde el alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados independientemente del grupo que consiste

halo trifluorometilo, trifluorometoxi, ciano, hidroxil, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alquenilo y alquinilo,

R^b representa un grupo arilo o heteroarilo en donde el grupo arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados independientemente del grupo que incluye

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halo, trifluorometilo, trifluorometoxi, clano, hidroxil, amino, nitró, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alqueno y alquino, cada uno de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 independientemente entre sí representa hidrógeno o alquilo, con la condición que al menos uno de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 represente alquilo

En una realización, R^a representa hidrógeno o alquilo. En una realización especial, R^a representa hidrógeno. En otra realización, R^a representa alquilo, como por ejemplo metilo.

En aun otra realización, R^b representa un anillo opcionalmente sustituido, como por ejemplo un fenilo opcionalmente sustituido.

En otra realización, R^b representa un grupo fenilo que es opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados del grupo que incluye halo, trifluorometilo, trifluorometoxi, clano y alcoxi.

En aun otra realización, R^b representa un grupo fenilo, que es opcionalmente sustituido dos veces con halo. En una realización especial, R^b representa diclorofenilo, como por ejemplo 3,4-diclorofenilo o 2,4-diclorofenilo.

En otra realización, R^b representa un grupo fenilo, que es sustituido una vez con halo. En una realización especial, R^b representa clorofenilo, como por ejemplo 4-clorofenilo. En otra realización, R^b representa bromofenilo, como por ejemplo 4-bromofenilo. En aun otra realización, R^b representa yodofenilo, como por ejemplo 4-yodofenilo.

En aun otra realización, R^b representa un grupo fenilo, que es sustituido una vez con trifluorometilo o trifluorometoxi. En una realización especial, R^b

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representa trifluormetilfenilo como por ejemplo 4 trifluormetilfenilo En otra realización, R^b representa trifluorometoxifenilo, como por ejemplo 4-trifluorometoxifenilo

En otra realización, R^b representa un grupo naftilo, que es opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados del grupo que incluye halo, trifluorometilo, trifluorometoxi, clavo y alcoxi En una realización especial, R^b representa naftilo, como por ejemplo naftalen-2-ilo En otra realización R^b representa alcoxinaftilo, como por ejemplo metoxinaftilo, como por ejemplo 6-metoxinaftalen-2-ilo

En otra realización, dos de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 representan alquilo y los restantes seis de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 representan hidrógeno

En una realización especial, R^2 y R^5 representan alquilo, como por ejemplo metilo, y R^2 , R^3 , R^3 , R^5 , R^5 y R^6 representan hidrógeno En otra realización, R^3 y R^5 representan alquilo, como por ejemplo metilo, y R^2 , R^2 , R^3 , R^5 , R^5 y R^6 representan hidrógeno En aun otra realización, R^2 y R^5 representan alquilo, como por ejemplo metilo, y R^2 , R^3 , R^3 , R^5 , R^5 , y R^6 representan hidrógeno En aun otra realización, R^3 representa alquilo, como por ejemplo metilo, y R^2 , R^2 , R^3 , R^5 , R^5 , R^6 y R^6 representan hidrógeno

En una realización especial, el compuesto de la invención es un derivado de *trans*-dialquil-piperazina, como por ejemplo un derivado de *trans*-dimetil-piperazina, como por ejemplo un derivado de *trans*-2,5-dimetilpiperazina En otra realización, el compuesto de la invención es un derivado de *cis*-dialquil-piperazina, como por ejemplo un derivado de *cis*-dimetilpiperazina, como por

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ejemplo un derivado de *cis*-3,5-dimetilpiperazina o un derivado de *cis*-2,6-dimetilpiperazina

En una realización especial, el compuesto químico es

- 1-(3,4-dicloro-fenil)-2,5-dimetil-piperazina,
- 1-(3,4-dicloro-fenil)-3,5-dimetil-piperazina,
- 1-(4-cloro-fenil)-2,5-dimetil-piperazina,
- 1-(4-yodo-fenil)-2,5-dimetil-piperazina,
- 1-(3,4-dicloro-fenil)-2,6-dimetil-piperazina
- 1-(4-bromo-fenil)-2,5-dimetil-piperazina,
- 1-(4-trifluormetil-fenil)-2,5-dimetil-piperazina,
- 1-(4-trifluorometoxi-fenil)-2,5-dimetil-piperazina,
- 1-(2,4-dicloro-fenil)-2,5-dimetil-piperazina,
- 1-(2,4-dicloro-fenil)-3,5-dimetil-piperazina,
- 1-(3,4-dicloro-fenil)-3-metil-piperazina,
- 1-(2-naftil)-2,5-dimetil-piperazina,
- 1-(6-metoxi-naft-2-il)-2,5-dimetil-piperazina,
- 1-(3,4-dicloro-fenil)-4-metil-2,5-dimetil-piperazina
- 1-(3,4-dicloro-fenil)-4-metil-3,5-dimetil-piperazina,
- 1-(4-cloro-fenil)-4-metil-2,5-dimetil-piperazina,
- 1-(3,4-dicloro-fenil)-4-metil-2,6-dimetil-piperazina,
- 1-(4-trifluorometoxi-fenil)-4-metil-2,5-dimetil-piperazina,
- 1-(2-naftil)-4-metil-2,5-dimetil-piperazina

cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos

En una realización especial, el compuesto químico de la invención es

(±)-1-(3,4-dicloro-fenil)-*trans*-2,5-dimetil-piperazina,
1-(3,4-dicloro-fenil)-*cis*-3,5-dimetil-piperazina
(±)-1-(4-cloro-fenil)-*trans*-2,5-dimetil-piperazina,
(±)-1-(4-yodo-fenil)-*trans*-2,5-dimetil-piperazina,
1-(3,4-dicloro-fenil)-*cis*-2,6-dimetil-piperazina,
(±)-1-(4-bromo-fenil)-*trans*-2,5-dimetil-piperazina,
(±)-1-(4-trifluorometil-fenil)-*trans*-2,5-dimetil-piperazina,
(±)-1-(4-trifluorometoxi-fenil)-*trans*-2,5-dimetil-piperazina,
(±)-1-(2,4-dicloro-fenil)-*trans*-2,5-dimetil-piperazina,
(1-(2,4-dicloro-fenil)-*cis*-3,5-dimetil-piperazina,
(±)-1-(3,4-dicloro-fenil)-3-metil-piperazina
(±)-1-(2-naftil)-*trans*-2,5-dimetil-piperazina,
(±)-1-(6-metoxi-naft-2-il)-*trans*-2,5-dimetil-piperazina,
1-(3,4-dicloro-fenil)-4-metil-*trans*-2,5-dimetil-piperazina
(±)-1-(3,4-dicloro-fenil)-4-metil-*cis*-3,5-dimetil-piperazina,
(±)-1-(4-cloro-fenil)-4-metil-*trans*-2,5-dimetil-piperazina,
1-(3,4-dicloro-fenil)-4-metil-*cis*-2,6-dimetil-piperazina,
(±)-1-(4-trifluorometoxi-fenil)-4-metil-*trans*-2,5-dimetil-piperazina,
(±)-1-(2-naftil)-4-metil-*trans*-2,5-dimetil-piperazina
o una sal farmacéuticamente aceptable de los mismos

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Cualquier combinación de dos o más de las realizaciones descriptas precedentemente se considera comprendida dentro del alcance de la presente invención

Definición de los sustituyentes

En el contexto de la presente invención, halo representa fluor, cloro, bromo o yodo

En el contexto de la presente invención, un grupo alquilo designa una cadena de hidrocarburo recta o ramificada, saturada, univalente. La cadena de hidrocarburo preferentemente contiene de uno a seis átomos de carbono (alquilo (C₁-C₆)), incluidos pentilo, isopentilo, neopentilo, pentilo terciario, hexilo e isohexilo. En una realización preferida, alquilo representa un grupo alquilo (C₁-C₄), incluidos butilo, isobutilo, butilo secundario, y butilo terciario. En otra realización preferida de la presente invención, alquilo representa un grupo alquilo (C₁-C₃), que en particular puede ser metilo, etilo, propilo o isopropilo.

En el contexto de la presente invención, un grupo alqueno designa una cadena de carbono que contiene uno o más dobles enlaces, incluidos dienos, trienos y polienos. En una realización preferida, el grupo alqueno de la invención incluye de dos a seis átomos de carbono (alqueno (C₂-C₆)), que incluye al menos un doble enlace. En una realización de mayor preferencia, el grupo alqueno de la invención es etenilo, 1- o 2-propenilo, 1-, 2- o 3-butenilo, o 1,3-butadienilo, 1-, 2-, 3-, 4- o 5-hexenilo, o 1,3-hexadienilo, o 1,3,5-hexatrienilo.

En el contexto de la presente invención, un grupo alquino designa una cadena de carbono que contiene uno o más triples enlaces, incluidos diinos, triinos y polinos. En una realización preferida, el grupo alquino de la invención

Incluye de dos a seis átomos de carbono (alquínilo (C_2-C_6)), que incluye al menos un triple enlace. En su realización más preferida, el grupo alquínilo de la invención es etínilo, 1- o 2-propínilo, 1-, 2- o 3-butínilo, o 1,3-butadiénilo, 1-, 2-, 3-, 4-pentínilo, o 1,3-pentadiénilo, 1-, 2-, 3-, 4-, o 5-hexínilo, o 1,3-hexadiénilo o 1,3,5-hexatriénilo.

En el contexto de la presente invención, un grupo cicloalquilo designa un grupo alquilo cíclico, que contiene preferentemente de tres a siete átomos de carbono (cicloalquilo (C_3-C_7)) que incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

Alcoxi es O-alquilo, en el que el alquilo se define de acuerdo con la definición precedente.

Cicloalcoxi significa O-cicloalquilo, en el que cicloalquilo se define de acuerdo con la definición precedente.

Cicloalquilalquilo significa cicloalquilo de acuerdo con la definición precedente y alquilo de acuerdo con lo definido anteriormente, que significa, por ejemplo, ciclopropilmetilo.

Amino es NH_2 o NH -alquilo o N -(alquilo) $_2$, en el que alquilo es tal como se definió precedentemente.

En el contexto de la presente invención, un grupo aro designa un sistema de anillo aromático carbocíclico, como por ejemplo fenilo, naftilo (1-naftilo o 2-naftilo) o fluorenilo.

En el contexto de la presente invención, un grupo heteroarilo designa un grupo heterocíclico mono- o bicíclico, que contiene uno o más heteroátomos en su

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estructura de anillo Los heteroátomos preferidos incluyen nitrógeno (N), oxígeno (O), y azufre (S)

Los grupos heteroarilo monocíclicos preferidos de la invención incluyen grupos monocíclicos, heterocíclicos de 5 y 6 miembros, que incluyen por ejemplo, sin limitación, oxazolilo (oxazol-2-ilo, -4-ilo, o -5-ilo), isoxazolilo (isoxazol-3-ilo, -4-ilo, o -5-ilo), tiazolilo (tiazol-2-ilo, -4-ilo, o -5-ilo), isotiazolilo (isotiazol-3-ilo, -4-ilo, o -5-ilo), 1,2,4-oxadiazolilo (1,2,4-oxadiazol-3-ilo o -5-ilo), 1,2,4-tiadiazolilo (1,2,4-tiadiazol-3-ilo o -5-ilo), 1,2,5-oxadiazolilo (1,2,5-oxadiazol-3-ilo, o -4-ilo), 1,2,5-tiadiazolilo (1,2,5-tiadiazol-3-ilo o -4-ilo), imidazolilo (2-, 4- o 5-imidazolilo), pirrolilo (2-, o 3-pirrolilo), furanilo (2- o 3-furanilo), tienilo (2- o 3-tienilo), piridilo (2-, 3- o 4-piridilo), pirimidilo (2-, 4-, 5-, o 6-pirimidilo), o piridazinilo (3- o 4-piridazinilo)

Los grupos heteroarilo bicíclicos preferidos de la invención incluyen, por ejemplo pero sin limitación, indolizínilo (2-, 5- o 6-indolizínilo), indolilo (2-, 5- o 6-indolilo), isoindolilo (2-, 5- o 6-isoindolilo), indazolilo (1- o 3-indazolilo), benzofuranilo (2-, 5- o 6-benzofuranilo), benzo[b]tienilo (2-, 5- o 6-benzotienilo), bencimidazolilo (2-, 5- o 6-bencimidazolilo), benzoxazolilo (2-, 5- o 6-benzoxazolilo), benzotiazolilo (2-, 5- o 6-benzotiazolilo), benzo[d]isotiazolilo (1,2-benzo[d]isotiazol-3-ilo), purínilo (2- u 6-purínilo), quinolínilo (2-, 3- 6-, 7-, u 8-quinolínilo) isoquinolínilo (1-, 3-, 5-, 6-, o 7-isoquinolínilo), cinolínilo (6- o 7-cinolínilo), falazinilo (6- o 7-falazinilo), quinazolinilo (2- 6- o 7-quinazolinilo), quinoxalínilo (2- o 6-quinoxalínilo), 1,8-naftiridinilo (1,8-naftiridin-2-, 3-, 6- o 7-ilo), pteridinilo (2-, 6- o 7-pteridinilo) e indenilo (1-, 2-, 3-, 5- o 5-indenilo)

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Sales farmacéuticamente aceptables

El compuesto químico de la invención puede proporcionarse en cualquier forma adecuada para la administración deseada. Las formas adecuadas incluyen sales farmacéuticamente (es decir, fisiológicamente) aceptables, y formas en profármacos o profármacos del compuesto químico de la invención.

Entre los ejemplos de sales de adición farmacéuticamente aceptables se incluyen, sin limitación, las sales de adición de ácidos orgánicos e inorgánicos no tóxicos, como por ejemplo el clorhidrato derivado del ácido clorhídrico, el bromhidrato derivado del ácido bromhídrico, el nitrato derivado del ácido nítrico, el perclorato derivado del ácido perclórico, el fosfato derivado del ácido fosfónico, el sulfato derivado del ácido sulfúrico, el formiato derivado del ácido fórmico, el acetato derivado del ácido acético, el aconato derivado del ácido aconítico, el ascorbato derivado del ácido ascórbico, el bencensulfonato derivado del ácido bencensulfónico, el benzoato derivado del ácido benzoico, el cinamato derivado del ácido cinámico, el citrato derivado del ácido cítrico, el embonato derivado del ácido embónico, el enantato derivado del ácido enántico, el fumarato derivado del ácido fumánico, el glutamato derivado del ácido glutámico, el glicolato derivado del ácido glicólico, el lactato derivado del ácido láctico, el maleato derivado del ácido maleico, el malonato derivado del ácido malónico, el mandelato derivado del ácido mandélico, el metansulfonato derivado del ácido metansulfónico, el naftalen-2-sulfonato derivado del ácido naftalen-2-sulfónico, el ftalato derivado del ácido ftálico, el salicilato derivado del ácido salicílico, el sorbato derivado del ácido sórbico, el estearato derivado del ácido esteárico, el succinato derivado del ácido succínico, el tartrato derivado del ácido tartárico, el toluen-p-sulfonato derivado del

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ácido p-toluensulfónico, y similares. Dicha sales se pueden formar mediante procedimientos bien conocidos y descritos en la técnica.

Otros ácidos, como por ejemplo el ácido oxálico, que no puede ser considerado como farmacéuticamente aceptable, puede ser útil en la preparación de sales útiles como intermedios para obtener un compuesto químico de la invención y su sal de adición de ácido farmacéuticamente aceptable.

Entre los ejemplos de sales catiónicas farmacéuticamente aceptables de un compuesto químico de la invención, se incluyen, sin limitación, el sodio, el potasio, el calcio, el magnesio, el zinc, el aluminio, el litio, la colina, la lisina, y la sal de amonio, y similares, de un compuesto químico de la invención que contiene un grupo aniónico. Dichas sales catiónicas se pueden formar mediante procedimientos bien conocidos y descritos en la técnica.

En el contexto de la presente invención, las "sales de onio" de compuestos que contienen N también son consideradas sales farmacéuticamente aceptables. Las "sales de onio" preferidas incluyen las sales de alquilonio, sales de cicloalquilonio, y sales de cicloalquilalquilonio.

Entre los ejemplos de formas de pre- o profármacos del compuesto químico de la invención se incluyen ejemplos de profármacos adecuados de las sustancias de acuerdo con la invención que incluyen compuestos modificados en uno o más grupos reactivos o derivables del compuesto madre. De particular interés son los compuestos modificados en un grupo carboxilo, en un grupo hidroxilo o en un grupo amino. Ejemplos de derivados adecuados son los ésteres o las amidas.

El compuesto químico de la invención puede proporcionarse en formas solubles o insolubles junto con un solvente farmacéuticamente aceptable, como

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por ejemplo agua, etanol, y similares. Las formas solubles también incluyen formas hidratadas, como por ejemplo el monohidrato, el dihidrato, el hemihidrato, el trihidrato, el tetrahidrato, y similares.

En general, las formas solubles se consideran como equivalentes a las formas insolubles para los fines de la presente invención.

Isómeros estéricos

Los expertos en la técnica apreciarán que los compuestos de la presente invención pueden contener uno o más centros quirales, y que dichos compuestos existen en forma de isómeros.

Por ejemplo, los compuestos de la presente invención pueden existir en las configuraciones cis o trans así como también en mezclas de las mismas. Por ejemplo, aquellas de los sustituyentes R^2/R^2 , R^3/R^3 , R^4/R^4 , y R^5/R^5 que representan alquilo pueden ser hallarse particularmente en la configuración cis o trans respecto del otro (por ejemplo, R^2 respecto de R^5 , o R^3 respecto de R^5). Entre los ejemplos se incluyen, sin limitación, los derivados de trans-2,5-dimetilpiperazina y cis-3,5-dimetilpiperazina. La invención incluye todos dichos isómeros y cualquier mezcla de los mismos con inclusión de mezclas racémicas.

Asimismo, los compuestos químicos de la presente invención pueden existir como enantiómeros en formas (+) y (-) así como también en formas racémicas ($\pm$). Los racematos de estos isómeros y los mismos isómeros individuales se encuentran dentro del alcance de la presente invención.

La invención incluye todos esos isómeros y cualquier mezcla de los mismos que incluyen mezclas racémicas.

Las formas racémicas se pueden resolver en los antípodos ópticos mediante métodos y técnicas conocidas. Un modo de separar las sales isoméricas es mediante el uso de un ácido ópticamente activo, y liberar el compuesto amina ópticamente activo mediante un tratamiento con una base. Otro método para resolver racematos en los antípodos ópticos se basa en una cromatografía sobre una matriz activa óptica. Los compuestos racémicos de la presente invención pueden entonces resolverse en sus antípodos ópticos, por ejemplo, mediante cristalización fraccional de, por ejemplo, sales de d- o l- (tartratos, mandelatos, o canforsulfonato).

Los compuestos químicos de la presente invención también se pueden resolver mediante la formación de amidas diaestereoméricas mediante la reacción de los compuestos químicos de la presente invención con un ácido carboxílico activado ópticamente activo, como por ejemplo aquel derivado de (+) o (-) fenilalanina, (+) o (-) fenilglicina, ácido (+) o (-) canfánico o mediante la formación de carbamatos diaestereoméricos mediante la reacción del compuesto químico de la presente invención con un cloroformiato ópticamente activo o similares.

Los métodos adicionales para resolver los isómeros ópticos son conocidos en la técnica. Dichos métodos incluyen aquellos descritos por Jaques J. Collet A. & Willen S en "Enantiomers Racemates and Resolutions", John Wiley e Hijos, New York, (1981).

Los compuestos ópticamente activos también se pueden preparar a partir de materiales de partida ópticos activos.

Compuestos etiquetados

Los compuestos de la invención se pueden utilizar en forma etiquetada o sin etiquetar. En el contexto de la presente invención, el compuesto etiquetado posee uno o más átomos reemplazados por un átomo que posee una masa atómica o un número de masa diferente de la masa atómica o número de masa hallado normalmente en la naturaleza. El etiquetado permitirá una fácil detección cuantitativa de dicho compuesto.

Los compuestos etiquetados de la invención pueden ser útiles como herramientas de diagnóstico, radio rastreadores, o agentes de control en diversos métodos de diagnóstico, y para imágenes de receptores *in vivo*.

El isómero etiquetado de la invención contiene preferentemente al menos un radionúclido como etiqueta. Se pueden utilizar todos los radionúclidos que emiten positrones. En el contexto de la presente invención, el radionúclido se selecciona preferentemente 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 etiquetado de la presente invención puede seleccionarse de la Tomografía de Emisión de Posición (PET), Tomografía Computada por Imagen de Fotón Único (SPECT), Espectroscopia de Resonancia Magnética (MRS), Imagen por Resonancia Magnética (MRI), y Tomografía por Rayos X Axial Computada (CAT), o combinaciones de las mismas.

Métodos de Preparación

Los compuestos químicos de la invención pueden prepararse mediante métodos convencionales para la síntesis química, por ejemplo, aquellos

descritos en los ejemplos de trabajo. Los materiales de partida para los procesos descritos en la presente solicitud son bien conocidos o pueden prepararse fácilmente mediante métodos convencionales a partir de productos químicos disponibles en el comercio.

Asimismo, un compuesto de la presente invención se puede convertir en otro compuesto de la invención mediante métodos convencionales.

Los productos finales de las reacciones descritas en la presente se pueden aislar mediante técnicas convencionales, por ejemplo mediante extracción, cristalización, destilación, cromatografía, etc.

Actividad biológica

Los compuestos de la invención se pueden someter a ensayo para determinar su capacidad para inhibir la recaptación de las monoaminas dopamina, noradrenalina y serotonina en sinaptosomas, por ejemplo como las descritas en WO 97/30997. En base a la actividad equilibrada observada en estos ensayos, se considera que el compuesto de la invención es útil para el tratamiento, prevención o alivio de una enfermedad, o de un trastorno o de una afección de un mamífero, incluido el ser humano, cuya enfermedad, trastorno o afección responde a la inhibición de la recaptación de un neurotransmisor monoamina en el sistema nervioso central.

En una realización especial, los compuestos de la invención se consideran útiles para el tratamiento, prevención o alivio de trastornos 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 una afección médica.

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general, trastorno del estado de ánimo inducido por una sustancia, pseudodemencia, síndrome de Ganser, trastorno obsesivo compulsivo, trastornos de pánico, trastorno de pánico sin agorafobia, trastorno de pánico con agorafobia, agorafobia sin historia de trastorno de pánico, ataque de pánico, fallas de la memoria, pérdida de la memoria, trastorno por déficit en la atención con hiperactividad, obesidad, ansiedad, trastorno de ansiedad generalizado, trastorno alimenticio, enfermedad de Parkinson parkinsonismo, demencia, demencia por envejecimiento, demencia senil, enfermedad de Alzheimer, complejo de demencia por síndrome de inmunodeficiencia adquirida, disfunción de la memoria en el envejecimiento, fobia específica, fobia social, trastorno de estrés pos-traumático, trastorno de estrés agudo, adicción a las drogas, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso de tabaco, adicción al alcohol, alcoholismo, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor por migraña, dolor de cabeza tipo tensión, dolor de cabeza tipo tensión crónico, dolor asociado con depresión, fibromialgia, artritis, osteoartritis, artritis reumatoidea, dolor de espalda, dolor por cáncer, dolor debido al intestino irritable, síndrome del intestino irritable, dolor pos-operatorio, síndrome del dolor pos-mastectomía (PMPS), dolor pos-ataque apoplético, neuropatía inducida por fármacos, neuropatía diabética, dolor mantenido simpáticamente, neuralgia trigémina, dolor dental, dolor miofacial, dolor de extremidad fantasma, bulimia, síndrome premenstrual, síndrome de la fase luteal tardía, síndrome pos-traumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia urgente, incontinencia nocturna, disfunción sexual, eyaculación prematura, dificultad eréctil, disfunción eréctil, orgasmo femenino prematuro, síndrome de las piemas

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Inquietas, trastornos alimenticios, anorexia nerviosa, trastornos del sueño, autismo, mutismo, tricotilomanía, narcolepsia depresión pos-ataque apoplético, daño cerebral inducido por un ataque daño neuronal inducido por un ataque apoplético o enfermedad de Gilles de la Tourettes En una realización preferida, los compuestos se consideran útiles para el tratamiento, prevención o alivio de la depresión

Actualmente se considera que una dosis adecuada del ingrediente farmacéutico activo (API) se encuentra en el rango de alrededor de 0,1 a alrededor de 1000 mg de API por día, de mayor preferencia de alrededor de 10 a alrededor de 500 mg de API por día, de mayor preferencia de alrededor de 30 a alrededor de 100 mg de API por día, según, sin embargo, del modo exacto de administración, la forma de administración, la indicación considerada, el sujeto y, en particular el peso corporal del sujeto como también la preferencia y la experiencia del médico o veterinario actuante

Los compuestos preferidos de la invención muestran una actividad biológica en el rango submicromolar y micromolar, es decir desde menos de 1 a alrededor de 100 μ M

Composiciones farmacéuticas

En otro aspecto, la invención proporciona nuevas composiciones farmacéuticas que incluyen una cantidad terapéuticamente efectiva del compuesto químico de la invención

Mientras que un compuesto químico de la invención para utilizarse en una terapia se puede administrar en forma del compuesto químico puro, se prefiere introducir el ingrediente activo, opcionalmente en forma de una sal

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fisiológicamente aceptable, en una composición farmacéutica junto con uno o más adyuvantes, excipientes, vehículos, tampones, diluyentes, y/u otros auxiliares farmacéuticos habituales

En una realización preferida, la invención proporciona composiciones farmacéuticas que incluyen el compuesto químico de la invención, o una sal farmacéuticamente aceptable o derivado del mismo, junto con uno o más vehículos farmacéuticamente aceptables y, opcionalmente, otros ingredientes terapéuticos y/o profilácticos conocidos y utilizados en la técnica. Los vehículos deben ser "aceptables" en el sentido de ser compatibles con los otros ingredientes de la formulación y no dañinos para su receptor.

Las composiciones farmacéuticas de la invención pueden ser aquellas adecuadas para la administración oral, rectal, bronquial, nasal, pulmonar, tópica (tanto bucal como sublingual), transdérmica, vaginal o parenteral (con inclusión de inyecciones o infusiones cutáneas, subcutáneas, intramusculares, intraperitoneales, intravenosas, intraarteriales, intracerebrales, intraoculares), o aquellas en una forma adecuada para la administración mediante inhalación o insuflación, con inclusión de la administración de polvos y aerosoles líquidos, o mediante sistemas de liberación sostenida. Entre los ejemplos adecuados de sistemas de liberación sostenida se incluyen matrices semipermeables de polímeros hidrófobos sólidos que contienen el compuesto de la invención, cuyas matrices pueden hallarse en forma de artículos formados, por ejemplo, películas o microcápsulas.

El compuesto químico de la invención, junto con un adyuvante, vehículo o diluyente convencional, puede colocarse de este modo en forma de

composiciones farmacéuticas y dosis únicas del mismo. Dichas formas incluyen, sólidos, y en particular comprimidos, cápsulas rellenas, formas en polvo y en pastillas, y líquidos, particularmente soluciones acuosas y no acuosas suspensiones, emulsiones, elixires, y cápsulas rellenas con las mismas, todos para uso oral; supositorios para la administración rectal, y soluciones inyectables estériles para uso parenteral. Dichas composiciones farmacéuticas y las formas de dosis únicas pueden incluir ingredientes convencionales en proporciones convencionales, con o sin compuestos o principios activos adicionales, y dichas formas de dosis únicas pueden contener cualquier cantidad efectiva adecuada del ingrediente activo en proporción al rango de dosis diaria deseado que ha de emplearse.

El compuesto químico de la presente invención se puede administrar en una amplia variedad de formas de dosis orales y parenterales. Será obvio para los expertos en la técnica que las siguientes formas de dosis pueden incluir, como componente activo, un compuesto químico de la invención o una sal farmacéuticamente aceptable de un compuesto químico de la invención.

Para preparar composiciones farmacéuticas a partir de un compuesto químico de la presente invención, los vehículos farmacéuticamente aceptables pueden consistir en un líquido o en un sólido. Las preparaciones en forma sólida incluyen polvos, comprimidos, píldoras, cápsulas selladas, supositorios, y gránulos dispersables. Un vehículo sólido puede consistir en una o más sustancias que también pueden actuar como diluyentes, agentes saborizantes, solubilizantes, lubricantes, agentes de suspensión, aglutinantes, conservantes, agentes de desintegración de comprimidos, o un material encapsulante.

En el caso del polvo, el vehículo es un sólido finamente dividido, que consiste en una mezcla con el componente activo finamente dividido

En el caso de los comprimidos, el componente activo se mezcla con el vehículo que posee la capacidad de unión necesaria en proporciones adecuadas compactado en la forma y en el tamaño deseados

El polvo y los comprimidos preferentemente contienen de cinco a diez hasta alrededor del setenta por ciento del compuesto activo. Los vehículos adecuados son carbonato de magnesio, estearato de magnesio, talco, azúcar, lactosa, pectina, dextrina, almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa de sodio, una cera de baja fusión, manteca de cacao, y similares. El término "preparación" incluye la formulación del compuesto activo con el material encapsulante como vehículo que proporciona una cápsula en la que el componente activo, con o sin vehículos, es rodeado por un vehículo que se encuentra de ese modo en asociación con el mismo. De manera similar, se incluyen sellos y tabletas. Los comprimidos, polvos, cápsulas, píldoras, sellos y tabletas se pueden utilizar en forma sólida adecuada para la administración oral.

Para preparar los supositorios, se funde primero una cera de baja fusión, como por ejemplo una mezcla de un glicérido de ácido graso o manteca de cacao y el componente activo se dispersa homogéneamente en dicha cera, por ejemplo mediante agitación. La mezcla homogénea fundida se vierte luego en moldes de tamaño convencional, se deja enfriar y de ese modo solidificar.

Las composiciones adecuadas para la administración vaginal se pueden presentar como pesarios, tampones, cremas, geles, pastas, espumas, o rocíos.

que contienen, además del ingrediente activo, dichos vehículos conocidos en la técnica como adecuados

Las preparaciones líquidas incluyen soluciones, suspensiones, y emulsiones, por ejemplo agua o soluciones de agua-propilenglicol. Por ejemplo, las preparaciones líquidas para inyecciones parenterales se pueden formular como soluciones en una solución acuosa de polietilenglicol.

El compuesto químico de acuerdo con la presente invención puede entonces formularse para la administración parenteral (por ejemplo, mediante inyección por ejemplo una inyección de bolo o una infusión continua) y puede presentarse en forma de dosis única en ampollas, jeringas prerrellenas, infusiones de pequeño volumen o en recipientes de dosis múltiples con un conservante agregado. Las composiciones pueden tomar la forma de suspensiones, soluciones o emulsiones en vehículos aceitosos o acuosos, y pueden contener agentes de formulación, como por ejemplo agentes de suspensión, estabilizantes y/o dispersantes. Alternativamente, el ingrediente activo puede hallarse en forma de polvo, obtenido mediante el aislamiento aséptico de un sólido estéril o mediante la liofilización de la solución, para formarse con un vehículo adecuado, por ejemplo, agua estéril libre de pirógeno, antes de utilizar.

Las soluciones acuosas adecuadas para uso oral pueden prepararse mediante la disolución del componente activo en agua y el agregado de agentes colorantes, saborizantes, estabilizantes y espesantes adecuados, según se desee.

Las suspensiones acuosas adecuadas para uso oral se pueden preparar mediante la dispersión del componente activo finamente dividido en agua con un

maternal viscoso, como por ejemplo gomas naturales o sintéticas, resinas, metilcelulosa, carboximetilcelulosa de sodio, u otros agentes de suspensión bien conocidos

También se incluyen preparaciones en forma sólida, para la conversión poco antes de su uso en preparaciones de forma líquida para la administración oral. Dichas formas líquidas incluyen soluciones, suspensiones, y emulsiones. Además del componente activo, dichas preparaciones pueden incluir agentes colorantes, saborizantes, estabilizantes, tampones, edulcorantes artificiales y naturales, dispersantes, espesantes, solubilizantes, y similares.

Para la administración tópica en la epidermis, el compuesto químico de la invención se puede formular como pomadas, cremas o lociones, o como parches transdérmicos. Las pomadas y cremas se pueden formular por ejemplo, con una base acuosa o aceitosa con el agregado de agentes espesantes y/o gelificantes adecuados. Las lociones se pueden formar con una base acuosa o aceitosa y en general también contendrán uno o más agentes emulsionantes, agentes estabilizantes, agentes dispersantes, agentes de suspensión, agentes espesantes, o agentes colorantes.

Las composiciones adecuadas para la administración tópica en la boca incluyen tabletas que contienen el agente activo en una base saborizada, usualmente sucrosa y acacia o tragacanto, pastillas que contienen el ingrediente activo en una base inerte, como por ejemplo gelatina y glicerina o sucrosa y acacia, y lavados bucales que incluyen el ingrediente activo en un vehículo líquido adecuado.

Las soluciones o suspensiones se aplican directamente en la cavidad nasal mediante medios convencionales, por ejemplo, con un gotero, pipeta o atomizador. Las composiciones pueden proporcionarse en una forma de dosis única o de varias dosis.

La administración por el tracto respiratorio también se puede lograr mediante una formulación en aerosol en la que el ingrediente activo se proporciona en un envase presurizado con un impelente, como por ejemplo un clorofluorcarbono (CFC) por ejemplo diclorodifluorometano, triclorofluorometano, o diclorotetrafluorometano, dióxido de carbono, u otro gas adecuado. El aerosol también puede contener de manera conveniente un tensioactivo, como por ejemplo lecitina. La dosis del fármaco se puede controlar mediante una válvula dosificadora.

Alternativamente, los ingredientes activos se pueden proporcionar en forma de un polvo seco, por ejemplo una mezcla en polvo del compuesto con una base en polvo adecuada, como por ejemplo lactosa, almidón, derivados de almidón, como por ejemplo hidroxipropilmetilcelulosa y polivinilpirrolidona (PVP). En forma conveniente, el vehículo del polvo formará un gel en la cavidad nasal. La composición en polvo puede presentarse en una forma de dosis única, por ejemplo en cápsulas o cartuchos, por ejemplo, gelatina, o envases blíster desde los que se puede administrar el polvo mediante un inhalador.

En las composiciones destinadas para administración en el tracto respiratorio, incluidas las composiciones intranasales, el compuesto tendrá generalmente un pequeño tamaño de partícula, por ejemplo del orden de 5

micrones o menos. Dicho tamaño de partícula puede obtenerse mediante medios conocidos en la técnica, por ejemplo mediante micronización.

Si se desea, se pueden emplear composiciones adaptadas para proporcionar una liberación sostenida del ingrediente activo.

Las preparaciones farmacéuticas se presentan preferentemente en formas de dosis únicas. En dicha forma, la preparación se subdivide en dosis únicas que contienen las cantidades adecuadas del componente activo. La forma de dosis única puede ser una preparación envasada, en la que el envase contiene cantidades discretas de la preparación, como por ejemplo comprimidos, cápsulas, y polvos envasados en frascos o ampollas. Asimismo, la forma de dosis única puede consistir en una cápsula, comprimido, sello o tableta misma, o puede ser la cantidad adecuada de cualquiera de estas formas envasadas.

Los comprimidos o las cápsulas para la administración oral y los líquidos para la administración intravenosa y las infusiones continuas constituyen las composiciones preferidas.

Otros datos sobre las técnicas para la formulación y la administración se pueden hallar en la última edición de Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA).

Una dosis terapéuticamente efectiva se refiere a aquella cantidad de ingrediente activo, que alivia los síntomas o afección. La eficacia terapéutica y la toxicidad, por ejemplo ED_{50} y LD_{50} , pueden determinarse mediante procedimientos farmacológicos estándar en cultivos celulares o en animales experimentales. La relación de dosis entre los efectos terapéutico y tóxico es el índice terapéutico y puede expresarse mediante la relación LD_{50}/ED_{50} . Se

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prefieren las composiciones farmacéuticas que presentan grandes índices terapéuticos

La dosis administrada debe ajustarse cuidadosamente a la edad, peso y afección del individuo que se desea tratar, así como también la vía de administración, la forma de dosis y el régimen, como también el resultado deseado y la dosis exacta deberían ser determinadas por el profesional

La dosis real depende de la naturaleza y de la gravedad de la enfermedad que se desea tratar, y depende de la consideración del médico, y puede variarse mediante la titulación de la dosis a las circunstancias particulares de la invención para producir el efecto terapéutico deseado. Sin embargo, se considera que las composiciones farmacéuticas que contienen de alrededor de 0,1 a alrededor de 500 mg de ingrediente activo por dosis individual, preferentemente de alrededor de 1 a alrededor de 100 mg de mayor preferencia de alrededor de 1 a alrededor de 10 mg, son adecuadas para tratamientos terapéuticos

El ingrediente activo se puede administrar en una o varias dosis por día. Se puede obtener un resultado satisfactorio en ciertas circunstancias con dosis tan bajas como 0,1 µg/kg iv y 1 µg/kg po. El límite superior del rango de dosis se considera actualmente en alrededor de 10 mg/kg iv y 100 mg/kg po. Los rangos preferidos son de alrededor de 0,1 µg/kg a alrededor de 10 mg/kg/día iv, y de alrededor de 1 µg/kg a alrededor de 100 mg/kg/día po.

Métodos de terapia

En otro aspecto, la invención proporciona un método para el tratamiento, prevención o alivio de una enfermedad o de un trastorno o de una afección de un cuerpo animal vivo, incluido el ser humano, cuya enfermedad, trastorno o afección

responde a la inhibición de la recaptación del neurotransmisor monoamina en el sistema nervioso central, y dicho método consiste en administrar a dicho cuerpo animal vivo, incluido el ser humano, que la necesite una cantidad efectiva de un compuesto químico de la invención

Actualmente, se considera que los rangos de dosis adecuados son de 0,1 a 1000 miligramos diarios, 10-500 miligramos diarios, y especialmente de 30-100 miligramos diarios, según lo habitual ante el modo exacto de administración, la forma de administración, la indicación a la que se dirige la administración, el sujeto de que se trate, y el peso corporal del sujeto que se desea tratar, como también la preferencia y la experiencia del médico o del veterinario

EJEMPLOS

La invención se ilustrará aun más con referencia a los siguientes ejemplos, que no han de limitar el alcance de la invención reivindicada

General Todas las reacciones que incluyen reactivos o intermedios sensibles al aire se realizaron en una atmósfera de nitrógeno y en solventes anhidros. Se utilizó sulfato de magnesio como agente de secado en los procedimientos de diagnóstico y los solventes se evaporaron bajo presión reducida

Método A

Sal de ácido (+)-1-(3,4-diclorofenil)-*trans*-2,5-dimetil-piperazinfumárico

Una mezcla de *trans*-2,5-dimetilpiperazina (10 g, 88 mmol), 1-bromo-3,4-diclorobenceno (22 g, 97 mmol), K₂CO₃ (20 g, 176 mmol), paladaclo (100 mg) y dioxano (100 ml) se agitó a reflujo durante 1 hora. Se agregó agua (100 ml) a la mezcla. La mezcla se extrajo con dietiléter (2 x 100 ml). La cromatografía sobre

gel de sílice con metanol, diclorometano y amoníaco concentrado (10 89 1) proporcionó el compuesto del título Rendimiento 7,0 g (31 %) La sal correspondiente se obtuvo mediante la adición de una mezcla de dietiléter y metanol (9 1) saturada con ácido fumárico Pf 209-211°C

Sal de ácido 1-(3,4-dicloro-fenil)-*cis*-3,5-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A a partir de *cis*-3,5-dimetilpiperazina- Pf 225-227°C

Sal de ácido (+)-1-(4-clorofenil)-*trans*-2,5-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A Pf 165-168°C

Sal de ácido (+)-1-(4-yodo-fenil)-*trans*-2,5-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A Pf 160-166°C

Sal de ácido 1-(3,4-dicloro-fenil)-*cis*-2,6-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A a partir de *terc*-butiléster de ácido *cis*-3,5-dimetil-piperazin-1-carboxílico seguido de la desprotección del *terc*-butiléster de ácido 1-carboxílico con una mezcla de ácido clorhídrico y ácido acético Pf 170-173°C

Sal de ácido (+)-1-(4-bromo-fenil)-*trans*-2,5-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A Pf 168-170°C

Sal de ácido (+)-1-(4-trifluormetilfenil)-*trans*-2,5-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A Pf 186-187°C

Sal de ácido (+)-1-(4-trifluorometoxifenil)-*trans*-2,5-dimetilpiperazinfumárico

Se preparó de acuerdo con el método A Pf 157-160°C

Sal de ácido (+)-1-(2,4-diclorofenil)-*trans*-2,5-dimetilpiperazinciorhídrico

Se preparó de acuerdo con el método A Pf 197-200°C

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63**Sal de ácido (1-(2,4-dicloro-fenil)-*cis*-3,5-dimetilpiperazina)fumárico**

Se preparó de acuerdo con el método A a partir de *cis*-3,5-dimetilpiperazina Pf >270°C

Sal de ácido (+)-1-(3,4-diclorofenil)-3-metil-piperazinafumárico

Se preparó de acuerdo con el método A a partir de (+)-3-metil-piperazina Pf 190-192°C

Sal de ácido (+)-1-(2-naftil)-*trans*-2,5-dimetilpiperazinafumárico

Se preparó de acuerdo con el método A Pf 178-179°C

Sal de ácido (+)-1-(6-metoxi-naft-2-il)-*trans*-2,5-dimetilpiperazinafumárico

Se preparó de acuerdo con el método A Pf 207°C

Método B**Sal de ácido (+)-1-(3,4-diclorofenil)-4-metil-*trans*-2,5-dimetilpiperazinafumárico**

Se agitó a 70°C durante 15 horas, una mezcla de (+)-1-(3,4-diclorofenil)-*trans*-2,5-dimetilpiperazina (8,0 g, 23 mmol), ácido fórmico (80 ml) y formaldehído (80 ml) La mezcla se evaporó Se agregó una solución acuosa de amoníaco (100 ml, 1 M) seguido de la extracción con dietiléter (2 x 100 ml) La sal correspondiente se obtuvo mediante la adición de una mezcla de dietiléter y metanol (9 1) saturada con ácido fumárico Rendimiento 3,0 g (33%) Pf 166-169°C

Base libre de 1-(3,4-diclorofenil)-4-metil-*cis*-3,5-dimetilpiperazina

Se preparó de acuerdo con el método B a partir de (+)-1-(3,4-diclorofenil)-*cis*-3,5-dimetil-piperazina El producto se aisló en forma de aceite

Sal de ácido (+)-1-(4-clorofenil)-4-metil-*trans*-2,5-dimetilpiperazinafumárico

Se preparó de acuerdo con el método B a partir de $(\pm)$ -1-(4-cloro-fenil)-*trans*-2,5-dimetil-piperazina Pf 142-144,5°C

Base libre de 1-(3,4-diclorofenil)-4-metil-*cis*-2,6-dimetilpiperazina

Se preparó de acuerdo con el método B a partir de $(\pm)$ -1-(3,4-diclorofenil)-*cis*-2,6-dimetil-piperazina El producto se aisló en forma de un aceite

Sal de ácido $(+)$ -1-(4-trifluorometoxi-fenil)-4-metil-*trans*-2,5-dimetilpiperazinclorhídrico

Se preparó de acuerdo con el método B a partir de $(\pm)$ -1-(4-trifluorometoxifenil)-*trans*-2,5-dimetilpiperazina Pf 167-170°C

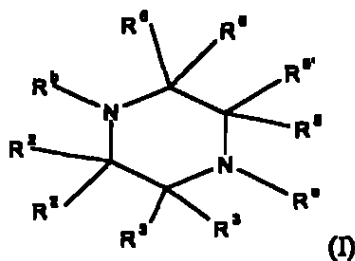
Sal de ácido $(\pm)$ -1-(2-naftil)-4-metil-*trans*-2,5-dimetil-piperazinfumárico

Se preparó de acuerdo con el método A a partir de $(\pm)$ -1-(2-naftil)-*trans*-2,5-dimetil-piperazina El producto se aisló en forma de aceite

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma cómo la misma ha de ser llevada a la práctica se declara reivindicar como de propiedad y derecho exclusivo

1 Un derivado de piperazina de fórmula



cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos,

en la que,

R^a representa hidrógeno o alquilo,

en donde el alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados independientemente del grupo que incluye

halo, trifluometilo, trifluometoxi, ciano, hidroxil, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alqueno y alquínico,

R^b representa un grupo arilo o heteroarilo, en donde el grupo arilo o heteroarilo se sustituye opcionalmente con uno o más sustituyentes seleccionados independientemente del grupo que incluye

halo, trifluometilo, trifluometoxi, ciano, hidroxil, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alqueno y alquínico,

cada uno de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 independientemente entre sí representa hidrógeno o alquilo,

con la condición que al menos uno de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 represente alquilo

2 El compuesto químico de la reivindicación 1, en el que R^a representa hidrógeno o alquilo

3 El compuesto químico de las reivindicaciones 1 o 2, en el que R^b representa un grupo fenilo que es opcionalmente sustituido con uno o más sustituyentes seleccionados independientemente del grupo que incluye halo, trifluorometilo, trifluorometoxi, ciano y alcoxi

4 El compuesto químico de las reivindicaciones 1 o 2, en el que R^b representa un grupo fenilo que es opcionalmente sustituido dos veces con halo

5 El compuesto químico de cualquiera de las reivindicaciones 1-4, en el que dos de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 representan alquilo, y los seis restantes de R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 y R^6 representan hidrógeno

6 El compuesto químico de la reivindicación 1, que es

(±)-1-(3,4-dicloro-fenil)-*trans*-2,5-dimetil-piperazina,

1-(3,4-dicloro-fenil)-*cis*-3,5-dimetil-piperazina,

(±)-1-(4-cloro-fenil)-*trans*-2,5-dimetil-piperazina

(±)-1-(4-yodo-fenil)-*trans*-2,5-dimetil-piperazina,

1-(3,4-dicloro-fenil)-*cis*-2,6-dimetil-piperazina,

(±)-1-(4-bromo-fenil)-*trans*-2,5-dimetil-piperazina,

(±)-1-(4-trifluorometil-fenil)-*trans*-2,5-dimetil-piperazina,

(±)-1-(4-trifluorometoxi-fenil)-*trans*-2,5-dimetil-piperazina,

(±)-1-(2,4-dicloro-fenil)-*trans*-2,5-dimetil-piperazina,
(1-(2,4-dicloro-fenil)-*cis*-3,5-dimetil-piperazina
(±)-1-(3,4-dicloro-fenil)-3-metil-piperazina,
(±)-1-(2-naftil)-*trans*-2,5-dimetil-piperazina,
(±)-1-(6-metoxi-naft-2-il)-*trans*-2,5-dimetil-piperazina,
1-(3,4-dicloro-fenil)-4-metil-*trans*-2,5-dimetil-piperazina,
(±)-1-(3,4-dicloro-fenil)-4-metil-*cis*-3,5-dimetil-piperazina,
(±)-1-(4-cloro-fenil)-4-metil-*trans*-2,5-dimetil-piperazina,
1-(3,4-dicloro-fenil)-4-metil-*cis*-2,6-dimetil-piperazina,
(±)-1-(4-trifluorometoxi-fenil)-4-metil-*trans*-2,5-dimetil-piperazina,
(±)-1-(2-naftil)-4-metil-*trans*-2,5-dimetil-piperazina,
o una sal farmacéuticamente aceptable de los mismos

7 Una composición farmacéutica, que incluye una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-6, cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos, junto con al menos un vehículo, excipiente o diluyente farmacéuticamente aceptable

8 Uso del compuesto químico de cualquiera de las reivindicaciones 1-6, cualquiera de sus isómeros o cualquiera mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos, para la preparación de un medicamento

9 El uso de acuerdo con la reivindicación 8, para la preparación de una composición farmacéutica para el tratamiento, prevención o alivio de una enfermedad o de un trastorno o de un afección de un mamífero, incluido el ser

humano, cuya enfermedad, trastorno o afección responde a la inhibición de la recaptación del neurotransmisor monoamina en el sistema nervioso central

10 El uso de acuerdo con la reivindicación 9, en el que la enfermedad, trastorno o afección es trastornos 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 una afección médica general, trastorno del estado de ánimo inducido por una sustancia, pseudodemencia, síndrome de Ganser, trastorno obsesivo compulsivo, trastornos de pánico, trastorno de pánico sin agorafobia, trastorno de pánico con agorafobia, agorafobia sin historia de trastorno de pánico, ataque de pánico, fallas de la memoria pérdida de la memoria, trastorno por déficit en la atención con hiperactividad, obesidad, ansiedad, trastorno de ansiedad generalizado, trastorno alimenticio, enfermedad de Parkinson, parkinsonismo, demencia, demencia por envejecimiento, demencia senil, enfermedad de Alzheimer, complejo de demencia por síndrome de inmunodeficiencia adquirida, disfunción de la memoria en el envejecimiento, fobia específica, fobia social, trastorno de estrés pos-traumático, trastorno de estrés agudo, adicción a las drogas, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso de tabaco adicción al alcohol, alcoholismo, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor por migraña, dolor de cabeza tipo tensión, dolor de cabeza tipo tensión crónico, dolor asociado con depresión fibromialgia, artritis, osteoartritis, artritis reumatoidea dolor de espalda, dolor por cáncer, dolor debido al intestino irritable, síndrome del intestino irritable, dolor pos-operatorio, síndrome del dolor pos-mastectomía (PMPS), dolor

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pos-ataque apoplético, neuropatía inducida por fármacos, neuropatía diabética, dolor mantenido simpáticamente, neuralgia trigémina, dolor dental, dolor miofacial, dolor de extremidad fantasma, bulimia, síndrome premenstrual, síndrome de la fase luteal tardía, síndrome pos-traumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia urgente, incontinencia nocturna, disfunción sexual eyaculación prematura, dificultad eréctil, disfunción eréctil, orgasmo femenino prematuro, síndrome de las piernas inquietas, trastornos alimenticios, anorexia nerviosa, trastornos del sueño, autismo, mutismo, tricotilomanía, narcolepsia, depresión pos-ataque apoplético, daño cerebral inducido por un ataque apoplético, daño neuronal inducido por un ataque apoplético o enfermedad de Gilles de la Tourettes

11 Un método para el tratamiento, prevención o alivio de una enfermedad o de un trastorno o de una afección de un cuerpo animal vivo, con inclusión del ser humano, cuyo trastorno, enfermedad o afección responde a la inhibición de la recaptación del neurotransmisor monoamina en el sistema nervioso central, cuyo método incluye el paso de administrar a dicho cuerpo animal vivo que necesita una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-6, cualquiera de sus isómeros o cualquier mezcla de sus isómeros, o una sal farmacéuticamente aceptable de los mismos

p NEUROSEARCH A/S

RESUMEN**NUEVOS COMPUESTOS**

La presente invención se refiere a nuevos derivados de piperazina sustituidos por alquilo útiles como inhibidores de la recaptación del neurotransmisor monoamina

En otros aspectos, la invención se refiere al uso de estos compuestos en un método para terapia y a composiciones farmacéuticas que incluyen los compuestos de la invención

PATENT COOPERATION TREATY

FRIST

From the
INTERNATIONAL SEARCHING AUTHORITY

To

PCT

see form PCT/ISA/220 *MA*

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

Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220 252-253-254	FOR FURTHER ACTION See paragraph 2 below
International application No PCT/EP2005/052732	International filing date (day/month/year) 14 08 2005
Priority date (day/month/year) 18 08 2004	

International Patent Classification (IPC) or both national classification and IPC
C07D295033 A81K31A95 A61P2500 C07D295073 C07D295096

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 68 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



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Authorized Officer

Gregoire A

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/EP2005/052732

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

Box No II Priority

- 1 ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or where required a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 84.1) is the claimed priority date
- 2 ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 84.1). Thus for the purposes of this opinion the international filing date indicated above is considered to be the relevant date
- 3 Additional observations, if necessary

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/EP2005/052732

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 1 5(part) 7 11(part)

because

- ☒ the said international application or the said claims Nos 11 (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 1 5(part), 7 11(part)
- ☐ 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

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/EP2005/052732

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

1 Statement

Novelty (N)	Yes	Claims	6
	No	Claims	1 5 7 11
Inventive step (IS)	Yes	Claims	
	No	Claims	1 11
Industrial applicability (IA)	Yes	Claims	1 10
	No	Claims	

2 Citations and explanations

see separate sheet

Box No VI Certain documents cited

1 Certain published documents (Rules 43bis 1 and 70 10)

and / or

2 Non-written disclosures (Rules 43bis 1 and 70 9)

see form 210

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

International application No

PCT/EP2005/052732

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims 1-5, 7-11 may be said to define subject matter for which protection might legitimately be sought (Article 8 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1-5, 7-11. The search of these claims was restricted to compounds of formula I comprising only two ring systems and having the features disclosed in claim 4 in combination with those of claim 5. The search was moreover limited to optical and stereo isomers of the compounds of formula I.

Claim 11 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

Reasoned statement with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1) Reference is made to the following documents

- D1 WO 01/46144 A (A CARLSSON RESEARCH AB, SVAN, INGELA, MARIANNE LF, CARLBERG, JENNY LF) 28 June 2001 (2001-06-28)
- D2 WO 01/46146 A (A CARLSSON RESEARCH AB, SVAN, INGELA, MARIANNE LF, CARLBERG, JENNY, M) 28 June 2001 (2001-06-28)
- D3 US 2003/158202 A1 (CALDIROLA PATRIZIA ET AL) 21 August 2003 (2003-08-21)
- D4 GB 115 649 A (DAVID JOHN SCOTT) 23 May 1918 (1918-05-23)
- D5 US-A-3 247 206 (YOST WILLIAM LASSITER ET AL) 19 April 1966 (1966-04-19)
- D6 US-A-3 192 208 (EASTON NELSON R ET AL) 29 June 1965 (1965-06-29)

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

International application No

PCT/EP2005/052732

- 76
- 27
- D7 GB-A 1 178 420 (ESSO RESEARCH AND ENGINEERING COMPANY) 21 January 1970 (1970-01 21)
- D8 BARLUENGA, J ET AL "A convenient synthesis of substituted piperazines via aminomercuration-demercuration of diallylamines" JOURNAL OF HETEROCYCLIC CHEMISTRY 17(5), 917-21 CODEN JHTCAD, ISSN 0022-152X 1980, XP002348513
- D9 DILLARD, ROBERT D ET AL "Acetylenic amines X Piperazines from substituted N-(2-hydroxyalkyl)propargylamines" JOURNAL OF ORGANIC CHEMISTRY, 29(8) 2464-6 CODEN JOCEAH, ISSN 0022 3263, 1964, XP002348514
- D10 BRENNER E ET AL "Nickel-catalysed selective N-arylation or N,N'-diarylation of secondary diamines" August 2002 (2002 08), TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, PAGE(S) 6913-6924, XP004377343 ISSN 0040-4020
- D11 EP-A-0 675 118 (EISAI CO, LTD) 4 October 1995 (1995-10-04)

2) Novelty (Art. 33 (1) and (2) PCT)

Numerous compounds falling in the scope of claim 1 are reported in the art (see examples of compounds in documents cited in the international search report) Example 35 of D2 for instance falls in the scope of claims 1-5, 7-11 which do thus not comply with Art. 33(2) PCT

Claim 6 does comply with Art. 33(2) PCT

3) Inventive Step (Art. 33 (1) and (3) PCT)

The technical problem underlying the present application is the provision of further compounds active in a disease which is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system

Numerous alkyl substituted piperazine derivatives directly attached to a phenyl ring are known in the pharmaceutical field possessing different activities comprising the treatment of disorders of the central nervous system (see e.g. D1-D3, D6) This core structure can thus not be considered as a novel unifying feature over the art

Since no clear novel unifying feature can be identified, the presence of an inventive step

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

International application No

PCT/EP2005/052732

can not be assessed for the present application
The present application does not comply with Art 33(3) PCT

4) Industrial applicability (Art 33(1) and (4) PCT)

For the assessment of the present claim 11 on the question whether it is 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.

Re Item VI

Certain document cited

D12 WO 2005/016902 A (ARENA PHARMACEUTICALS, INC, SMITH, BRIAN,
TSAI, JAMES, CHEN, RITA) 24 February 2005 (2005-02 24)

283-204-WO

1/8

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	283-204-WO
I	Title of invention	NOVEL ALKYL SUBSTITUTED PIPERAZINE 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
III-4	Applicant and/or inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST First)	SCHNEEL-KRÜGER, Jørgen
III-4-5	Address	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-4-6	State of nationality	DK
III-4 7	State of residence	DK

PCT REQUEST

Print Out (Original in Electronic Form)

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 8080
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	18 June 2004 (18 06 2004)
VI 1-2	Number	PA 2004 00959
VI 1-3	Country	DK
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	22 June 2004 (22 06 2004)
VI-2-2	Number	60/581,363
VI-2-3	Country	US
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

283-204-WO

4/6

PCT REQUEST

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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

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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(i)		NeuroSearch A/S is entitled as employer of the inventor, SCHEEL-KRÜGER, Jørgen
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	17	✓
IX-3	Claims	4	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	28	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-17	PCT-SAFE physical media	-	-
IX-18	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	/Michael Abildgren/	
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	
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283-204-WO

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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	
8-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared Using	PCT Online Filing Version 3 50 (Build 0001 169)
0-8	Applicant's or agent's file reference	283-204-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) H	902
12-4	Remaining sheets	0
12-5	Additional amount OQ	0
12-6	Total additional amount I2	0
12-7	H + 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 OQ	30
12-16	Total priority document fee P	⇒
12-17	TOTAL FEES PAYABLE (T+S++P)	⇒ 2423
12-18	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	2803 0031
12-22	Date	14 June 2005 (14 06 2005)
12-23	Name and signature	MICHAEL ABILDGREN, /Michael Abildgren/

df 85

NOVEL ALKYL SUBSTITUTED PIPERAZINE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

5

This invention relates to novel alkyl substituted piperazine 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

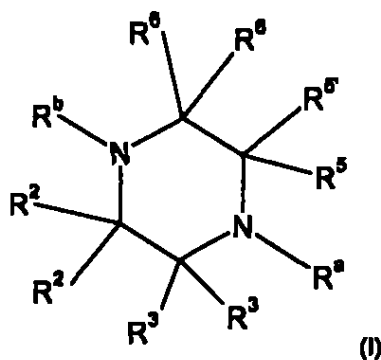
WO 97/30997 (NeuroSearch A/S) describes tropane derivatives active as
15 neurotransmitter re-uptake inhibitors

However, 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

20

SUMMARY OF THE INVENTION

In its first aspect, the invention provides a piperazine derivative of the Formula I



25

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

wherein R^a , R^b , R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 are as defined below

In its second aspect, the invention provides a pharmaceutical composition,
30 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, 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

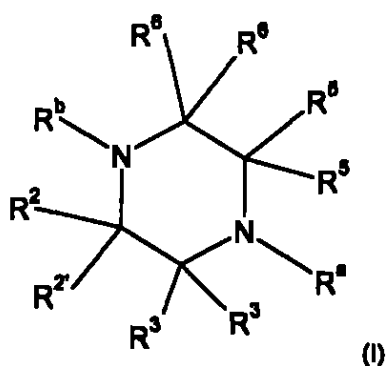
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to inhibition of monoamine neurotransmitter re-uptake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

Alkyl substituted piperazine derivatives

In its first aspect the present invention provides piperazine derivatives of formula I



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

R^a represents hydrogen or alkyl,

which alkyl is optionally substituted with one or more substituents independently selected from the group consisting of

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

R^b represents an aryl or a heteroaryl group,



which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of

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

each of R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 independently of each other represents hydrogen or alkyl,

with the proviso that at least one of R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 represents alkyl

In one embodiment, R^a represents hydrogen or alkyl In a special embodiment,

5 R^a represents hydrogen In a further embodiment, R^a represents alkyl, such as methyl

In a still further embodiment, R^b represents an optionally substituted aryl, such as an optionally substituted phenyl

In a further embodiment, R^b represents a phenyl group, which phenyl group is optionally substituted with one or more substituents independently selected from the

10 group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy

In a still further embodiment, R^b represents a phenyl group, which phenyl group is optionally substituted twice with halo In a special embodiment, R^b represents dichloro-phenyl, such as 3,4-dichloro-phenyl or 2,4-dichlorophenyl

In a further embodiment, R^b represents a phenyl group, which phenyl group is substituted once with halo In a special embodiment, R^b represents chloro-phenyl, such as 4-chloro-phenyl In a further embodiment, R^b represents bromo-phenyl, such as 4-bromo-phenyl In a still further embodiment, R^b represents iodo-phenyl, such as 4-iodo-phenyl

In a still further embodiment, R^b represents a phenyl group, which phenyl group is substituted once with trifluoromethyl or trifluoromethoxy, In a special embodiment, R^b represents trifluoromethyl-phenyl, such as 4-trifluoromethyl-phenyl In a further embodiment, R^b represents trifluoromethoxy-phenyl, such as 4-trifluoromethoxy-phenyl

In a further embodiment, R^b represents a naphthyl group, which naphthyl group is optionally substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy In a special embodiment, R^b represents naphthyl, such as naphthalen-2-yl In a further embodiment, R^b represents alkoxynaphthyl, such as methoxynaphthyl, such as 6-methoxy-naphthalen-2-yl

30 In a further embodiment, two of R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 represent alkyl, and the remaining six of R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 represent hydrogen

In a special embodiment, R^2 and R^5 represent alkyl, such as methyl, and R^2 , R^3 , R^3 , R^5 , R^6 and R^6 represent hydrogen In a further embodiment, R^3 and R^5 represent alkyl, such as methyl, and R^2 , R^2 , R^3 , R^5 , R^6 and R^6 represent hydrogen In

a still further embodiment, R^2 and R^5 represent alkyl, such as methyl, and R^2 , R^3 , R^3 , R^6 , R^6 and R^6 represent hydrogen. In a still further embodiment, R^3 represents alkyl, such as methyl, and R^2 , R^2 , R^3 , R^5 , R^5 , R^6 and R^6 represent hydrogen.

In a special embodiment, the compound of the invention is a *trans*-dialkyl-
5 piperazine derivative, such as a *trans*-dimethyl-piperazine derivative, such as a *trans*-2,5-dimethyl-piperazine derivative. In a further embodiment, the compound of the invention is a *cis*-dialkyl-piperazine derivative, such as a *cis*-dimethyl-piperazine derivative, such as a *cis*-3,5-dimethyl-piperazine derivative or a *cis*-2,6-dimethyl-piperazine derivative.

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In a special embodiment the chemical compound of the invention is

- 1-(3,4-Dichloro-phenyl)-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-3,5-dimethyl-piperazine,
 - 1-(4-Chloro-phenyl)-2,5-dimethyl-piperazine,
 - 15 1-(4-Iodo-phenyl)-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-2,6-dimethyl-piperazine
 - 1-(4-Bromo-phenyl)-2,5-dimethyl-piperazine,
 - 1-(4-Trifluoromethyl-phenyl)-2,5-dimethyl-piperazine,
 - 1-(4-Trifluoromethoxy-phenyl)-2,5-dimethyl-piperazine,
 - 20 1-(2,4-Dichloro-phenyl)-2,5-dimethyl-piperazine,
 - 1-(2,4-Dichloro-phenyl)-3,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-3-methyl-piperazine,
 - 1-(2-Naphthyl)-2,5-dimethyl-piperazine,
 - 1-(6-Methoxy-naphth-2-yl)-2,5-dimethyl-piperazine,
 - 25 1-(3,4-Dichloro-phenyl)-4-methyl-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-4-methyl-3,5-dimethyl-piperazine,
 - 1-(4-Chloro-phenyl)-4-methyl-2,5-dimethyl-piperazine,
 - 1-(3,4-Dichloro-phenyl)-4-methyl-2,6-dimethyl-piperazine,
 - 1-(4-Trifluoromethoxy-phenyl)-4-methyl-2,5-dimethyl-piperazine,
 - 30 1-(2-Naphthyl)-4-methyl-2,5-dimethyl-piperazine,
- any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

In a special embodiment the chemical compound of the invention is

- (±)-1-(3,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
- 35 1-(3,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
- (±)-1-(4-Chloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
- (±)-1-(4-Iodo-phenyl)-*trans*-2,5-dimethyl-piperazine,
- 1-(3,4-Dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine
- (±)-1-(4-Bromo-phenyl)-*trans*-2,5-dimethyl-piperazine,

- (±)-1-(4-Trifluoromethyl-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(2,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
(1-(2,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
5 (±)-1-(3,4-Dichloro-phenyl)-3-methyl-piperazine,
(±)-1-(2-Naphthyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(6-Methoxy-naphth-2-yl)-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
(±)-1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-3,5-dimethyl-piperazine,
10 (±)-1-(4-Chloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-2,6-dimethyl-piperazine,
(±)-1-(4-Trifluoromethoxy-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
(±)-1-(2-Naphthyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
or a pharmaceutically acceptable salt thereof

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

Definition of Substituents

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

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contains of from one to six carbon atoms (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
25 embodiment of this invention alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a
30 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-butenyl, or 1,3-butadienyl, 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexadienyl, or 1,3,5-hexatrienyl.

35 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 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-

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butynyl, or 1,3-butadiynyl, 1-, 2-, 3-, 4-pentynyl, or 1,3-pentadiynyl, 1-, 2-, 3-, 4-, or 5-hexynyl, or 1,3-hexadiynyl or 1,3,5-hexatriynyl

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C₃₋₇-cycloalkyl),

5 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

In the context of this invention an aryl group designates a carbocyclic aromatic ring system such as phenyl, naphthyl (1-naphthyl or 2-naphthyl) or fluorenyl

10 In the context of this invention a heteroaryl group designates an aromatic mono- or bicyclic heterocyclic group, which holds one or more heteroatoms in its ring structure Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S)

Preferred monocyclic heteroaryl groups of the invention include aromatic 5- and 6-membered heterocyclic monocyclic groups, including for example, but not limited to, 15 oxazolyl (oxazol-2-yl, -4-yl, or -5-yl), isoxazolyl (isoxazol-3-yl, -4-yl, or -5-yl), thiazolyl (thiazol-2-yl, -4-yl, or -5-yl), isothiazolyl (isothiazol-3-yl, -4-yl, or -5-yl), 1,2,4-oxadiazolyl (1,2,4-oxadiazol-3-yl or -5-yl), 1,2,4-thiadiazolyl (1,2,4-thiadiazol-3-yl or -5-yl), 1,2,5-oxadiazolyl (1,2,5-oxadiazol-3-yl or -4-yl), 1,2,5-thiadiazolyl (1,2,5-thiadiazol-3-yl or -4-yl), imidazolyl (2-, 4-, or 5-imidazolyl), pyrrolyl (2- or 3-pyrrolyl), furanyl (2- or 3- 20 furanyl), thienyl (2- or 3-thienyl) pyndyl (2-, 3- or 4-pyridyl), pynmidyl (2-, 4-, 5- or 6-pynmidyl), or pyndazyl (3- or 4-pyndazyl)

Preferred bicyclic heteroaryl groups of the invention include for example, but not limited to, indolizyl (2-, 5- or 6-indolizyl), indolyl (2-, 5- or 6-indolyl), isoindolyl (2-, 5- or 6-isoindolyl), indazolyl (1- or 3-indazolyl), benzofuranyl (2-, 5- or 6-benzofuranyl), 25 benzo[b]thienyl (2-, 5- or 6-benzothienyl), benzimidazolyl (2-, 5- or 6-benzimidazolyl), benzoxazolyl (2-, 5- or 6-benzoxazolyl), benzothiazolyl (2-, 5- or 6-benzothiazolyl), benzo[d]isothiazolyl (1,2-benzo[d]isothiazol-3-yl), punnyl (2- or 8-puriny), quinollnyl (2-, 3-, 6-, 7- or 8-quinoliny), isoquinoliny (1-, 3-, 5-, 6- or 7-isoquinoliny), cinnoliny (6- or 7-cinnoliny), phthalaziny (6- or 7-phthalaziny), quinazoliny (2-, 6- or 7-quinazoliny), 30 quinoxaliny (2- or 6-quinoxaliny), 1,8-naphthyndiny (1,8-naphthyndin-2-, 3-, 6- or 7-yl), ptendiny (2-, 6- or 7-ptendiny), and indenyl (1-, 2-, 3-, 5- or 5-indenyl)

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable 35 for the intended administration Suitable forms include pharmaceutically (i e

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physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzenesulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, 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 lysine, 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

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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.

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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.

For example, the compounds of the present invention may exist in cis or trans configurations as well as in mixtures thereof. E.g., those of the substituents R^2/R^2 , R^3/R^3 , R^5/R^5 , and R^6/R^6 which represent alkyl may in particular be in cis or trans configuration relative to each another (e.g., R^2 relative to R^5 , or R^3 relative to R^6). Examples include, without limitation, trans-2,5-dimethyl-piperazine and cis-3,5-dimethyl-piperazine derivatives. The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Moreover, the chemical compounds of the present invention may exist as enantiomers in (+) and (-) forms as well as in racemic forms ($\pm$). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

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

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the 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 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 from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphoric 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
5 "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

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

15 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
20 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 Positron Emission Tomography (PET), Single Photon Imaging, Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS),
25 Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of Preparation

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

Also one compound of the invention can be converted to another compound of
35 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.

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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. Based on the balanced activity observed in these tests

5 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

10 In a special embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, 15 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 20 complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, 25 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, late luteal phase syndrome, post-traumatic 30 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, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, 35 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,

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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
5 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

10 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
15 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
20 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,
25 rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of
30 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
35 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

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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

5 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

10 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, 15 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.

20 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 25 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.

30 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 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, 35 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.

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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

5 The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use

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

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic
15 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
20 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. Ointments and creams may, for example, be formulated with an aqueous or oily base
25 with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents

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

Solutions or suspensions are applied directly to the nasal cavity by conventional
35 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 a suitable propellant such as a chlorofluorocarbon (CFC) for example

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dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

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

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

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

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

5 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
10 $\mu\text{g/kg}$ 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.

Methods of Therapy

15 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
20 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
25 involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

30

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.

General All reactions involving air sensitive reagents or intermediates were
35 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.

100

Method A**(±)-1-(3,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt**

A mixture of *trans*-2,5-dimethylpiperazine (10 g, 88 mmol), 1-bromo-3,4-dichlorobenzene (22 g, 97 mmol), KO^tBu (20 g, 176 mmol), palladacycle (100 mg) and

- 5 dioxane (100 ml) was stirred at reflux for 1 h. Water (100 ml) was added to the mixture. The mixture was extracted with diethyl ether (2 x 100 ml). Chromatography on silica gel with methanol, dichloromethane and conc. ammonia (10:89:1) gave the title compound. Yield 7.0 g (31 %). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 209-211°C

10

1-(3,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from *cis*-3,5-dimethyl-piperazine. Mp 225-227°C

- 15 **(±)-1-(4-Chloro-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt**

Was prepared according to method A. Mp 165-168°C

(±)-1-(4-Iodo-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 160-166°C

20

1-(3,4-Dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from *cis*-3,5-Dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester followed by deprotection of the 1-carboxylic acid *tert*-butyl ester with a mixture of hydrochloric acid and acetic acid. Mp 170-173°C

25

(±)-1-(4-Bromo-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 168-170°C

(±)-1-(4-Trifluoromethyl-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

- 30 Was prepared according to method A. Mp 186-187°C

(±)-1-(4-Trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A. Mp 157-160°C

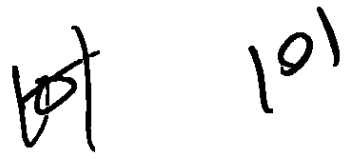
- 35 **(±)-1-(2,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine hydrochloric acid salt**

Was prepared according to method A. Mp 197-200°C

1-(2,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A from *cis*-3,5-dimethyl-piperazine. Mp >270°C

40



(±)-1-(3,4-Dichloro-phenyl)-3-methyl-piperazine fumaric acid salt

Was prepared according to method A from (±)-3-methyl-piperazine Mp 190-192°C

(±)-1-(2-Naphthyl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

5 Was prepared according to method A Mp 178-179°C

(±)-1-(6-Methoxy-naphth-2-yl)-*trans*-2,5-dimethyl-piperazine fumaric acid salt

Was prepared according to method A Mp 207°C

10 Method B

(±)-1-(3,4-Dichloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine fumaric acid salt

A mixture of (±)-1-(3,4-dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine (6.0 g, 23 mmol), formic acid (60 ml) and formaldehyde (60 ml) was stirred at 70°C for 15 h. The mixture

15 was evaporated. An aqueous solution of ammonia (100 ml, 1 M) was added followed by extraction with diethyl ether (2 x 100 ml). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 3.0 g (33 %) Mp 166-169°C

20 **1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-3,5-dimethyl-piperazine free base**

Was prepared according to method B from (±)-1-(3,4-dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine. The product was isolated as an oil.

(±)-1-(4-Chloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine fumaric acid salt

25 Was prepared according to method B from (±)-1-(4-chloro-phenyl)-*trans*-2,5-dimethyl-piperazine. Mp 142-144.5°C

(±)-1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-2,6-dimethyl-piperazine free base

Was prepared according to method B from (±)-1-(3,4-dichloro-phenyl)-*cis*-2,6-

30 dimethyl-piperazine. The product was isolated as an oil.

(±)-1-(4-Trifluoromethoxy-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine hydrochloric acid salt

Was prepared according to method B from (±)-1-(4-trifluoromethoxy-phenyl)-*trans*-2,5-

35 dimethyl-piperazine. Mp 167-170°C

(±)-1-(2-Naphthyl)-4-methyl-*trans*-2,5-dimethyl-piperazine fumaric acid salt

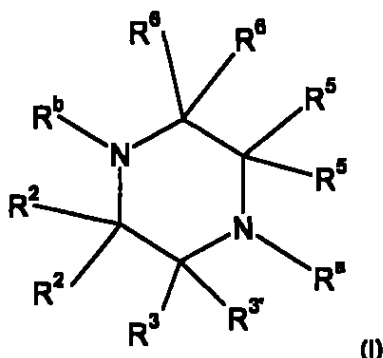
Was prepared according to method A from (±)-1-(2-naphthyl)-*trans*-2,5-dimethyl-piperazine. The product was isolated as an oil.

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CLAIMS

1 A piperazine dervative of the Formula I

5



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

10 R^a represents hydrogen or alkyl,

which alkyl is optionally substituted with one or more substituents
independently selected from the group consisting of

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

15

R^b represents an aryl or a heteroaryl group,

which aryl or heteroaryl group is optionally substituted with one or more
substituents independently selected from the group consisting of

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

each of R², R², R³, R³, R⁵, R⁵, R⁶ and R⁶ independently of each other
represents hydrogen or alkyl,

with the proviso that at least one of R², R², R³, R³, R⁵, R⁵, R⁶ and R⁶ represents
alkyl

20 2 The chemical compound of claim 1, wherein
R^a represents hydrogen or alkyl

3 The chemical compound of claims 1 or 2, wherein
R^b represents a phenyl group,

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which phenyl group is optionally substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy

- 4 The chemical compound of claims 1 or 2, wherein
5 R^b represents a phenyl group,
which phenyl group is optionally substituted twice with halo
- 5 The chemical compound of any one claims 1-4, wherein
two of R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 represent alkyl, and
the remaining six of R^2 , R^2 , R^3 , R^3 , R^5 , R^5 , R^6 and R^6 represent hydrogen
- 10 6 The chemical compound of claim 1, which is
(±)-1-(3,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
(±)-1-(4-Chloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Iodo-phenyl)-*trans*-2,5-dimethyl-piperazine,
15 1-(3,4-Dichloro-phenyl)-*cis*-2,6-dimethyl-piperazine
(±)-1-(4-Bromo-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Trifluoromethyl-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(4-Trifluoromethoxy-phenyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(2,4-Dichloro-phenyl)-*trans*-2,5-dimethyl-piperazine,
20 1-(2,4-Dichloro-phenyl)-*cis*-3,5-dimethyl-piperazine,
(±)-1-(3,4-Dichloro-phenyl)-3-methyl-piperazine
(±)-1-(2-Naphthyl)-*trans*-2,5-dimethyl-piperazine,
(±)-1-(6-Methoxy-naphth-2-yl)-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
25 (±)-1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-3,5-dimethyl-piperazine,
(±)-1-(4-Chloro-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
1-(3,4-Dichloro-phenyl)-4-methyl-*cis*-2,6-dimethyl-piperazine,
(±)-1-(4-Trifluoromethoxy-phenyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
(±)-1-(2-Naphthyl)-4-methyl-*trans*-2,5-dimethyl-piperazine,
30 or a pharmaceutically acceptable salt thereof
- 7 A pharmaceutical composition, comprising a therapeutically effective amount of a
compound of any one of claims 1-6, any of its isomers or any mixture of its
isomers, or a pharmaceutically acceptable salt thereof, together with at least one
35 pharmaceutically acceptable carrier, excipient or diluent

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- 8 Use of the chemical compound of any of claims 1-6, any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament
- 5 9 The use according to claim 8, 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
- 10 10 The use according to claim 9, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse alcohol addiction, alcoholism, 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, 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, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourettes disease
- 15 20 25 30 35

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- 11 A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to
- 5 such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-6, any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof

ABSTRACT

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**NOVEL ALKYL SUBSTITUTED PIPERAZINE DERIVATIVES AND THEIR USE AS
MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS**

This invention relates to novel alkyl substituted piperazine denvatives 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 96463
10X 10X

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) NeuroSearch A/S

domicilado(s) en

domiciled in 93 Pederstrupvej
DK-2750 Ballerup, Denmark

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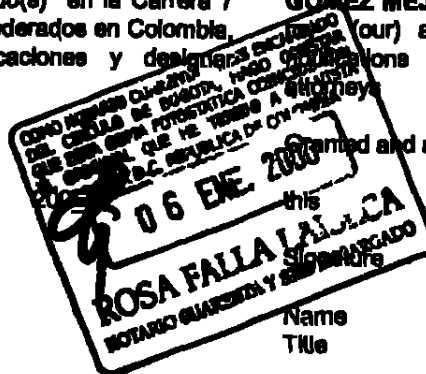
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Otorgado y firmado en

hoy de de

Firma

Nombre
Cargo



Granted and signed in

this day of 200_

Name
Title

Peder Velling
Head of Patente

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NOTARIAL CERTIFICATE (CORPORATION)

Hoy de de
personalmente compareció ante mí

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

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

Peder Velling
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signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

de

Head of patent department
of
Neurosearch A/S

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

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

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

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

Estado de
con fecha

State of Denmark
under date of 14 April 2005

y que quien confiere el presente poder es su representante

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

Notario Público (sello)

Public Notary (Seal)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

HENNING BROMAN
Fettersessor
**NOTARIAL CERTIFICATE
NATURAL PERSON**

Hoy de de , compareció(eron) ante mí

On this 14th day of April of 2005
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persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que ratifican el mismo para los fines y
propósitos que en él

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



LEGALIZACION POR APOSTILLA ES REQUERIDA.

Notary Public (Seal)

HENNING BROMAN
Fettersessor
LEGALIZATION BY APOSTILLE IS REQUIRED

The City Court of Ballerup
Blegdamevej 6
2200 Copenhagen
Denmark

109



THE TRUE SIGNATURE OF
Henning Brown

IS HEREBY CERTIFIED.

COPENHAGEN, 11 APR. 2005
FOR THE MINISTER FOR FOREIGN AFFAIRS.
B.A.

Henning

BIRGITTE THORELL

RECHOSAR
DERECHOS
COLOMBIA

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120 110
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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 COMPAÑIA PARA CONFERIR ESTE PODER, QUE EL SELLO ESTAMPADO POR ÉL AL PIE DE TAL PODER, EN NOMBRE Y REPRESENTACIÓN DE LA EXPRESADA COMPAÑIA, 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



147 111
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

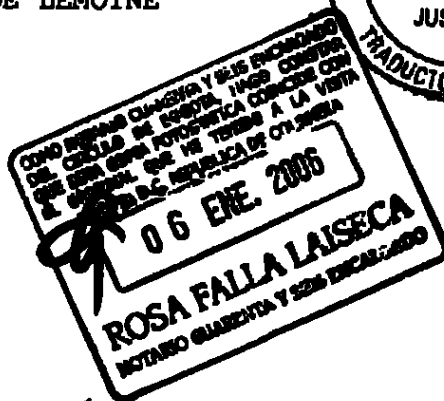
FIRMADO OLE WAAGE PEDERSEN, CÓNSUL AD-HONOREM

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 FL NO 355460 DEL 27
DE ABRIL DE 2005

LA TRADUCTORA OFICIAL

Helena Uribe de Lemoine

HELENA URIBE DE LEMOINE



**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 ☐

Firma Responsable 

Fecha _____

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

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 113

2020
Bogotá D C ,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
NEUROSEARCH A/S

REFERENCIA	Radicación No	06 119265
	Solicitud internacional	PCT/EP2005/052732
	Fecha inicio fase nacional	18/01/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No	2607
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial

Cúmplase
Dado en Bogotá DC,

5 FEB 2007

ALIX CARMENZA ESPEDRES DE VERGEL
Jefe de la división de Nuevas Creaciones

lerazo