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División de Nuevas Creaciones

PCT

SOLICITUD
PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

08-83690

21. EXPEDIENTE No.

54. TITULO

NOVEDOSOS DERIVADOS DE CROMEN-2-ONA Y SU USO COMO
INHIBIDORES DE REABSORCIÓN DEL NEUROTRANSMISOR DE
MONOAMINA

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE

NEUROSEARCH A/S

DOMICILIO

BALLERUP, DINAMARCA

74. APODERADO

JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

PETITORIO

AS: 107.727



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-083690- -00000-0000

Fecha: 2008-08-12 16:33:35 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 110FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE
(71)Nombre: **NEUROSEARCH A/S**Dirección: 93 Pederstrupvej, DK-2750 Ballerup,
Dinamarca

Nacionalidad o Domicilio: Dinamarca

Lugar de Constitución: Dinamarca

Teléfono:

Fax:

E-mail:

IDENTIFICACIÓN

C.C. ☐NIT ☐C.E. ☐Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

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IDENTIFICACIÓN

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Cual _____

Número 80.410.337 TP 57492

4

INVENTOR (ES)
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Nombre: Dan PETERS, John Paul REDROBE, Elsebet Østergaard NIELSEN.

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NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup, DK; c/o NeuroSearch A/S, 93
Pederstrupvej, DK-2750 Ballerup, DK (Respectivamente).

Nacionalidad o Domicilio: Dinamarca (Respectivamente).

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23-08-20076 Título (54): **NOVEDOSOS DERIVADOS DE CROMEN-2-ONA Y SU USO COMO INHIBIDORES DE REABSORCIÓN DEL NEUROTRANSMISOR DE MONOAMINA**

7 Clasificación Internacional (51): _____

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SI ☒NO ☐

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17-02-2006

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PA 2006 00233

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08 - 44, 582

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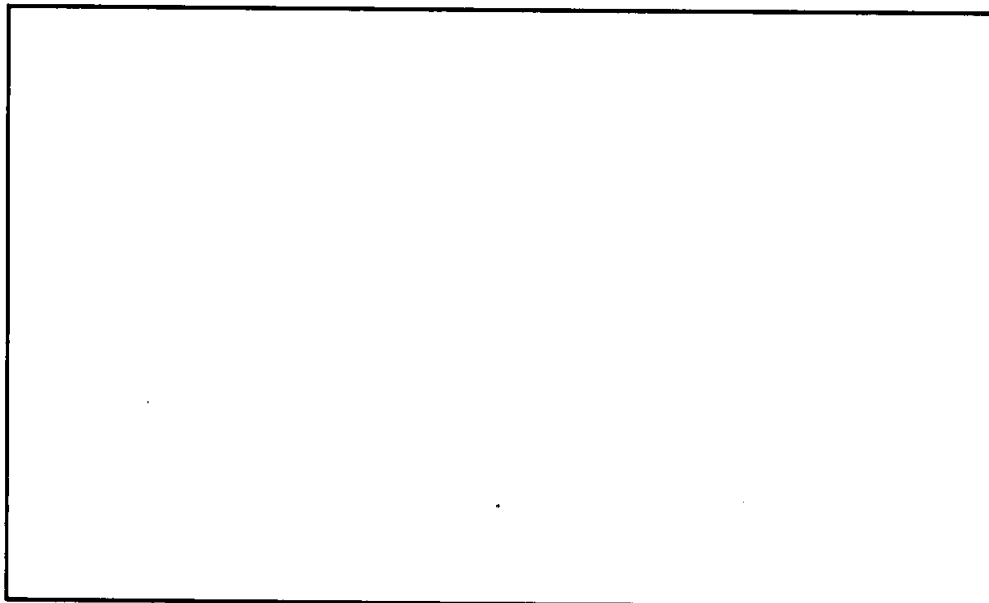
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 501.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Declaraciones bajo la Regla 4.17
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Extracto para Publicación y Tarjeta de Archivo Temático
Tarjeta de Propietarios
Documentos PCT

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

[Firma]
C.C. 80.410.337 de Usaquén TP. 57492 del C.S.J.

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

107 727

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-083690- -00000-0000

Fecha: 2008-08-12 16:33:35 Dep. 2020 NUECREACION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 44,582
FECHA : JUNIO 5 DE 2008

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3255976	04/06/2008	53,900,000.00

**** C O N C E P T O ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
TOTAL : .			\$ 501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

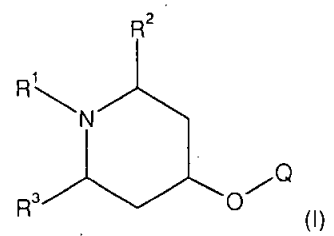
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

(21) No. de solicitud:		(22) Fecha de solicitud:		FIGURA CARACTERÍSTICA 6 x 6 cm		
(51) Clasificación Internacional:						
(71) Solicitante(s): NEUROSEARCH A/S						
(72) Inventor(es): Dan PETERS, John Paul REDROBE, Elsebet Østergaard NIELSEN.						
(74) Agente: JUAN PABLO CADENA SARMIENTO						
(30) Prioridad	(31)	No. Prioridad	(32)	Fecha	(33)	País
		PA 21.02.2006		17-02-2006		DK
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(86) Datos relativos a la presentación de la solíc. PCT				Fecha: 23-08-2007		
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No. de solicitud: PCT/EP2007/051401						

(54) Título: NOVEDOSOS DERIVADOS DE CROMEN-2-ONA Y SU USO COMO INHIBIDORES DE REABSORCIÓN DEL NEUROTRANSMISOR DE MONOAMINA

(55) Reivindicaciones:

1. Un compuesto de Fórmula I:



cualquiera de sus isómeros o cualquier mezcla de sus isómeros,

o su sal farmacéuticamente aceptable,
en donde

Q representa un grupo cromen-2-ona;

el cual grupo cromen-2-ona se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por :

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

R¹ representa hidrógeno o alquilo;

el cual alquilo se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por :

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

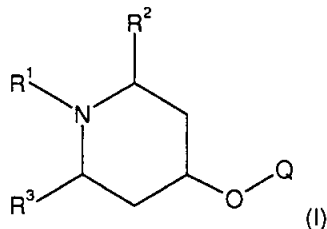
R² y R³ conjuntamente forman $-(CH_2)-(CH_2)-p-(CH)=(CH)-$.

8. Una composición farmacéutica que contiene una cantidad terapéuticamente efectiva de un compuesto de una cualquiera de las reivindicaciones 1-7, cualquiera de sus isómeros, o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, junto con por lo menos una sustancia portadora, excipiente o diluyente farmacéuticamente aceptables.

 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT	
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	PA 21.02.2006	17-02-2006	DK
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(54) Título: NOVEDOSOS DERIVADOS DE CROMEN-2-ONA Y SU USO COMO INHIBIDORES DE REABSORCIÓN DEL NEUROTRANSMISOR DE MONOAMINA			

(55) Reivindicaciones:

1. Un compuesto de Fórmula I:



cualquiera de sus isómeros o cualquier mezcla de sus isómeros,
o su sal farmacéuticamente aceptable,
en donde

Q representa un grupo cromen-2-ona;

el cual grupo cromen-2-ona se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por :

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

R¹ representa hidrógeno o alquilo;

el cual alquilo se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por :

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

R² y R³ conjuntamente forman -(CH₂)-(CH₂)- o -(CH)=(CH)-.

8. Una composición farmacéutica que contiene una cantidad terapéuticamente efectiva de un compuesto de una cualquiera de las reivindicaciones 1-7, cualquiera de sus isómeros, o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, junto con por lo menos una sustancia portadora, excipiente o diluyente farmacéuticamente aceptables.

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A61K 31/135 (2006.01)(74) Common Representative: NEUROSEARCH A/S;
Patent Department, 93 Pederstrupvej, DK-2750 Ballerup
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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (for all designated States except US): NEU-
ROSEARCH A/S [DK/DK]; 93 Pederstrupvej, DK-2750
Ballerup (DK).

(72) Inventors; and

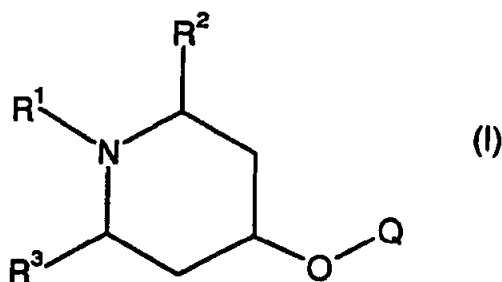
(75) Inventors/Applicants (for US only): PETERS, Dan
[SE/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej,
DK-2750 Ballerup (DK). REDROBE, John, Paul
[GB/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej,
DK-2750 Ballerup (DK). NIELSEN, Elsebet, Øster-
gaard [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej,
DK-2750 Ballerup (DK).

Declaration under Rule 4.17:

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

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.(54) Title: NOVEL CHROMEN-2-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER
RE-UPTAKE INHIBITORS(57) Abstract: This invention relates to novel chromen-2-one
derivatives of formula (I) useful as monoamine neurotransmit-
ter 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. Formula (I) wherein Q represents a chromen-2-one
group; which chromen-2-one 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; R¹ 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; and R² and R³ together form
-(CH₂)₂-(CH₂)- or -(CH)=-(CH)-.

WO 2007/093604 A1

NOVEL CHROMEN-2-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS

TECHNICAL FIELD

5

This invention relates to novel chromen-2-one derivatives useful as monoamine neurotransmitter re-uptake inhibitors.

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

BACKGROUND ART

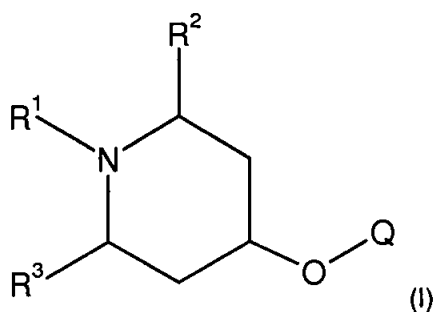
Serotonin Selective Reuptake Inhibitors (SSRIs) currently provide efficacy in the
15 treatment of several CNS disorders, including depression and panic disorder. SSRIs are generally perceived by psychiatrists and primary care physicians as effective, well-tolerated and easily administered. However, they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

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

SUMMARY OF THE INVENTION

25

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



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

wherein R¹, R², R³ and Q are as defined below.

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

its 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.

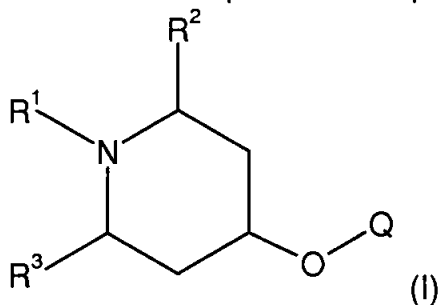
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central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

Chromen-2-one derivatives

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



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

Q represents a chromen-2-one group;

which chromen-2-one 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;

R¹ 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; and

5 R² and R³ together form $-(CH_2)-(CH_2)-$ or $-(CH)=(CH)-$.

In one embodiment of the compound of Formula I, R² and R³ together form $-(CH_2)-(CH_2)-$; and R¹ is as defined above. In a special embodiment, R¹ represents alkyl, alkenyl or alkoxyalkyl. In a further embodiment, R¹ represents C₂₋₆-alkyl, alkenyl
10 or alkoxyalkyl. In a still further embodiment, R¹ represents C₂₋₆-alkyl, such as ethyl or propyl, in particular isopropyl. In a further embodiment, R¹ represents alkenyl, such as allyl. In a still further embodiment, R¹ represents alkoxyalkyl, such as alkoxyethyl, in particular methoxyethyl. In a further embodiment, R¹ represents hydrogen. In a still further embodiment, R¹ represents alkyl, such as methyl.

15 In a further embodiment of the compound of Formula I, R² and R³ together form $-(CH)=(CH)-$; and R¹ is as defined in claim 1. In a special embodiment, R¹ represents hydrogen or alkyl. In a further embodiment, R¹ represents hydrogen. In a still further embodiment, R¹ represents alkyl, such as methyl.

In a further embodiment of the compound of Formula I, Q represents chromen-
20 2-one-yl. In a special embodiment of the compound of Formula I, Q represents chromen-2-one-7-yl. In a special embodiment of the compound of Formula I, Q represents chromen-2-one-6-yl.

In a still further embodiment of the compound of Formula I, Q represents substituted chromen-2-one-yl, such as halo, cyano or alkyl substituted chromen-2-one-
25 yl. In a special embodiment of the compound of Formula I, Q represents substituted chromen-2-one-7-yl, such as halo, cyano or alkyl substituted chromen-2-one-7-yl. In a special embodiment of the compound of Formula I, Q represents substituted chromen-2-one-6-yl, such as halo, cyano or alkyl substituted chromen-2-one-6-yl.

In a further embodiment, Q represents chromen-2-one-yl; which chromen-2-
30 one-yl group is substituted in the 3-position with a substituent selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.

In a still further special embodiment, Q represents 3-halo-chromen-2-one-yl, such as 3-halo-chromen-2-one-6-yl or 3-halo-chromen-2-one-7-yl. In a special
35 embodiment, Q represents 3-bromo-chromen-2-one-6-yl, 3-bromo-chromen-2-one-7-yl, 3-chloro-chromen-2-one-6-yl or 3-chloro-chromen-2-one-7-yl.

In a further special embodiment, Q represents 3-cyano-chromen-2-one-yl, such as 3-cyano-chromen-2-one-6-yl or 3-cyano-chromen-2-one-7-yl.

In a further special embodiment, Q represents alkyl-cyano-chromen-2-one-yl, such as methyl-cyano-chromen-2-one-yl, such as 4-methyl-3-cyano-chromen-2-one-yl. In a special embodiment, Q represents 4-methyl-3-cyano-chromen-2-one-6-yl or 4-methyl-3-cyano-chromen-2-one-7-yl.

- 5 In a special embodiment the chemical compound of the invention is
exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-2-oxo-2*H*-chromene-3-carbonitrile;
exo-6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-bromo-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-chloro-chromen-2-one;
10 *exo*-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-4-methyl-2-oxo-2*H*-chromene-3-carbonitrile;
exo-7-(8-Ethyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Isopropyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-[8-(2-Methoxy-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yloxy]-chromen-2-one;
exo-7-(8-Allyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
15 *exo*-7-(8-Aza-bicyclo[3.2.1]oct-6-en-3-yl)oxy)-chromen-2-one;
exo-7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one;
exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-3-Chloro-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
or a pharmaceutically acceptable salt thereof.
20 Any combination of two or more of the embodiments as described above is
considered within the scope of the present invention.

Definition of Substituents

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

- 25 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
30 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 preferred embodiment the alkenyl group of the invention comprises of from two to six
35 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.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C₂₋₆-alkynyl), including at least one triple bond. In its most preferred
5 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), including
10 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.

15 Amino is NH₂ or NH-alkyl or N-(alkyl)₂, wherein alkyl is as defined above.

Pharmaceutically Acceptable Salts

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

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate,
25 the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the
30 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.

35 Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysinium, and the ammonium salt, and the like, of a chemical compound of the invention containing an

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anionic group. Such cationic salts may be formed by procedures well known and described in the art.

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

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

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

20 Steric Isomers

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

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

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

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the 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 (-) camphanic acid or by

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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 or intermediates.

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 Position 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 (NeuroSearch A/S). Based on the balanced activity

5 observed in these tests the compound of the invention is considered useful for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a special embodiment, the compounds of the invention are considered useful
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, social anxiety disorder, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with
25 depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-mastectomy pain syndrome (PMPS), post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual
30 dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg syndrome, periodic limb movement disorder, eating disorders, anorexia nervosa, sleep disorders, pervasive
35 developmental disorders, autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, learning disabilities, motor skills disorders, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, Gilles de la Tourettes disease, tinnitus, tic disorders, body dysmorphic disorders, oppositional defiant disorder or post-stroke disabilities. In a

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preferred embodiment, the compounds are considered useful for the treatment, prevention or alleviation of depression.

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

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

Pharmaceutical Compositions

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

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

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

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

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules,

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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
5 ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

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

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid
15 form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

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

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

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium
25 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 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
30 can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.
35

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

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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.

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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.

- 5 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
10 (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 intra-
15 nasal 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.

- 20 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
25 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.,
30 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. ED₅₀ and LD₅₀, 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 LD₅₀/ED₅₀. 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 $\mu\text{g/kg}$ 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

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

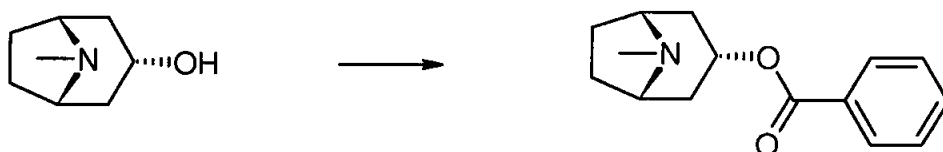
It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed,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

EXAMPLES

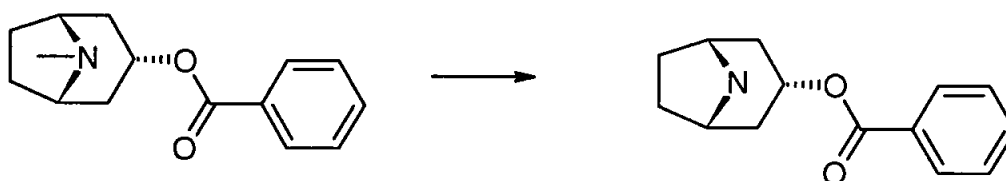
The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Preparatory Examples

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

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

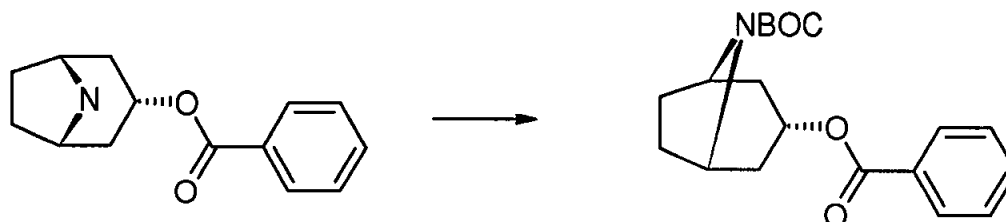
Benzoylchloride (84.3 g, 600 mmol) was added during 30 min at <30 °C to a mixture of
5 tropine (70.6 g, 500 mmol), potassium *tert*-butoxide (67.3 g, 600 mmol) and THF (500 ml). The mixture was stirred at room temperature for 2 h. Water (1 L) was added followed by extraction with diethylether (2 x 500 ml). The organic phase was washed twice with water (2 x 200 ml) followed by a solution of saturated aqueous sodium chloride (200 ml). The ether phase was dried and hydrochloric acid in ethanol (170 ml,
10 3 M) was added. The precipitated hydrochloride was filtered and washed with diethylether. The free base was obtained by adding an excess of aqueous ammonia followed by extraction with a mixture of ethylacetate and diethylether. Yield 66.8 g (54%).



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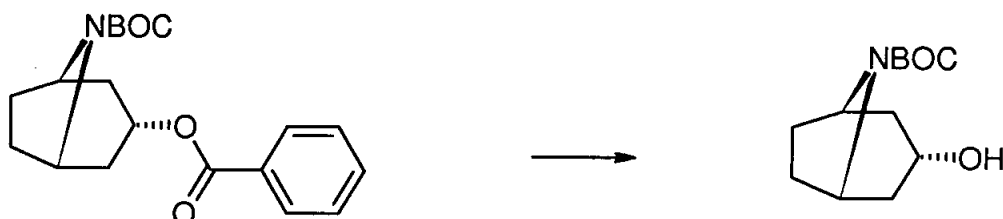
endo-Benzoic acid 8-aza-bicyclo[3.2.1]oct-3-yl ester

2,2,2-Trichloroethylchloroformate (75.0 ml, 544 mmol) was added dropwise to a mixture of *endo*-benzoic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl ester (66.8 g, 272 mmol) and dry toluene (500 ml). The mixture was allowed to stir for 1 h at room
20 temperature, followed by 15 h at 100°C. Water (250 ml) was added followed by stirring 1h. The phases were separated and the organic phase was washed twice with water (2 x 200 ml). The mixture of the intermediate 3-benzoyloxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid trichloromethyl ester, was dried and evaporated. Acetic acid (350 ml) was added followed by addition of zinc (53.4 g, 817 mmol) over 3 h time period. Water
25 (100 ml) was added, cooled by adding ice and made alkaline by adding concentrated aqueous ammonia (ca: 400 ml) and the mixture was extracted with dichloromethane (2 X 300 ml). Yield 44.5 g (61%).

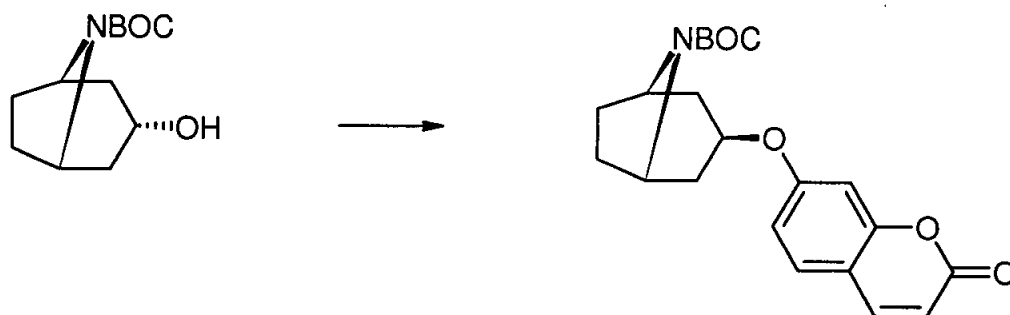


***endo*-3-Benzoyloxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester**

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

***endo*-3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester**

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

**Method 1*****exo*-7-(8-*tert*-Butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one**

Triphenylphosphine (7.5 g, 28.6 mmol) was solved in dioxane (70 ml) and cooled to 8°C. Diethylazodicarboxylate (5.0 g, 28.6 mmol) was added to the mixture below 15°C, followed by stirring for 15 minutes. *endo*-3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (5.0 g, 22.0 mmol) and 7-hydroxycoumarin (4.3 g, 26.4 mmol) was added to the mixture. The temperature raised due to an exothermic reaction. The mixture was allowed to stir for 15 h at room temperature. Water (200 ml) was added followed by extraction with diethylether (2 x 100 ml). The mixture was dried and evaporated. Chromatography on silica gel with dichloromethane and 5% methanol

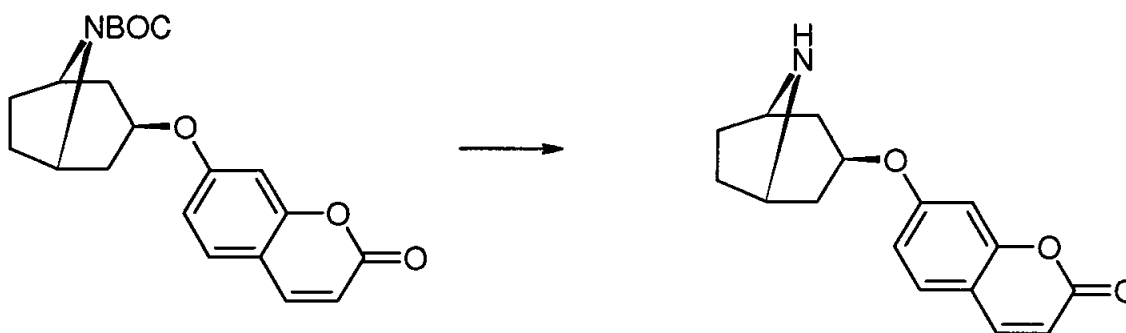
as solvent. The crude product was solved in diethylether (200 ml) and washed with aqueous sodium hydroxide (3 x 200 ml, 1 M). The product was dried and evaporated. Yield 5.32 g (65%).

5 ***exo*-3-(3-cyano-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester** (intermediate)

Was prepared according to method 1 from 7-hydroxy-2-oxo-2*H*-chromene-3-carbonitrile and *endo*-3-hydroxy-8-aza-bicyclo[3.2.1] octane-8-carboxylic acid *tert*-butyl ester.

10

Method 2A



***exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt**

15 A mixture of *exo*-7-(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one (0.60 g, 1.6 mmol) and hydrochloric acid (10 ml, 1 M) in acetic acid (10 ml) was stirred for 1 h. Diethylether (50 ml) was added and the precipitate was filtered and washed with diethylether (10 ml). Yield 0.28 g (57%). Mp > 300°C.

20 **Method 2B**

***exo*-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt**

A mixture of *exo*-7-[(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yl)oxy]-3-bromo-chromen-2-one (30 g, 65.3 mmol) and hydrogen chloride in acetic acid (500 ml, 1 M) was stirred at room-temperature for 3 h. Diethylether (500 ml) was added, the precipitation was stirred and isolated by filtration. Yield 25 g (99%). LC-ESI-HRMS of [M+H]⁺ shows 350.0405 Da. Calc. 350.039182 Da, dev. 3.8 ppm.

30 ***exo*-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-2-oxo-2*H*-chromene-3-carbonitrile hydrochloric acid salt**

Was prepared from *exo*-3-(3-cyano-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-HRMS of [M+H]⁺ shows 297.1238 Da. Calc. 297.123918 Da, dev. -0.4 ppm.

exo-6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-bromo-chromen-2-one hydrochloric acid salt

Was prepared from *exo*-3-(3-bromo-2-oxo-2*H*-chromen-6-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-
5 HRMS of [M+H]⁺ shows 350.0379 Da. Calc. 350.039182 Da, dev. -3.7 ppm.

exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-chloro-chromen-2-one hydrochloric acid salt

Was prepared from *exo*-3-(3-chloro-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-
10 HRMS of [M+H]⁺ shows 306.0894 Da. Calc. 306.089697 Da, dev. -1 ppm.

exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-4-methyl-2-oxo-2*H*-chromene-3-carbonitrile hydrochloric acid salt

15 Was prepared from *exo*-3-(3-cyano-4-methyl-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-HRMS of [M+H]⁺ shows 311.1401 Da. Calc. 311.139568 Da, dev. 1.7 ppm.

Method 3**20 exo-7-(8-Ethyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt**

A mixture of *exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one (3.1 g, 10.1 mmol), sodium hydride, 60% in mineral oil (0.29 g 12.1 mmol), iodoethane (2.46 g, 15.8 mmol) and tetrahydrofuran (75 ml) was stirred at 60°C for 3 h. The hydrochloride
25 was precipitated by adding ethanol (75 ml) and concentrated hydrochloric acid (1 ml). The crystalline product was recrystallised from ethanol (100 ml, 96%). Yield 1.71 g (51%). LC-ESI-HRMS of [M+H]⁺ shows 300.1596 Da. Calc. 300.159969 Da, dev. -1.2 ppm.

30 exo-7-(8-Isopropyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt

Was prepared according to method 1A from *exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 314.1746 Da. Calc. 314.175619 Da, dev. -3.2 ppm.

35

exo-7-[8-(2-Methoxy-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yloxy]-chromen-2-one hydrochloric acid salt

Was prepared according to method 1A from *exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 330.1691 Da. Calc.
40 330.170534 Da, dev. -4.3 ppm.

25

exo-7-(8-Allyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt

Was prepared according to method 1A from *exo*-7-(8-H-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 312.1584 Da. Calc. 312.159969 Da, dev. -5 ppm.

Method 4A**exo-7-(8-Aza-bicyclo[3.2.1]oct-6-en-3-yl)oxy)-chromen-2-one hydrochloric acid salt**

2,2,2-Trichloroethyl chloroformate (3.7 g, 17.6 mmol) was added to a mixture of *exo*-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one (1.0 g, 3.5 mmol) and toluene (20 ml). The mixture was stirred for 30 min at room temperature followed by 15 h at 100°C. Water (10 ml) was added and the organic phase was separated and was washed with water (2 x 25 ml). The crude mixture obtained by evaporation was solved in acetic acid (10 ml) and water (10 ml). Zinc powder (2.3 g, 35.3 mmol) was added to the mixture in portions followed by stirring for 5 h. Ice-water (20 ml) was added followed by concentrated aqueous ammonia (20 ml). The mixture was extracted with dichloromethane (2 x 20 ml). The hydrochloric acid salt was precipitated by adding hydrochloric acid solved in ethanol to the free base solved diethylether. Yield 70 mg (5%). Mp >280°C (dec.). LC-ESI-HRMS of [M+H]⁺ shows 270.1117 Da. Calc. 270.113019 Da, dev. -4.9 ppm.

Method 4B**exo-7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one hydrochloric acid salt**

A mixture of diethylazodicarboxylate (10.5 g, 60.3 mmol) in dioxane (100 ml) was added to triphenylphosphine (15.8 g, 60.3 mmol), solved in dioxane (80 ml) at room temperature. The mixture was stirred for 15 min. *endo*-8-Methyl-8-aza-bicyclo[3.2.1]oct-6-ene-3-ol (7.0 g, 50.3 mmol) solved in dioxane (30 ml) was added to the mixture at 15°C followed by 7-hydroxycoumarine (9.0 g, 55.3 mmol). The temperature was raised to 30°C due to an exothermic reaction. The mixture was stirred at room temperature overnight followed by reflux for 4 h. Water (200 ml) and aqueous hydrochloric acid (15 ml, 4 M) was added and was washed with diethylether (3 x 50 ml). The aqueous phase was made alkaline by adding sodium hydroxide (50 ml, 4 M) followed by extraction with diethylether (3 x 100 ml). Yield 1.2 g (8%). The hydrochloric acid salt was prepared by adding a mixture of hydrochloric acid solved in ethanol. Mp >275°C. LC-ESI-HRMS of [M+H]⁺ shows 284.1275 Da. Calc. 284.128669 Da, dev. -4.1 ppm.

Method 4C***endo*-8-Methyl-8-aza-bicyclo[3.2.1]oct-6-ene-3-ol (intermediate)**

A mixture of zinc powder (10 g) and hydrochloric acid (10 ml, 1 M) was stirred for 1 minute and washed with hydrochloric acid (3 x 10 ml, 1 M) and water (5 x 10 ml)

- 5 followed by aqueous cupper sulphate (25 ml, 2%), water (5 x 10 ml), ethanol (10 ml, 96%) and diethylether (10 ml) followed by drying. The title compound was prepared from scopolamine hydrobromide trihydrate and zinc powder followed by hydrolysis by treatment with aqueous sodium hydroxide according to Tetrahedron Letters 42 (2001), p 1975.

10

Method 5***exo*-7-[(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yl)oxy]-3-bromo-chromen-2-one (intermediate)**

Bromine (1.38 ml, 27.0 mmol) was added to a mixture of *exo*-7-(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one (7.8 g, 21.0 mmol), acetic acid (150 ml) and sodium acetate (5.2 g, 63.0 mmol). The mixture was stirred for 90 min at room-temperature. Water (100 ml) was added. The precipitation was filtered and washed with water (10 ml), methanol (5 ml) and diethylether (20 ml). Yield 7.5 g (79%).

- 20 ***exo*-3-(3-Chloro-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl (intermediate)**

Was prepared according to method 5 from *exo*-7-(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one and chlorine (instead of bromine), solved in acetic acid.

25

***exo*-3-(3-Bromo-2-oxo-2*H*-chromen-6-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (intermediate)**

Was prepared according to method 5 from 3-(2-oxo-2*H*-chromen-6-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester.

30

***exo*-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one free base**

Was prepared according to method 5 from *exo*-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 364.0547 Da. Calc.

- 35 364.054832 Da, dev. -0.4 ppm.

2X

**exo-3-Chloro-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one
hydrochloric acid salt**

Was prepared according to method 5 from *exo*-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one and chlorine (instead of bromine), solved in acetic acid. LC-ESI-
5 HRMS of [M+H]⁺ shows 320.1068 Da. Calc. 320.105347 Da, dev. 4.5 ppm.

Test Example

In vitro inhibition activity

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

The test values are given as IC₅₀ (the concentration (μM) of the test substance which inhibits the specific binding of ³H-DA, ³H-NA, or ³H-5-HT by 50%).

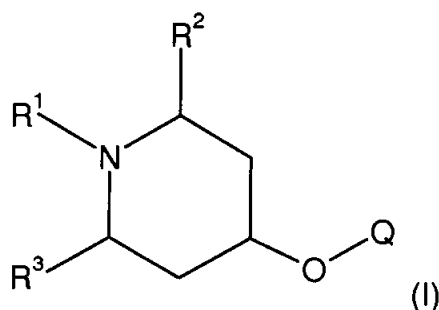
Test results obtained by testing selected compounds of the present invention
15 appear from the below table:

Table 1

Test compound	DA-uptake IC ₅₀ (μM)	NA-uptake IC ₅₀ (μM)	5-HT-uptake IC ₅₀ (μM)
<i>First compound of Method 2B:</i> <i>exo</i> -3-Bromo-7-(8-methyl-8-aza-bicyclo- [3.2.1]oct-3-yloxy)-chromen-2-one	0.044	0.017	0.0012
<i>Second last compound of Method 2B:</i> <i>exo</i> -7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3- chloro-chromen-2-one	0.054	0.014	0.00059
<i>First compound of Method 4B:</i> <i>exo</i> -7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6- en-3-yloxy)-chromen-2-one	0.70	0.72	0.036

CLAIMS

1. A compound of Formula I:



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

Q represents a chromen-2-one group;

- 10 which chromen-2-one 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;

R¹ represents hydrogen or alkyl;

- 15 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; and

- 20 R² and R³ together form $-(CH_2)-(CH_2)-$ or $-(CH)=(CH)-$.

2. The chemical compound of claim 1, wherein
R² and R³ together form $-(CH_2)-(CH_2)-$; and
R¹ is as defined in claim 1.

- 25 3. The chemical compound of claim 2, wherein
R¹ represents alkyl, alkenyl or alkoxyalkyl.

- 30 4. The chemical compound of claim 1, wherein
R² and R³ together form $-(CH)=(CH)-$; and
R¹ is as defined in claim 1.

5. The chemical compound of claim 4, wherein
R¹ represents hydrogen or alkyl.

6. The chemical compound of any one of claims 1-5, wherein
Q represents chromen-2-one-yl; which chromen-2-one-yl group is substituted in
the 3-position with a substituent selected from the group consisting of:
- 5 halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy,
cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.
7. The chemical compound of claim 1, which is
exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
10 *exo*-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-2-oxo-2*H*-chromene-3-carbonitrile;
exo-6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-bromo-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-chloro-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-4-methyl-2-oxo-2*H*-chromene-3-
carbonitrile;
15 *exo*-7-(8-Ethyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Isopropyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-[8-(2-Methoxy-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yloxy]-chromen-2-one;
exo-7-(8-Allyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-6-en-3-yl)oxy)-chromen-2-one;
20 *exo*-7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one;
exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-3-Chloro-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
or a pharmaceutically acceptable salt thereof.
- 25 8. A pharmaceutical composition, comprising a therapeutically effective amount of a
compound of any one of claims 1-7, 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.
- 30 9. Use of the chemical compound of any of claims 1-7, any of its isomers or any
mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the
manufacture of a medicament.
10. The use according to claim 9, for the manufacture of a pharmaceutical
35 pharmaceutical composition for the treatment, prevention or alleviation of a
disease or a disorder or a condition of a mammal, including a human, which
disease, disorder or condition is responsive to inhibition of monoamine
neurotransmitter re-uptake in the central nervous system.

11. The use according to claim 10, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, social anxiety disorder, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-mastectomy pain syndrome (PMPS), post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg syndrome, periodic limb movement disorder, eating disorders, anorexia nervosa, sleep disorders, pervasive developmental disorders, autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, learning disabilities, motor skills disorders, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, Gilles de la Tourettes disease, tinnitus, tic disorders, body dysmorphic disorders, oppositional defiant disorder or post-stroke disabilities.
12. 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

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such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-7, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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C07D A61K

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2006/035034 A (NEUROSEARCH AS [DK]; PETERS DAN [DK]; OLSEN GUNNAR M [DK]; SCHEEL-KRUE) 6 April 2006 (2006-04-06) the whole document	1-12
A	EP 1 130 020 A (NEUROSEARCH AS [DK]) 5 September 2001 (2001-09-05)	
A	WO 02/102801 A (NEUROSEARCH AS [DK]; GOULIAEV ALEX HAAHR [DK]; DAHL BJARNE H [DK]; PET) 27 December 2002 (2002-12-27)	

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

☒ See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2006035034	A	06-04-2006	NONE	
EP 1130020	A	05-09-2001	SI 885220 T1	31-12-2001
WO 02102801	A	27-12-2002	EP 1397358 A1	17-03-2004
			JP 2005508872 T	07-04-2005
			US 2004106643 A1	03-06-2004

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Declaraciones bajo la Regla 4.17:

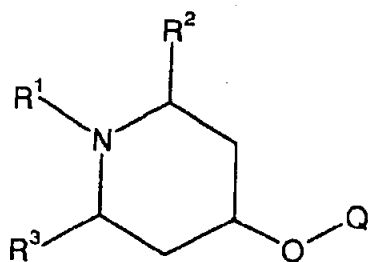
— en lo que respecta al derecho del solicitante de solicitar y de que se le otorgue una patente, (Regla 4.17(ii))

Publicado:

— con informe internacional de búsqueda

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

(54) Título: NOVEDOSOS DERIVADOS DE CROMEN-2-ONA Y SU USO COMO INHIBIDORES DE REABSORCIÓN DEL NEUROTRANSMISOR DE MONOAMINA



(I)

(57) Extracto: Esta invención se refiere a derivados novedosos de cromen-2-ona de fórmula (I), útiles como inhibidores de la reabsorción de neurotransmisor de monoamina. En otros aspectos la invención se refiere al uso de estos compuestos en un método de terapia y a composiciones farmacéuticas que contienen los compuestos de la invención de Fórmula (I), en donde Q representa un grupo cromen-2-ona; el cual grupo cromen-2-ona se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por: halo, trifluorometilo, trifluorometoxi, ciano, hidroxilo, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alquenoilo y alquinoilo; R¹ representa hidrógeno o alquilo; el cual alquilo se sustituye opcionalmente con ciano, hidroxilo, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alquenoilo y alquinoilo; y R² y R³ juntos forman -(CH₂)-(CH₂)- o -(CH)=(CH)-.

WO 2007/093604 A1

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**NOVEDOSOS DERIVADOS DE CROMEN-2-ONA Y SU USO
COMO INHIBIDORES DE REABSORCIÓN DEL
NEUROTRANSMISOR DE MONOAMINA**

CAMPO TÉCNICO

Esta invención se refiere a novedosos derivados de cromen-2-ona, útiles como inhibidores de reabsorción del neurotransmisor de monoamina.

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

ARTE PREVIO

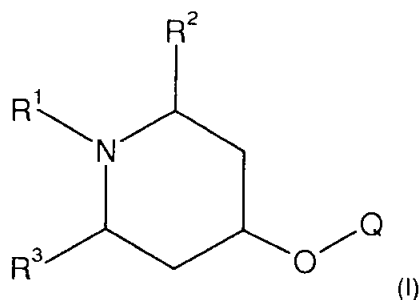
Los inhibidores selectivos de reabsorción de serotonina (SSRI, por sus siglas en inglés) ofrecen actualmente eficacia en el tratamiento de trastornos del sistema nervioso central SNC, incluidos depresión y trastorno de pánico. Generalmente los SSRI son considerados por psiquiatras y médicos generales ("*primary care physicians*") como efectivos, bien tolerados y de fácil administración. No obstante, se asocian con un número de características indeseables.

En consecuencia, existe aún una fuerte necesidad de compuestos con un perfil farmacológico optimizado en lo que respecta a la actividad sobre la reabsorción de los neurotransmisores de monoamina serotonina, dopamina y noradrenalina, tal como el índice de reabsorción de serotonina versus la actividad de reabsorción de noradrenalina y dopamina.

SUMARIO DE LA INVENCION

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

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cualquiera de sus isómeros, o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable,

en donde R^1 , R^2 , R^3 y Q son como se define a continuación.

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

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

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

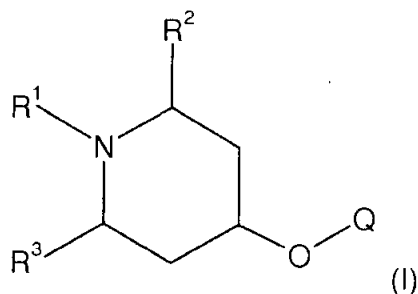
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Otros objetos de la invención serán evidentes a la persona experta en el arte a partir de la siguiente descripción detallada y los ejemplos.

DIVULGACIÓN DETALLADA DE LA INVENCION

Derivados de cromen-2-ona

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



cualquiera de sus isómeros o cualquier mezcla de sus isómeros,
o su sal farmacéuticamente aceptable,
en donde

Q representa un grupo cromen-2-ona;

el cual grupo cromen-2-ona se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por :

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

R¹ representa hidrógeno o alquilo;

el cual alquilo se sustituye opcionalmente con uno o más radicales seleccionados independientemente del grupo conformado por:

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

R² y R³ conjuntamente forman -(CH₂)-(CH₂)- o -(CH)=(CH)-.

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En una incorporación del compuesto de Fórmula I, R^2 y R^3 conjuntamente forman $-(CH_2)-(CH_2)-$; y R^1 es como se define anteriormente. En una incorporación especial, R^1 representa alquilo, alquenilo o alcoxialquilo. En una incorporación adicional, R^1 representa C_{2-6} -alquilo, alquenilo o alcoxialquilo. En todavía otra incorporación, R^1 representa C_{2-6} -alquilo, tal como etilo o propilo, en particular isopropilo. En una incorporación adicional, R^1 representa alquenilo, tal como alilo. En todavía otra incorporación, R^1 representa alcoxialquilo, tal como alcoxietilo, en particular metoxietilo. En una incorporación adicional, R^1 representa hidrógeno. En todavía otra incorporación, R^1 representa alquilo, tal como metilo.

En una incorporación adicional del compuesto de Fórmula I, R^2 y R^3 conjuntamente forman $-(CH)=(CH)-$; y R^1 es como se define en la reivindicación 1. En una reivindicación especial, R^1 representa hidrógeno o alquilo. En una incorporación adicional, R^1 representa hidrógeno. En todavía otra incorporación, R^1 representa alquilo, tal como metilo.

En una incorporación adicional del compuesto de Fórmula I, Q representa cromen-2-on-ilo. En una reivindicación especial del compuesto de Fórmula I, Q representa cromen-2-on-7-ilo. En una reivindicación especial del compuesto de Fórmula I, Q representa cromen-2-on-6-ilo.

En todavía otra incorporación del compuesto de Fórmula I, Q representa cromen-2-on-ilo sustituido, tal como cromen-2-on-ilo halo, ciano o alquilo sustituido. En una reivindicación especial del compuesto de Fórmula I, Q representa cromen-2-on-7-ilo sustituido, tal como cromen-2-on-7-ilo halo, ciano o alquilo sustituido. En una reivindicación especial del compuesto de Fórmula I, Q representa cromen-2-on-6-ilo sustituido, tal como cromen-2-on-6-ilo; halo, ciano o alquilo sustituido.

En una incorporación adicional, Q representa cromen-2-on-ilo; el cual grupo cromen-2-on-ilo se sustituye en la posición 3 con un radical seleccionado del grupo conformado por: halo, trifluorometilo, trifluorometoxi, ciano, hidroxilo, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alquenilo y alquinilo.

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En todavía otra incorporación especial, Q representa 3-halo-cromen-2-on-ilo, tal como 3-halo-cromen-2-on-6-ilo o 3-halo-cromen-2-on-7-ilo, En una reivindicación especial, Q representa 3-bromo-cromen-2-on-6-ilo, 3-bromo-cromen-2-on-7-ilo, 3-cloro-cromen-2-on-6-ilo o 3-cloro-cromen-2-on-7-ilo.

En otra incorporación especial, Q representa 3-ciano-cromen-2-on-ilo, tal como 3-ciano-cromen-2-on-6-ilo o 3-ciano-cromen-2-on-7-ilo.

En otra incorporación especial, Q representa alquil-ciano-cromen-2-on-ilo, tal como metil-ciano-cromen-2-on-ilo, tal como 4-metil-3-ciano-cromen-2-on-ilo. En una incorporación especial, Q representa 4-metil-3-ciano-cromen-2-on-6-ilo o 4-metil-3-ciano-cromen-2-on-7-ilo.

En una reivindicación especial el compuesto químico de la invención es

exo-3-Bromo-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-2-oxo-2*H*-cromen-3-carbonitrilo;
exo-6-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-3-bromo-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-3-cloro-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-4-metil-2-oxo-2*H*-cromen-3-carbonitrilo;
exo-7-(8-Etil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-(8-Isopropil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-[8-(2-Metoxi-etil)-8-aza-biciclo[3.2.1]oct-3-iloxi]-cromen-2-ona;
exo-7-(8-Allyl-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-6-en-3-iloxi)-cromen-2-ona;
exo-7-(8-Metil-8-aza-biciclo[3.2.1]oct-6-en-3-iloxi)-cromen-2-ona;
exo-3-Bromo-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-3-Cloro-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
o su sal farmacéuticamente aceptable.

Cualquier combinación de dos o más de las incorporaciones, como se describen anteriormente, se considera dentro del ámbito de la presente invención.

Definición de Radicales

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

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

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

En el contexto de esta invención un grupo cicloalquilo designa un grupo alquilo cíclico, que contiene preferiblemente desde tres a siete

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átomos de carbono (C_{3-7} -cicloalquilo), incluidos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

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

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

Cicloalquilalquilo significa cicloalquilo y alquilo como ya se anotó, significando por ejemplo, ciclopropilmetilo. Amino es NH_2 o NH -alquilo o N -(alquilo)₂, en donde alquilo es como se define anteriormente.

Sales Farmacéuticamente Aceptables

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

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

Otros ácidos, tales como ácido oxálico, que puedan no considerarse farmacéuticamente aceptables, pueden ser útiles en la preparación de sales útiles como intermedios para obtener un compuesto químico de la invención y su sal de ácido farmacéuticamente aceptable.

Ejemplos de sales catiónicas farmacéuticamente aceptables de un compuesto químico de la invención incluyen, sin limitación, la sal de sodio, potasio, calcio, magnesio, zinc, aluminio, litio, colina, lisinio, y amonio y

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similares, de un compuesto químico de la invención que contiene un grupo aniónico. Tales sales catiónicas pueden formarse por procedimientos bien conocidos y descritos en el arte.

En el contexto de esta invención las "sales de onio" de compuestos con contenido de N se contemplan igualmente como sales farmacéuticamente aceptables. "Sales de onio" preferidas incluyen las sales de alquil-onio, las sales de cicloalquil-onio y las sales de cicloalquilalquil-onio.

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

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

Isómeros Estéricos

Se observará por los expertos en el arte que los compuestos de la presente invención pueden existir en diferentes formas estereoisoméricas – incluidos enantiómeros, diastereómeros y cis-trans-isómeros.

Por ejemplo, el grupo O-Q de Fórmula I puede estar en particular en la configuración *exo* o *endo* relativa al anillo azabíclico.

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

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Las formas racémicas pueden resolverse en los antípodas ópticos por métodos y técnicas conocidos. Una forma de separar las sales isoméricas es mediante el empleo de un ácido ópticamente activo y liberar el compuesto amina ópticamente activo por tratamiento con una base. Otro método para resolver racematos en los antípodas ópticos se basa cromatografía en una matriz ópticamente activa. En consecuencia, compuestos racémicos de la presente invención pueden resolverse en sus antípodas ópticos, por ejemplo, por cristalización fraccionaria de sales d- o l- (tartratos, mandelatos, o alcanforsulfonato).

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

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

Compuestos ópticamente activos pueden prepararse además de materiales de partida o intermedios ópticamente activos.

Compuestos Marcados

Los compuestos de la invención pueden usarse en su forma marcada o no marcada. En el contexto de esta invención el compuesto marcado tiene uno o más átomos reemplazados por un átomo con una masa atómica o número de masa diferentes de la masa atómica o número de masa hallados usualmente en la naturaleza. La marcación permitirá una fácil cuantificación del compuesto citado.

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

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

El método físico para detectar el isómero marcado de la presente invención puede seleccionarse de tomografía de emisión de positrones (PET), tomografía computarizada de emisión de fotón (SPECT), resonancia magnética espectroscópica (MRS), imagen de resonancia magnética (MRI), y tomografía axial computarizada (CAT), o sus combinaciones.

Métodos de Preparación

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

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

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

Actividad Biológica

Los compuestos de la invención pueden examinarse con respecto a su capacidad de inhibir la reabsorción de las monoaminas dopamina, noradrenalina y serotonina en sinaptosomas, por ejemplo, como se describe

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en WO 97/30997 (NeuroSearch A/S). Basándose en la actividad balanceada observada en estos exámenes, el compuesto de la invención se considera útil para el tratamiento, prevención o alivio de una enfermedad o trastorno o afección de un mamífero, incluido un humano, enfermedad, trastorno o afección que es sensible a la inhibición de la reabsorción de un neurotransmisor de monoamina en el sistema nervioso central.

En una reivindicación especial, los compuestos de la invención se consideran útiles para el tratamiento, prevención o alivio de: trastorno del estado de ánimo, depresión, depresión atípica, depresión secundaria a 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 humor inducido por sustancias, seudodemencia, síndrome de Ganser, trastorno obsesivo compulsivo, trastorno de pánico, trastorno de pánico sin agorafobia, trastorno de pánico con agorafobia, agorafobia sin historia de trastorno de pánico, ataque de pánico, déficits de memoria, pérdida de memoria, trastorno de déficit de atención e hiperactividad, obesidad, ansiedad, trastorno de ansiedad generalizada, trastorno del comportamiento alimentario, enfermedad de Parkinson, parkinsonismo, demencia, demencia del envejecimiento, demencia senil, enfermedad de Alzheimer, complejo demencia-síndrome de inmunodeficiencia adquirida, disfunción de la memoria en el envejecimiento, fobia específica, fobia social, trastorno de ansiedad social, trastorno de estrés pos-traumático, trastorno de estrés agudo, drogadicción, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso del tabaco, adicción al alcohol, alcoholismo, cleptomanía, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor de migraña, cefalea tipo tensión, cefalea crónica tipo tensión, dolor asociado con depresión, fibromialgia, artritis, osteoartritis, artritis reumatoide, lumbalgia, dolor por cáncer, dolor de intestino irritable, síndrome de intestino irritable, dolor pos-operatorio, síndrome de dolor pos-mastectomía (PMPS), dolor pos-apoplejía, neuropatía inducida por drogas, neuropatía diabética, dolor mantenido simpáticamente, neuralgia del trigémino, dolor de muelas, dolor

miofacial, el dolor de miembro fantasma pos-amputación, bulimia, síndrome premenstrual, trastorno disfórico premenstrual, síndrome de fase lútea tardía, síndrome pos-traumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia imperiosa, incontinencia nocturna, disfunción sexual, eyaculación precoz, dificultad eréctil, disfunción eréctil, orgasmo precoz femenino, síndrome de las piernas inquietas, trastorno de movimiento periódico de los miembros, trastornos en el comportamiento alimentario, anorexia nerviosa, trastornos del sueño, trastornos generalizados del desarrollo, autismo, trastorno de Asperger, trastorno de Rett, trastorno desintegrativo de la niñez, limitaciones o trastornos de aprendizaje, trastornos de habilidades motoras, autismo, tricotilomanía, narcolepsia, depresión pos-apoplejía, lesión cerebral inducida por apoplejía, lesión neuronal inducida por apoplejía, enfermedad de Gilles de la Tourette, zumbido en los oídos, trastornos de contracciones nerviosas, trastornos dismórficos corporales, trastorno de oposición desafiante o incapacidades pos-apoplejía. En una incorporación preferida, los compuestos se consideran útiles para el tratamiento, prevención o alivio de depresión.

Se contempla en la actualidad que una posología apropiada del ingrediente farmacéutico activo (API, por sus siglas en inglés) está en el rango de desde alrededor de 0.1 a alrededor de 1000 mg API al día, más preferiblemente de desde alrededor de 10 a alrededor de 500 mg API al día, muy preferiblemente de desde alrededor de 30 a alrededor de 100 mg API al día, dependiendo, sin embargo, del modo exacto de administración, la forma en que se administra, la indicación considerada, el sujeto y, en particular, el peso corporal del sujeto involucrado y, además, la preferencia y experiencia del médico o veterinario encargado. Compuestos preferidos de la invención muestran actividad biológica en el rango sub-micromolar y micromolar, es decir, desde menos de 1 a alrededor de 100 μM .

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Composiciones Farmacéuticas

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

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

En una incorporación preferida, la invención provee composiciones farmacéuticas que contienen el compuesto químico de la invención, o su sal o derivado farmacéuticamente aceptable, junto con una o más sustancias portadoras farmacéuticamente aceptables y, opcionalmente, otros ingredientes terapéuticos y/o profilácticos, conocidos y usados en el arte. La sustancia(s) portadora(s) tiene que ser "aceptable" en el sentido de ser compatible con los otros ingredientes de la formulación y no nocivos para su receptor.

Composiciones farmacéuticas de la invención pueden ser las apropiadas para administración oral, rectal, bronquial, nasal, pulmonar, tópica (incluida bucal y sub-lingual), transdérmica, vaginal o parenteral (incluida inyección o infusión cutánea, subcutánea, intramuscular, intraperitoneal, intravenosa, intra-arterial, intracerebral, intraocular), o las en una forma apropiada para administración por inhalación o insuflación, incluida administración de polvos y aerosoles líquidos, o mediante sistemas de liberación sostenida. Ejemplos apropiados de sistemas de liberación sostenida incluyen matrices semipermeables de polímeros hidrófobos sólidos que contienen el compuesto de la invención, las cuales matrices pueden estar en forma de artículos moldeados, por ejemplo, películas o microcápsulas.

Por lo tanto, el compuesto químico de la invención, junto con un coadyuvante, sustancia portadora, o diluyente convencional, puede ponerse

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en la forma de composiciones farmacéuticas y sus posologías unitarias. Tales formas incluyen sólidos y, en particular, tabletas, cápsulas rellenas, formas en polvo y gránulos, y líquidos, en particular soluciones acuosas y no acuosas, suspensiones, emulsiones, elixires, y cápsulas rellenas con las mismas, todas para uso oral, supositorios para administración rectal, y soluciones inyectables estériles para uso parenteral. Tales composiciones farmacéuticas y sus presentaciones farmacéuticas unitarias pueden incluir ingredientes convencionales en proporciones convencionales, con o sin compuestos o principios activos adicionales, y tales formas farmacéuticas unitarias pueden contener cualquier cantidad efectiva apropiada del ingrediente activo en proporción con el rango posológico diario previsto que se va a emplear.

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

Para preparar composiciones farmacéuticas de un compuesto químico de la presente invención, sustancias portadoras farmacéuticamente aceptables pueden ser sólidas o líquidas. Las preparaciones de forma sólida incluyen polvos, tabletas, píldoras, cápsulas, cápsulas amiláceas, supositorios y gránulos dispersables. Una sustancia portadora sólida puede ser una o más sustancias, que pueden actuar también como diluyentes, agentes saborizantes, solubilizantes, lubricantes, agentes de suspensión, aglutinantes, preservantes, agentes desagregantes de tabletas, o un material encapsulante.

En polvos, la sustancia portadora es un sólido finamente dividido, que es una mezcla con el componente activo finamente dividido.

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

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Los polvos y tabletas contienen preferiblemente desde cinco o diez a alrededor de setenta por ciento del compuesto activo. Sustancias portadoras apropiadas son carbonato de magnesio, estearato de magnesio, talco, azúcar, lactosa, pectina, dextrina, almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa sódica, una cera con bajo punto de fusión, manteca de cacao y similares. El término "preparación" tiene como finalidad incluir la formulación del compuesto activo con material encapsulante como sustancia portadora, proveyendo una cápsula en la cual el componente activo, con o sin sustancias portadoras, se rodea por una sustancia portadora, la cual está así en asociación con él. Análogamente, se incluyen cápsulas amiláceas y pastillas para chupar. Tabletas, polvos, cápsulas, píldoras, cápsulas amiláceas y pastillas para chupar pueden usarse como formas sólidas apropiadas para administración oral.

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

Composiciones apropiadas para administración vaginal pueden presentarse como dispositivos intrauterinos, tampones, cremas, geles, pastas, espumas o atomizadores que contienen, además del ingrediente activo, aquellas sustancias portadoras conocidas en el arte por ser apropiadas.

Las preparaciones líquidas incluyen soluciones, suspensiones y emulsiones, por ejemplo, agua o soluciones de propilén glicol-agua. Por ejemplo, preparaciones líquidas para inyección parenteral pueden formularse como soluciones en solución acuosa de polietilén glicol.

Por lo tanto, el compuesto químico de acuerdo con la presente invención puede formularse para administración parenteral (por ejemplo, mediante inyección, por ejemplo inyección intravenosa rápida o infusión continua) y puede presentarse en forma farmacéutica unitaria en ampollas,

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jeringas precargadas, infusión de pequeño volumen o envases de dosis múltiples con un preservante agregado. Las composiciones pueden adoptar formas tales como suspensiones, soluciones, o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizantes y/o dispersantes. Alternativamente, el ingrediente activo puede estar en la forma de polvo, obtenido por aislamiento aséptico de un sólido estéril o por liofilización de una solución, para constitución con un vehículo apropiado, por ejemplo, agua libre de pirógenos, estéril, antes del empleo.

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

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

También se incluyen preparaciones en forma sólida, previstas para conversión antes del empleo en preparaciones en forma líquida para administración oral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones. Además del componente activo tales preparaciones pueden contener colorantes, saborizantes, estabilizantes, soluciones amortiguadoras, edulcorantes naturales y artificiales, dispersantes, espesantes, agentes solubilizantes y similares.

Para administración tópica a la epidermis el compuesto químico de la invención puede formularse como ungüentos, cremas o lociones, o como un parche transdérmico. Los ungüentos y cremas, por ejemplo, pueden formularse con una base acuosa y oleosa con la adición de agentes espesantes y/o gelatinizantes. Las lociones pueden formularse con una base acuosa u oleosa y, generalmente, contendrán uno o más agentes emulsionantes, agentes estabilizantes, agentes dispersantes, agentes de suspensión, agentes espesantes, o agentes colorantes.

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Composiciones apropiadas para administración tópica en la boca incluyen pastillas para chupar, que contienen el ingrediente activo en una base saborizada, usualmente sacarosa y acacia o tragacanto; pastillas que contienen el ingrediente activo en una base inerte tal como gelatina y glicerina o sacarosa y acacia; y lavados bucales que contienen el ingrediente activo en una sustancia portadora líquida apropiada.

Soluciones o suspensiones se aplican directamente a la cavidad nasal por medios convencionales, por ejemplo con un gotero, pipeta o atomizador. Las composiciones pueden proveerse en dosis única o dosis múltiples.

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

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

En composiciones previstas para administración al tracto respiratorio, incluidas composiciones intranasales, el compuesto tendrá generalmente un pequeño tamaño de partícula por ejemplo del orden de 5 micrones o menos. Tal tamaño de partícula puede obtenerse por medios conocidos en el arte, por ejemplo mediante micronización.

Cuando se desea, pueden emplearse las composiciones adaptadas para proporcionar una liberación sostenida del ingrediente activo.

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

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

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

Una dosis terapéuticamente efectiva se refiere a la cantidad de ingrediente activo, que mejora los síntomas o la afección. La eficacia terapéutica y la toxicidad, a saber, ED_{50} y LD_{50} , pueden determinarse mediante procedimientos farmacológicos estándar en cultivos de células o animales experimentales. La relación de dosis entre efectos terapéuticos y tóxicos es el índice terapéutico y puede expresarse por la relación LD_{50}/ED_{50} . Se prefieren composiciones farmacéuticas que exhiben índices terapéuticos elevados.

Por supuesto la dosis administrada tiene que ajustarse cuidadosamente a la edad, peso y estado del individuo que se está tratando, así como la vía de administración, presentación y régimen farmacéuticos, y el resultado deseado, y la posología exacta debe determinarse lógicamente por el facultativo.

La posología efectiva depende de la naturaleza y gravedad de la enfermedad que se está tratando, y queda a discreción del médico, y puede

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variarse mediante titulación de la posología a las circunstancias particulares de esta invención para producir el efecto terapéutico deseado. No obstante, se contempla actualmente que composiciones farmacéuticas que contienen de desde alrededor de 0.1 a alrededor de 500 mg de ingrediente activo por dosis individual, preferiblemente de desde alrededor de 1 a alrededor de 100 mg, muy preferiblemente de desde alrededor de 1 a alrededor de 10 mg, son apropiadas para tratamientos terapéuticos.

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

Métodos de Terapia

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

Actualmente se contempla que rangos posológicos apropiados son 0.1 a 1000 miligramos diariamente, 10-500 miligramos diariamente y, especialmente 30-100 miligramos diariamente, dependiendo, como es habitual, del modo exacto de administración, la forma en que se administra, la indicación a la cual se dirige la administración, el sujeto involucrado y el peso corporal del sujeto involucrado y, además, la preferencia y experiencia del médico o veterinario encargado.

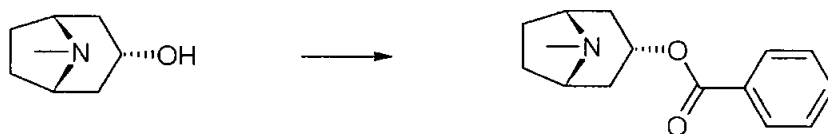
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EJEMPLOS

La invención se ilustra además con referencia a los siguientes ejemplos, que no pretenden en ningún modo limitar el ámbito de la invención como se reivindica.

Ejemplos de Preparación

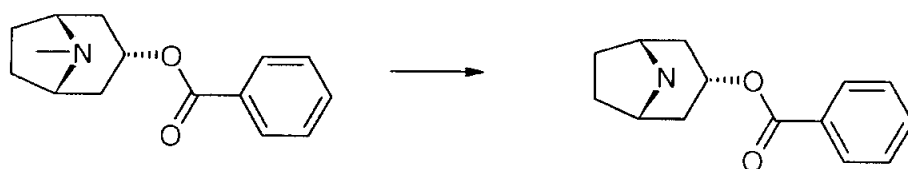
Todas las reacciones que implican reactivos o intermedios sensibles al aire se llevaron a cabo bajo nitrógeno y en disolventes anhidros. Se utilizó sulfato de magnesio como agente desecante en los procedimientos de las reacciones adicionales llevadas a cabo después de la reacción química principal para obtener el producto principal ("*workup-procedures*") y los disolventes se evaporaron bajo presión reducida.



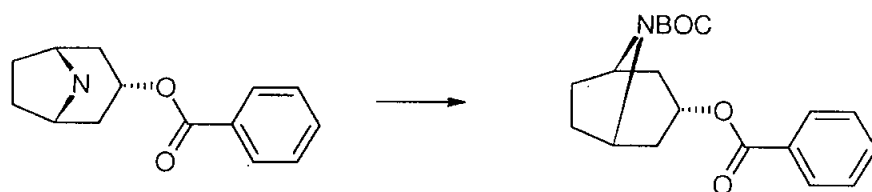
8-Metil-8-aza-biciclo[3.2.1]oct-3-il éster de ácido *endo*-benzoico

Cloruro de benzoilo (84.3 g, 600 mmol) se agregó durante 30 minutos a <30 °C a una mezcla de tropina (70.6 g, 500 mmol), *terc*-butóxido de potasio (67.3 g, 600 mmol) y THF (500 ml). La mezcla se agitó a temperatura de la sala durante 2 horas. Se agregó agua (1 L) seguida por extracción con éter dietílico (2 x 500 ml). La fase orgánica se lavó dos veces con agua (2 x 200 ml) seguida por una solución de cloruro de sodio acuoso saturado (200 ml). La otra fase éter se secó y se agregó ácido clorhídrico en etanol (170 ml, 3 M). El clorhidrato precipitado se filtró y se lavó con éter dietílico. La base libre se obtuvo agregando un exceso de amoníaco acuoso seguido por extracción con una mezcla de acetato de etilo y éter dietílico. Rendimiento 66.8 g (54%).

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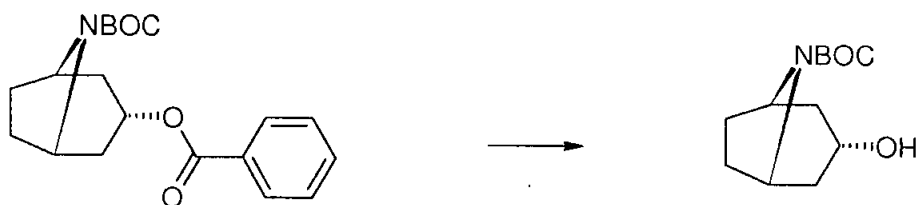
**8-Aza-biciclo[3.2.1]oct-3-il éster de ácido *endo*-benzoico**

2,2,2-Tricloroetilcloroformiato (75.0 ml, 544 mmol) se agregó gota a gota a una mezcla de 8-metil-8-aza-biciclo[3.2.1]oct-3-il éster de ácido *endo*-benzoico (66.8 g, 272 mmol) y tolueno seco (500 ml). La mezcla se dejó agitar durante 1 hora a temperatura de la sala, seguida por 15 horas a 100°C. Se agregó agua (250 ml) seguida por agitación durante 1 hora. Las fases se separaron y la fase orgánica se lavó dos veces con agua (2 x 200 ml). La mezcla del intermedio triclorometil éster de ácido 3-benzoiloxi-8-aza-biciclo[3.2.1]octan-8-carboxílico se secó y se evaporó. Se agregó ácido acético (350 ml) seguido por la adición de zinc (53.4 g, 817 mmol) durante un período de 3 horas. Se agregó agua (100 ml), se enfrió agregando hielo y se hizo alcalino agregando amoníaco acuoso concentrado (aproximadamente: 400 ml) y la mezcla se extrajo con diclorometano (2 X 300 ml). Rendimiento 44.5 g (61 %).

***tert*-Butil éster de ácido *endo*-3-benzoiloxi-8-aza-biciclo[3.2.1]octan-8-carboxílico**

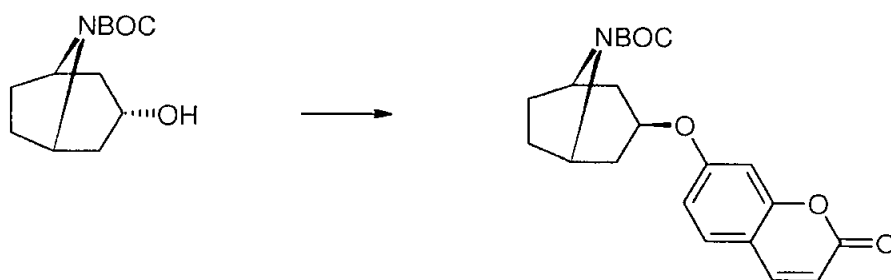
Di-*tert*-butil-dicarbonato (39.9 g, 183 mmol) disuelto en THF (100 ml) se agregó a una mezcla agitada de 8-aza-biciclo[3.2.1]oct-3-il éster de ácido *endo*-benzoico (44.5 g, 166.4 mmol), trietilamina (67.4 g, 666 mmol) y THF (250 ml) durante 0.5 hora a temperatura de la sala, seguida por agitación durante 1 hora. Se agregó agua (1 L) y la mezcla se extrajo con éter dietílico (2 x 300 ml). La fase éter recogida se lavó dos veces con agua (2 x 200 ml), se secó y se evaporó. Rendimiento 60.1 g (100%).

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***tert*-Butil éster de ácido *endo*-3-hidroxi-8-aza-biciclo[3.2.1]octan-8-carboxílico**

Una mezcla de *tert*-butil éster de ácido *endo*-3-benzoiloxi-8-aza-biciclo[3.2.1]octan-8-carboxílico (55.0 g, 166 mmol), hidróxido de potasio (11.2 g 199 mmol) y etanol (99%, 400 ml) se agitó durante 3 días a temperatura de la sala. Se separó benzoato de potasio por filtración y el filtrado se evaporó. Se agregó éter dietílico (200 ml) y el benzoato de potasio restante se separó por filtración y el filtrado se evaporó. El producto se trituyó con petróleo. Rendimiento 30.0 g (80%). Mp 139.5- 140.8°C.



Método 1

***exo*-7-(8-*tert*-Butoxicarbonil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona**

Trifenilfosfina (7.5 g, 28.6 mmol) se disolvió en dioxano (70 ml) y se enfrió a 8°C. Se agregó dietilazodicarboxilato (5.0 g, 28.6 mmol) a la mezcla por debajo de 15°C, seguido por agitación durante 15 minutos. *tert*-Butil éster de ácido *endo*-3-hidroxi-8-aza-biciclo[3.2.1]octan-8-carboxílico (5.0 g, 22.0 mmol) y 7-hidroxycumarina (4.3 g, 26.4 mmol) se agregaron a la mezcla. La temperatura se elevó debido a una reacción exotérmica. La mezcla se dejó agitar durante 15 horas a temperatura de la sala. Se agregó agua (200 ml) seguida por extracción con éter dietílico (2 x 100 ml). La mezcla se secó y se evaporó. Cromatografía en gel de sílice con diclorometano y 5% metanol como disolvente. El producto crudo se disolvió en éter dietílico (200 ml) y

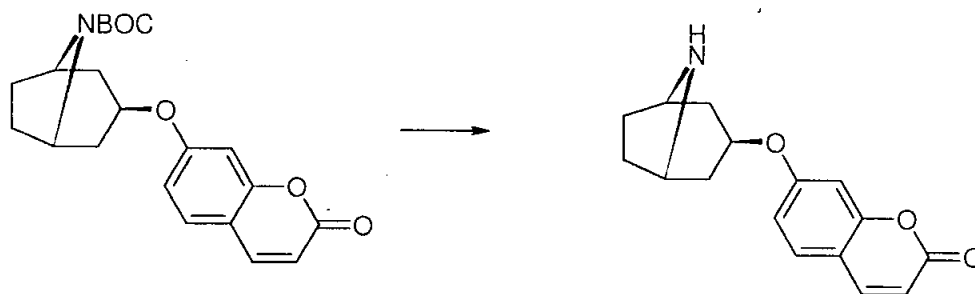
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se lavó con hidróxido de sodio acuoso (3 x 200 ml, 1 M). El producto se secó y se evaporó. Rendimiento 5.32 g (65%).

***tert*-Butil éster de ácido *exo*-3-(3-ciano-2-oxo-2*H*-cromen-7-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico (intermedio)**

Se preparó de acuerdo con método 1 de 7-hidroxi-2-oxo-2*H*-cromen-3-carbonitrilo y *tert*-butil éster de ácido *endo*-3-hidroxi-8-aza-biciclo[3.2.1]octan-8-carboxílico.

Método 2A



Sal de ácido clorhídrico de *exo*-7-(8-*H*-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona

Una mezcla de *exo*-7-(8-*tert*-butoxicarbonil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona (0.60 g, 1.6 mmol) y ácido clorhídrico (10 ml, 1 M) en ácido acético (10 ml) se agitó durante 1 hora. Se agregó éter dietílico (50 ml) y el precipitado se filtró y se lavó con éter dietílico (10 ml). Rendimiento 0.28 g (57%). Mp > 300°C.

Método 2B

Sal de ácido clorhídrico de *exo*-3-bromo-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona

Una mezcla de *exo*-7-[(8-*tert*-butoxicarbonil-8-aza-biciclo[3.2.1]oct-3-il)oxi]-3-bromo-cromen-2-ona (30 g, 65.3 mmol) y cloruro de hidrógeno en ácido acético (500 ml, 1 M) se agitó a temperatura de la sala durante 3 horas. Se agregó éter dietílico (500 ml), la precipitación se agitó y se aisló

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mediante filtración. Rendimiento 25 g (99%). LC-ESI-HRMS de $[M+H]^+$ muestra 350.0405 Da. Calc. 350.039182 Da, dev. 3.8 ppm.

Sal de ácido clorhídrico de *exo*-7-(8-aza-biciclo[3.2.1]oct-3-iloxi)-2-oxo-2*H*-cromen-3-carbonitrilo

Se preparó de *tert*-butil éster de ácido *exo*-3-(3-ciano-2-oxo-2*H*-cromen-7-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico de acuerdo con el método 2B. LC-ESI- HRMS de $[M+H]^+$ muestra 297.1238 Da. Calc. 297.123918 Da, dev. -0.4 ppm.

Sal de ácido clorhídrico de *exo*-6-(8-aza-biciclo[3.2.1]oct-3-iloxi)-3-bromo-cromen-2-ona

Se preparó de *tert*-butil éster de ácido *exo*-3-(3-bromo-2-oxo-2*H*-cromen-6-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico de acuerdo con método 2B. LC-ESI-HRMS de $[M+H]^+$ muestra 350.0379 Da. Calc. 350.039182 Da, dev. -3.7 ppm.

Sal de ácido clorhídrico de *exo*-7-(8-aza-biciclo[3.2.1]oct-3-iloxi)-3-cloro-cromen-2-ona

Se preparó de *tert*-butil éster de ácido *exo*-3-(3-cloro-2-oxo-2*H*-cromen-7-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico de acuerdo con método 2B. LC-ESI- HRMS de $[M+H]^+$ muestra 306.0894 Da. Calc. 306.089697 Da, dev. -1 ppm.

Sal de ácido clorhídrico de *exo*-7-(8-aza-biciclo[3.2.1]oct-3-iloxi)-4-metil-2-oxo-2*H*-cromen-3-carbonitrilo

Se preparó de *tert*-butil éster de ácido *exo*-3-(3-ciano-4-metil-2-oxo-2*H*-cromen-7-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico de acuerdo con método 2B. LC-ESI-HRMS de $[M+H]^+$ muestra 311.1401 Da. Calc. 311.139568 Da, dev. 1.7 ppm.

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Método 3**Sal de ácido clorhídrico de *exo*-7-(8-etil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona**

Una mezcla de *exo*-7-(8-*H*-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona (3.1 g, 10.1 mmol), hidruro de sodio, 60% en aceite mineral (0.29 g 12.1 mmol), yodoetano (2.46 g, 15.8 mmol) y tetrahidrofurano (75 ml) se agitó a 60°C durante 3 horas. El clorhidrato se precipitó agregando etanol (75 ml) y ácido clorhídrico concentrado (1 ml). El producto cristalino se recrystalizó de etanol (100 ml, 96%). Rendimiento 1.71 g (51%). LC-ESI-HRMS de [M+H]⁺ muestra 300.1596 Da. Calc. 300.159969 Da, dev. -1.2 ppm.

Sal de ácido clorhídrico de *exo*-7-(8-isopropil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona

Se preparó de acuerdo con método 1A de *exo*-7-(8-*H*-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona. LC-ESI-HRMS de [M+H]⁺ muestra 314.1746 Da. Calc. 314.175619 Da, dev. -3.2 ppm.

Sal de ácido clorhídrico de *exo*-7-[8-(2-metoxi-etil)-8-aza-biciclo[3.2.1]oct-3-iloxi]-cromen-2-ona

Se preparó de acuerdo con método 1A de *exo*-7-(8-*H*-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona. LC-ESI-HRMS de [M+H]⁺ muestra 330.1691 Da. Calc. 330.170534 Da, dev. -4.3 ppm.

Sal de ácido clorhídrico de *exo*-7-(8-alil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona

Se preparó de acuerdo con método 1A de *exo*-7-(8-*H*-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona. LC-ESI-HRMS de [M+H]⁺ muestra 312.1584 Da. Calc. 312.159969 Da, dev. -5 ppm.

Método 4A**Sal de ácido clorhídrico de *exo*-7-(8-aza-biciclo[3.2.1]oct-6-en-3-il)oxi)-cromen-2-ona**

2,2,2-Tricloroetil cloroformiato (3.7 g, 17.6 mmol) se agregó a una mezcla de *exo*-7-(8-metil-8-aza-biciclo[3.2.1]oct-6-en-3-iloxi)-cromen-2-ona (1.0 g, 3.5 mmol) y tolueno (20 ml). La mezcla se agitó durante 30 minutos a temperatura de la sala, seguida por 15 horas a 100°C. Se agregó agua (10 ml) y la fase orgánica se separó y se lavó con agua (2 x 25 ml). La mezcla cruda obtenida por evaporación se disolvió en ácido acético (10 ml) y agua (10 ml). Se agregó polvo de zinc (2.3 g, 35.3 mmol) a la mezcla en porciones agitando durante 5 horas. Se agregó agua helada (20 ml) seguida por amoníaco acuoso concentrado (20 ml). La mezcla se extrajo con diclorometano (2 x 20 ml). La sal de ácido clorhídrico se precipitó agregando ácido clorhídrico disuelto en etanol a la base libre disuelta en éter dietílico. Rendimiento 70 mg (5%). Mp >280°C (dec). LC-ESI-HRMS de [M+H]⁺ muestra 270.1117 Da. Calc. 270.113019 Da, dev. -4.9 ppm.

Método 4B**Sal de ácido clorhídrico de *exo*-7-(8-metil-8-aza-biciclo[3.2.1]oct-6-en-3-iloxi)-cromen-2-ona**

Una mezcla de dietilazodicarboxilato (10.5 g, 60.3 mmol) en dioxano (100 ml) se agregó a trifenilfosfina (15.8 g, 60.3 mmol), disuelta en dioxano (80 ml) a temperatura de la sala. La mezcla se agitó durante 15 minutos. *endo*-8-Metil-8-aza-biciclo[3.2.1]-oct-6-en-3-ol (7.0 g, 50.3 mmol) disuelto en dioxano (30 ml) se agregó a la mezcla a 15°C, seguido por 7-hidroxycumarina (9.0 g, 55.3 mmol). La temperatura se elevó a 30°C debido a una reacción exotérmica. La mezcla se agitó a temperatura de la sala de un día para otro, seguida por reflujo durante 4 horas. Se agregaron agua (200 ml) y ácido clorhídrico acuoso (15 ml, 4 M) y se lavó con éter dietílico (3 x 50 ml). La fase acuosa se hizo alcalina agregando hidróxido de sodio (50 ml, 4 M), seguido por extracción con éter dietílico (3 x 100 ml). Rendimiento 1.2 g (8%). La sal de ácido clorhídrico se preparó agregando

una mezcla de ácido clorhídrico disuelto en etanol. Mp >275°C. LC-ESI-HRMS de [M+H]⁺ muestra 284.1275 Da. Calc. 284.128669 Da, dev. -4.1 ppm.

Método 4C

***endo*-8-Metil-8-aza-biciclo[3.2.1]oct-6-en-3-ol** (intermedio)

Una mezcla de polvo de zinc (10 g) y ácido clorhídrico (10 ml, 1 M) se agitó durante 1 minuto y se lavó con ácido clorhídrico (3 x 10 ml, 1 M) y agua (5 x 10 ml), seguida por sulfato de cobre acuoso (25 ml, 2%), agua (5 x 10 ml), etanol (10 ml, 96%) y éter dietílico (10 ml), seguido por secamiento. El compuesto del título se preparó de trihidrato de hidrobromuro de escopolamina y polvo de zinc, seguido por hidrólisis mediante tratamiento con hidróxido de sodio acuoso de acuerdo con Tetrahedron Letters 42 (2001), p. 1975.

Método 5

***exo*-7-[(8-*terc*-Butoxicarbonil-8-aza-biciclo[3.2.1]oct-3-il)oxi]-3-bromocromen-2-ona** (intermedio)

Bromo (1.38 ml, 27.0 mmol) se agregó a una mezcla de *exo*-7-(8-*terc*-butoxicarbonil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona (7.8 g, 21.0 mmol), ácido acético (150 ml) y acetato de sodio (5.2 g, 63.0 mmol). La mezcla se agitó durante 90 minutos a temperatura de la sala. Se agregó agua (100 ml). La precipitación se filtró y se lavó con agua (10 ml), metanol (5 ml) y éter dietílico (20 ml). Rendimiento 7.5 g (79%).

***terc*-Butil éster de ácido *exo*-3-(3-cloro-2-oxo-2*H*-cromen-7-iloxi)-8-azabiciclo[3.2.1]octan-8-carboxílico** (intermedio)

Se preparó de acuerdo con método 5 de *exo*-7-(8-*terc*-butoxicarbonil-8-azabiciclo-[3.2.1]oct-3-iloxi)-cromen-2-ona y cloro (en vez de bromo), disuelto en ácido acético.

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***terc*-Butil éster de ácido *exo*-3-(3-bromo-2-oxo-2*H*-cromen-6-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico (intermedio)**

Se preparó de acuerdo con método 5 *terc*-butil éster de ácido 3-(2-oxo-2*H*-cromen-6-iloxi)-8-aza-biciclo[3.2.1]octan-8-carboxílico.

***exo*-3-Bromo-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona base libre**

Se preparó de acuerdo con método 5 de *exo*-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona. LC-ESI-HRMS de [M+H]⁺ muestra 364.0547 Da. Calc. 364.054832 Da, dev. -0.4 ppm.

Sal de ácido clorhídrico de *exo*-3-cloro-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona

Se preparó de acuerdo con método 5 de *exo*-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona y cloro (en vez de bromo), disuelto en ácido acético. LC-ESI-HRMS de [M+H]⁺ muestra 320.1068 Da. Calc. 320.105347 Da, dev. 4.5 ppm.

Ejemplo de Prueba

Actividad de inhibición *in vitro*

Un número de compuestos se examinaron con respecto a su capacidad de inhibir la reabsorción de los neurotransmisores de monoamina dopamina (DA), noradrenalina (NA) y serotonina (5-HT) en sinaptosomas como se describe en WO 97/16451.

Los valores de prueba se dan como IC₅₀ (la concentración (μM) de la sustancia de prueba que inhibe la unión específica de ³H-DA, ³H-NA, o ³H-5-HT by 50%).

Los resultados de prueba obtenidos examinando compuestos seleccionados de la presente invención aparecen en la siguiente tabla:

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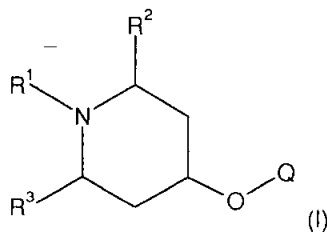
Tabla 1

Compuesto de prueba	Absorción de DA IC ₅₀ (μM)	Absorción de NA IC ₅₀ (μM)	Absorción de 5-HT IC ₅₀ (μM)
<i>Primer compuesto de Método 2B:</i> exo-3-Bromo-7-(8-metil-8-aza-biciclo- [3.2.1]oct-3-iloxi)-cromen-2-ona	0.044	0.017	0.0012
<i>Segundo último compuesto de Método 2B:</i> exo-7-(8-Aza-biciclo[3.2.1]oct-3- iloxi)-3-cloro-cromen-2-ona	0.054	0.014	0.00059
<i>Primer compuesto de Método 4B:</i> exo-7-(8-Metil-8-aza-biciclo[3.2.1] oct- 6-en-3-iloxi)-cromen-2-ona	0.70	0.72	0.036

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REIVINDICACIONES

1. Un compuesto de Fórmula I:



cualquiera de sus isómeros o cualquier mezcla de sus isómeros,
o su sal farmacéuticamente aceptable,
en donde

Q representa un grupo cromen-2-ona;

el cual grupo cromen-2-ona se sustituye opcionalmente con uno
o más radicales seleccionados independientemente del grupo
conformado por :

halo, trifluorometilo, trifluorometoxi, ciano, hidroxilo, amino,
nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo,
cicloalquilalquilo, alqueno y alquino;

R¹ representa hidrógeno o alquilo;

el cual alquilo se sustituye opcionalmente con uno o más
radicales seleccionados independientemente del grupo
conformado por :

halo, trifluorometilo, trifluorometoxi, ciano, hidroxilo, amino,
nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo,
cicloalquilalquilo, alqueno y alquino; y

R² y R³ conjuntamente forman -(CH₂)-(CH₂)- o -(CH)=(CH)-.

2. El compuesto químico de la reivindicación 1, en donde
R² y R³ conjuntamente forman -(CH₂)-(CH₂)-; y
R¹ es como se define en la reivindicación 1.
3. El compuesto químico de la reivindicación 2, en donde
R¹ representa alquilo, alqueno o alcoxialquilo.

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4. El compuesto químico de la reivindicación 1, en donde R^2 y R^3 conjuntamente forman $-(CH)=(CH)-$; y R^1 es como se define en la reivindicación 1.
5. El compuesto químico de la reivindicación 4, en donde R^1 representa hidrógeno o alquilo.
6. El compuesto químico de una cualquiera de las reivindicaciones 1-5, en donde Q representa cromen-2-on-ilo; el cual grupo cromen-2-on-ilo se sustituye en la posición 3 con un radical seleccionado del grupo conformado por:
halo, trifluorometilo, trifluorometoxi, ciano, hidroxilo, amino, nitro, alcoxi, cicloalcoxi, alquilo, cicloalquilo, cicloalquilalquilo, alquenilo y alquinilo.
7. El compuesto químico de la reivindicación 1, el cual es
exo-3-Bromo-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-2-oxo-2*H*-cromen-3-carbonitrilo;
exo-6-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-3-bromo-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-3-cloro-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-3-iloxi)-4-metil-2-oxo-2*H*-cromen-3-carbonitrilo;
exo-7-(8-Etil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-(8-Isopropil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-[8-(2-Metoxi-etil)-8-aza-biciclo[3.2.1]oct-3-iloxi]-cromen-2-ona;
exo-7-(8-Alil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-7-(8-Aza-biciclo[3.2.1]oct-6-en-3-iloxi)-cromen-2-ona;

exo-7-(8-Metil-8-aza-biciclo[3.2.1]oct-6-en-3-iloxi)-cromen-2-ona;
exo-3-Bromo-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
exo-3-Cloro-7-(8-metil-8-aza-biciclo[3.2.1]oct-3-iloxi)-cromen-2-ona;
o su sal farmacéuticamente aceptable.

8. Una composición farmacéutica que contiene una cantidad terapéuticamente efectiva de un compuesto de una cualquiera de las reivindicaciones 1-7, cualquiera de sus isómeros, o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, junto con por lo menos una sustancia portadora, excipiente o diluyente farmacéuticamente aceptables.
9. Uso del compuesto químico de una cualquiera de las reivindicaciones 1-7, cualquiera de sus isómeros, o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable, para la fabricación de un medicamento.
10. El uso de acuerdo con la reivindicación 9, para la fabricación de una composición farmacéutica para el tratamiento, prevención o alivio de una enfermedad o trastorno o afección de un mamífero, incluido un humano, enfermedad, trastorno o afección que es sensible a la inhibición de la reabsorción de un neurotransmisor de monoamina en el sistema nervioso central.
11. El uso de acuerdo con la reivindicación 10, en donde la enfermedad, trastorno o afección es trastorno del estado de ánimo, depresión, depresión atípica, depresión secundaria a 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 humor



inducido por sustancias, pseudodemencia, síndrome de Ganser, trastorno obsesivo compulsivo, trastorno de pánico, trastorno de pánico sin agorafobia, trastorno de pánico con agorafobia, agorafobia sin historia de trastorno de pánico, ataque de pánico, déficits de memoria, pérdida de memoria, trastorno de déficit de atención e hiperactividad, obesidad, ansiedad, trastorno de ansiedad generalizada, trastorno del comportamiento alimentario, enfermedad de Parkinson, parkinsonismo, demencia, demencia del envejecimiento, demencia senil, enfermedad de Alzheimer, complejo demencia-síndrome de inmunodeficiencia adquirida, disfunción de la memoria en el envejecimiento, fobia específica, fobia social, trastorno de ansiedad social, trastorno de estrés pos-traumático, trastorno de estrés agudo, drogadicción, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso del tabaco, adicción al alcohol, alcoholismo, cleptomanía, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor de migraña, cefalea tipo tensión, cefalea crónica tipo tensión, dolor asociado con depresión, fibromialgia, artritis, osteoartritis, artritis reumatoide, lumbalgia, dolor por cáncer, dolor de intestino irritable, síndrome de intestino irritable, dolor pos-operatorio, síndrome de dolor pos-mastectomía (PMPS), dolor pos-apoplejía, neuropatía inducida por drogas, neuropatía diabética, dolor mantenido simpáticamente, neuralgia del trigémino, dolor de muelas, dolor miofacial, el dolor de miembro fantasma pos-amputación, bulimia, síndrome premenstrual, trastorno disfórico premenstrual, síndrome de fase lútea tardía, síndrome pos-traumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia imperiosa, incontinencia nocturna, disfunción sexual, eyaculación precoz, dificultad eréctil, disfunción eréctil, orgasmo precoz femenino, síndrome de las piernas inquietas, trastorno de movimiento periódico de los miembros, trastornos en el comportamiento alimentario, anorexia nerviosa, trastornos del sueño, trastornos generalizados del desarrollo, autismo, trastorno de

Asperger, trastorno de Rett, trastorno desintegrativo de la niñez, limitaciones o trastornos de aprendizaje, trastornos de habilidades motoras, autismo, tricotilomanía, narcolepsia, depresión pos-apoplejía, lesión cerebral inducida por apoplejía, lesión neuronal inducida por apoplejía, enfermedad de Gilles de la Tourette, zumbido en los oídos, trastornos de contracciones nerviosas, trastornos dismórficos corporales, trastorno de oposición desafiante o incapacidades pos-apoplejía.

12. Un método para el tratamiento, prevención o alivio de una enfermedad o trastorno o afección de un cuerpo animal vivo, incluido un humano, trastorno, enfermedad o afección que es sensible a la inhibición de la reabsorción de un neurotransmisor de monoamina en el sistema nervioso central, método que comprende el paso de administrar a tal cuerpo animal vivo, necesitado de ello, una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-7, o cualquiera de sus isómeros, o cualquier mezcla de sus isómeros, o su sal farmacéuticamente aceptable.

PATENT COOPERATION TREATY

107727

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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

Date of mailing 23/04/2007
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 356-204-000

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2007/051401

International filing date (day/month/year)
13.02.2007

Priority date (day/month/year)
17.02.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D451/06 A61K31/135 A61K31/46

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") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 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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Date of completion of
this opinion

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PCT/ISA/210

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2007/051401

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
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) 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:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic 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 43*bis*.1 and 64.1) 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 43*bis*.1 and 64.1). 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:

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2007/051401

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.

because:

- ☒ the said international application, or the said claims Nos. 12 relate to the following subject matter which does not require an international search (*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. 1-12 are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ no international search report has been established for the whole application or for said claims Nos. ____
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☒ See Supplemental Box for further details

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2007/051401

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

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

Re Item III

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

For the assessment of the present claims 12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

For this reason, no opinion concerning Art. 33(4) PCT will be given for claim 12.

Re Item V

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

Reference is made to the following documents:

- D1: EP-A-1 130 020 (NEUROSEARCH AS [DK]) 5 September 2001 (2001-09-05)
- D2: WO 02/102801 A (NEUROSEARCH AS [DK]; GOULIAEV ALEX HAAHR [DK]; DAHL BJARNE H [DK]; PET) 27 December 2002 (2002-12-27)
- D3: WO 2006/035034 A (NEUROSEARCH AS [DK]; PETERS DAN [DK]; OLSEN GUNNAR M [DK]; SCHEEL-KRUE) 6 April 2006 (2006-04-06)

1) Incomplete Search :

The present claims relate to compounds of formula I as well as their "isomers" or any mixture of "isomers" thereof. As this term not only encompasses stereoisomers but

also isomers of position and isomers of structure, said claims therefore relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, see the examples. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9.19 and 9.23).

The search of the claims was restricted to the compounds of formula I and stereoisomers or mixtures of stereoisomers thereof.

Therefore, officially no opinion will be given for claims 1-12, as such an opinion would no make much sense.

Nevertheless, if the claims were restricted to stereoisomers, the applicant would be informed of the following :

2) Novelty (Art. 33(2) PCT) :

In the light of the cited prior art, the subject-matter of claims 1-12 **would** appear to meet the requirements of Art. 33(2) PCT.

3) Inventive Step (Art. 33(3) PCT) :

Since none of cited prior art **would** seem to suggest the combination of a tropane and a chromen-2-one moieties as monoamine neurotransmitter re-uptake inhibitors, the subject-matter of claims 1-12 would be considered inventive

4) Industrial Application (Art. 33(4) PCT) :

The subject-matter of claims 1-11 **would** comply with the requirements of Art. 33(4) PCT.

Concerning claim 12 , see Item III.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2007/051401

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2006/035034	06.04.2006	28.09.2005	30.09.2004

The above-mentioned document (D3), which is an intermediate document, is not prior art according to the Chap II PCT proceedings.

Nevertheless, the extensive examination of that document, on the question whether it constitutes prior art or not, will depend essentially on the analysis of the claimed priority rights of the present application and will only be performed in the regional European proceedings to come.

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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 3.5.000.176 MT/FOP 20020701/0.20.4rc.2.7
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	356-204-WO
I	Title of Invention	NOVEL CHROMEN-2-ONE 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	1308705.1

PCT REQUEST

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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)	REDROBE, John, Paul
III-2-5	Address	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-2-6	State of nationality	GB
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

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PCT REQUEST

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	NeuroSearch A/S
IV-1-2	Address	Patent Department 93 Pederstrupvej 2750 Ballerup Denmark
IV-1-3	Telephone No.	+45 4460 8000
IV-1-4	Facsimile No.	+45 4460 8084
IV-1-5	e-mail	patents@neurosearch.dk
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	17 February 2006 (17.02.2006)
VI-1-2	Number	PA 2006 00233
VI-1-3	Country	DK
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	21 February 2006 (21.02.2006)
VI-2-2	Number	60/774,669
VI-2-3	Country	US
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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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	-	

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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, REDROBE, John, Paul
VIII-2-1(i)		NeuroSearch A/S is entitled as employer of the inventor, NIELSEN, Elsebet, Østergaard
VIII-2-1(x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

PCT REQUEST

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	20	✓
IX-3	Claims	4	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	31	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-17	PCT-SAFE physical media	-	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	(PKCS7 Digital Signature)	
X-1-1	Name	DK, NeuroSearch A/S, M. Abildgren 844	
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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NOVEL CHROMEN-2-ONE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UP TAKE INHIBITORS

TECHNICAL FIELD

5

This invention relates to novel chromen-2-one derivatives useful as monoamine neurotransmitter re-uptake inhibitors.

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

BACKGROUND ART

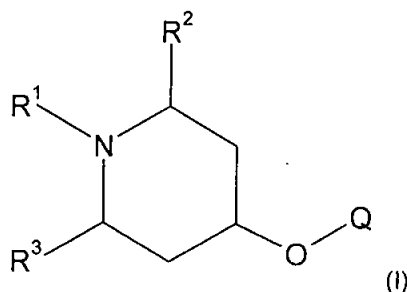
Serotonin Selective Reuptake Inhibitors (SSRIs) currently provide efficacy in the
15 treatment of several CNS disorders, including depression and panic disorder. SSRIs are generally perceived by psychiatrists and primary care physicians as effective, well-tolerated and easily administered. However, they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

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

SUMMARY OF THE INVENTION

25

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



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

wherein R¹, R², R³ and Q are as defined below.

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

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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 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.

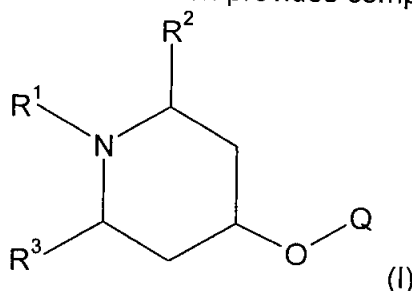
Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

20

DETAILED DISCLOSURE OF THE INVENTION

Chromen-2-one derivatives

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



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

Q represents a chromen-2-one group;

which chromen-2-one 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;

R¹ represents hydrogen or alkyl;

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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; and

5 R^2 and R^3 together form $-(CH_2)-(CH_2)-$ or $-(CH)=(CH)-$.

In one embodiment of the compound of Formula I, R^2 and R^3 together form $-(CH_2)-(CH_2)-$; and R^1 is as defined above. In a special embodiment, R^1 represents alkyl, alkenyl or alkoxyalkyl. In a further embodiment, R^1 represents C_{2-6} -alkyl, alkenyl
10 or alkoxyalkyl. In a still further embodiment, R^1 represents C_{2-6} -alkyl, such as ethyl or propyl, in particular isopropyl. In a further embodiment, R^1 represents alkenyl, such as allyl. In a still further embodiment, R^1 represents alkoxyalkyl, such as alkoxyethyl, in particular methoxyethyl. In a further embodiment, R^1 represents hydrogen. In a still further embodiment, R^1 represents alkyl, such as methyl.

15 In a further embodiment of the compound of Formula I, R^2 and R^3 together form $-(CH)=(CH)-$; and R^1 is as defined in claim 1. In a special embodiment, R^1 represents hydrogen or alkyl. In a further embodiment, R^1 represents hydrogen. In a still further embodiment, R^1 represents alkyl, such as methyl.

In a further embodiment of the compound of Formula I, Q represents chromen-
20 2-one-yl. In a special embodiment of the compound of Formula I, Q represents chromen-2-one-7-yl. In a special embodiment of the compound of Formula I, Q represents chromen-2-one-6-yl.

In a still further embodiment of the compound of Formula I, Q represents substituted chromen-2-one-yl, such as halo, cyano or alkyl substituted chromen-2-one-
25 yl. In a special embodiment of the compound of Formula I, Q represents substituted chromen-2-one-7-yl, such as halo, cyano or alkyl substituted chromen-2-one-7-yl. In a special embodiment of the compound of Formula I, Q represents substituted chromen-2-one-6-yl, such as halo, cyano or alkyl substituted chromen-2-one-6-yl.

In a further embodiment, Q represents chromen-2-one-yl; which chromen-2-
30 one-yl group is substituted in the 3-position with a substituent selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.

In a still further special embodiment, Q represents 3-halo-chromen-2-one-yl, such as 3-halo-chromen-2-one-6-yl or 3-halo-chromen-2-one-7-yl. In a special
35 embodiment, Q represents 3-bromo-chromen-2-one-6-yl, 3-bromo-chromen-2-one-7-yl, 3-chloro-chromen-2-one-6-yl or 3-chloro-chromen-2-one-7-yl.

In a further special embodiment, Q represents 3-cyano-chromen-2-one-yl, such as 3-cyano-chromen-2-one-6-yl or 3-cyano-chromen-2-one-7-yl.

In a further special embodiment, Q represents alkyl-cyano-chromen-2-one-yl, such as methyl-cyano-chromen-2-one-yl, such as 4-methyl-3-cyano-chromen-2-one-yl. In a special embodiment, Q represents 4-methyl-3-cyano-chromen-2-one-6-yl or 4-methyl-3-cyano-chromen-2-one-7-yl.

- 5 In a special embodiment the chemical compound of the invention is
 exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
 exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-2-oxo-2H-chromene-3-carbonitrile;
 exo-6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-bromo-chromen-2-one;
 exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-chloro-chromen-2-one;
 10 exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-4-methyl-2-oxo-2H-chromene-3-carbonitrile;
 exo-7-(8-Ethyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
 exo-7-(8-Isopropyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
 exo-7-[8-(2-Methoxy-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yloxy]-chromen-2-one;
 exo-7-(8-Allyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
 15 exo-7-(8-Aza-bicyclo[3.2.1]oct-6-en-3-yl)oxy)-chromen-2-one;
 exo-7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one;
 exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
 exo-3-Chloro-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
 or a pharmaceutically acceptable salt thereof.
- 20 Any combination of two or more of the embodiments as described above is considered within the scope of the present invention.

Definition of Substituents

- In the context of this invention halo represents fluoro, chloro, bromo or iodo.
- 25 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
- 30 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 preferred embodiment the alkenyl group of the invention comprises of from two to six
- 35 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.

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 (C_{2-6} -alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butadiynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentadiynyl; 1-, 2-, 3-, 4-, or 5-hexynyl, or 1,3-hexadiynyl or 1,3,5-hexatriynyl.

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

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

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

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

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

Pharmaceutically Acceptable Salts

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

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

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

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysinium, and the ammonium salt, and the like, of a chemical compound of the invention

containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

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

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

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

20 Steric Isomers

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

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

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

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the 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 (-) camphanic acid or by

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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 or intermediates.

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 Position 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 (NeuroSearch A/S). Based on the balanced activity
5 observed in these tests the compound of the invention is considered useful for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a special embodiment, the compounds of the invention are considered useful
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, social anxiety disorder, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with
25 depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-mastectomy pain syndrome (PMPS), post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome,
30 premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg syndrome, periodic limb movement disorder, eating disorders, anorexia nervosa, sleep
35 disorders, pervasive developmental disorders, autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, learning disabilities, motor skills disorders, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, Gilles de la Tourettes disease, tinnitus, tic disorders, body dysmorphic disorders, oppositional defiant disorder or post-stroke

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disabilities. In a preferred embodiment, the compounds are considered useful for the treatment, prevention or alleviation of depression.

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

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

Pharmaceutical Compositions

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

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

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

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

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules,

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powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

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

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

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

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

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 encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten 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 ingredient such carriers as are known in the art to be appropriate.

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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.

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

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

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

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

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

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, dos-

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age form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

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

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ 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

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

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

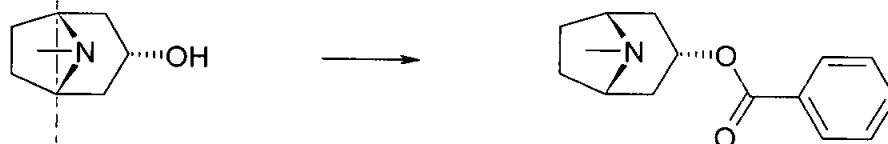
EXAMPLES

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

Preparatory Examples

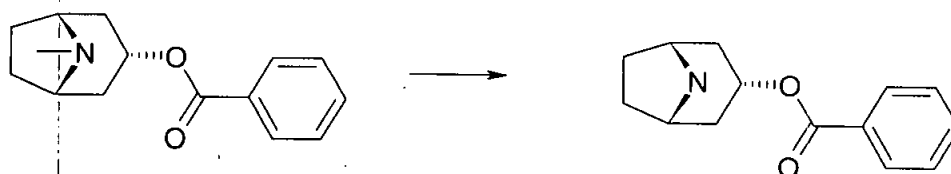
All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulphate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

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

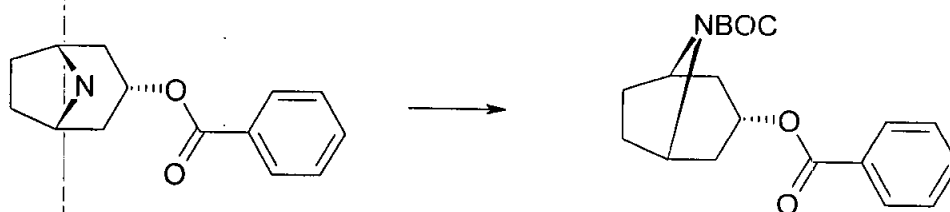
Benzoylchloride (84.3 g, 600 mmol) was added during 30 min at <30 °C to a mixture of tropine (70.6 g, 500 mmol), potassium *tert*-butoxide (67.3 g, 600 mmol) and THF (500 ml). The mixture was stirred at room temperature for 2 h. Water (1 L) was added followed by extraction with diethylether (2 x 500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



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

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



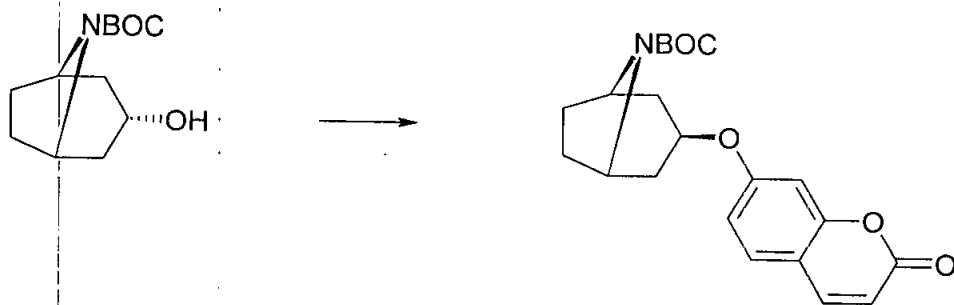
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endo-3-Benzoyloxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester

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

**endo-3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester**

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

**Method 1****exo-7-(8-*tert*-Butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one**

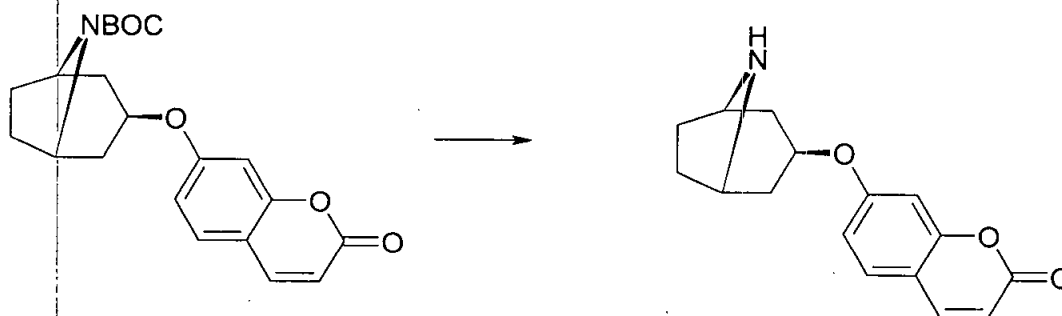
Triphenylphosphine (7.5 g, 28.6 mmol) was solved in dioxane (70 ml) and cooled to 8°C. Diethylazodicarboxylate (5.0 g, 28.6 mmol) was added to the mixture below 15°C, followed by stirring for 15 minutes. *endo*-3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (5.0 g, 22.0 mmol) and 7-hydroxycoumarin (4.3 g, 26.4 mmol) was added to the mixture. The temperature raised due to an exothermic reaction. The mixture was allowed to stir for 15 h at room temperature. Water (200 ml) was added followed by extraction with diethylether (2 x 100 ml). The mixture was dried and evaporated. Chromatography on silica gel with dichloromethane and 5% methanol

as solvent. The crude product was solved in diethylether (200 ml) and washed with aqueous sodium hydroxide (3 x 200 ml, 1 M). The product was dried and evaporated. Yield 5.32 g (65%).

5 **exo-3-(3-cyano-2-oxo-2H-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester** (intermediate)

Was prepared according to method 1 from 7-hydroxy-2-oxo-2H-chromene-3-carbonitrile and *endo*-3-hydroxy-8-aza-bicyclo[3.2.1] octane-8-carboxylic acid *tert*-butyl ester.

10 **Method 2A**



exo-7-(8-H-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt

A mixture of *exo*-7-(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one (0.60 g, 1.6 mmol) and hydrochloric acid (10 ml, 1 M) in acetic acid (10 ml) was stirred for 1 h. Diethylether (50 ml) was added and the precipitate was filtered and washed with diethylether (10 ml). Yield 0.28 g (57%). Mp > 300°C.

Method 2B

20 **exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt**

A mixture of *exo*-7-[(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yl)oxy]-3-bromo-chromen-2-one (30 g, 65.3 mmol) and hydrogen chloride in acetic acid (500 ml, 1 M) was stirred at room-temperature for 3 h. Diethylether (500 ml) was added, the precipitation was stirred and isolated by filtration. Yield 25 g (99%). LC-ESI-HRMS of [M+H]⁺ shows 350.0405 Da. Calc. 350.039182 Da, dev. 3.8 ppm.

exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-2-oxo-2H-chromene-3-carbonitrile hydrochloric acid salt

30 Was prepared from *exo*-3-(3-cyano-2-oxo-2H-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-HRMS of [M+H]⁺ shows 297.1238 Da. Calc. 297.123918 Da, dev. -0.4 ppm.

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exo-6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-bromo-chromen-2-one hydrochloric acid salt

Was prepared from *exo*-3-(3-bromo-2-oxo-2*H*-chromen-6-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-
5 HRMS of [M+H]⁺ shows 350.0379 Da. Calc. 350.039182 Da, dev. -3.7 ppm.

exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-chloro-chromen-2-one hydrochloric acid salt

Was prepared from *exo*-3-(3-chloro-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-
10 HRMS of [M+H]⁺ shows 306.0894 Da. Calc. 306.089697 Da, dev. -1 ppm.

exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-4-methyl-2-oxo-2*H*-chromene-3-carbonitrile hydrochloric acid salt

Was prepared from *exo*-3-(3-cyano-4-methyl-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester according to method 2B. LC-ESI-
15 HRMS of [M+H]⁺ shows 311.1401 Da. Calc. 311.139568 Da, dev. 1.7 ppm.

Method 3**20 exo-7-(8-Ethyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt**

A mixture of *exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one (3.1 g, 10.1 mmol), sodium hydride, 60% in mineral oil (0.29 g 12.1 mmol), iodoethane (2.46 g, 15.8 mmol) and tetrahydrofuran (75 ml) was stirred at 60°C for 3 h. The hydrochloride
25 was precipitated by adding ethanol (75 ml) and concentrated hydrochloric acid (1 ml). The crystalline product was recrystallised from ethanol (100 ml, 96%). Yield 1.71 g (51%). LC-ESI-HRMS of [M+H]⁺ shows 300.1596 Da. Calc. 300.159969 Da, dev. -1.2 ppm.

30 exo-7-(8-Isopropyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt

Was prepared according to method 1A from *exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 314.1746 Da. Calc. 314.175619 Da, dev. -3.2 ppm.

35

exo-7-[8-(2-Methoxy-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yloxy]-chromen-2-one hydrochloric acid salt

Was prepared according to method 1A from *exo*-7-(8-*H*-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 330.1691 Da. Calc.
40 330.170534 Da, dev. -4.3 ppm.

99

exo-7-(8-Allyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one hydrochloric acid salt

Was prepared according to method 1A from *exo*-7-(8-H-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 312.1584 Da. Calc. 312.159969 Da, dev. -5 ppm.

Method 4A**exo-7-(8-Aza-bicyclo[3.2.1]oct-6-en-3-yl)oxy)-chromen-2-one hydrochloric acid salt**

2,2,2-Trichloroethyl chloroformate (3.7 g, 17.6 mmol) was added to a mixture of *exo*-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one (1.0 g, 3.5 mmol) and toluene (20 ml). The mixture was stirred for 30 min at room temperature followed by 15 h at 100°C. Water (10 ml) was added and the organic phase was separated and was washed with water (2 x 25 ml). The crude mixture obtained by evaporation was solved in acetic acid (10 ml) and water (10 ml). Zinc powder (2.3 g, 35.3 mmol) was added to the mixture in portions followed by stirring for 5 h. Ice-water (20 ml) was added followed by concentrated aqueous ammonia (20 ml). The mixture was extracted with dichloromethane (2 x 20 ml). The hydrochloric acid salt was precipitated by adding hydrochloric acid solved in ethanol to the free base solved diethylether. Yield 70 mg (5%). Mp >280°C (dec.). LC-ESI-HRMS of [M+H]⁺ shows 270.1117 Da. Calc. 270.113019 Da, dev. -4.9 ppm.

Method 4B**exo-7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one hydrochloric acid salt**

A mixture of diethylazodicarboxylate (10.5 g, 60.3 mmol) in dioxane (100 ml) was added to triphenylphosphine (15.8 g, 60.3 mmol), solved in dioxane (80 ml) at room temperature. The mixture was stirred for 15 min. *endo*-8-Methyl-8-aza-bicyclo[3.2.1]oct-6-ene-3-ol (7.0 g, 50.3 mmol) solved in dioxane (30 ml) was added to the mixture at 15°C followed by 7-hydroxycoumarine (9.0 g, 55.3 mmol). The temperature was raised to 30°C due to an exothermic reaction. The mixture was stirred at room temperature overnight followed by reflux for 4 h. Water (200 ml) and aqueous hydrochloric acid (15 ml, 4 M) was added and was washed with diethylether (3 x 50 ml). The aqueous phase was made alkaline by adding sodium hydroxide (50 ml, 4 M) followed by extraction with diethylether (3 x 100 ml). Yield 1.2 g (8%). The hydrochloric acid salt was prepared by adding a mixture of hydrochloric acid solved in ethanol. Mp >275°C. LC-ESI-HRMS of [M+H]⁺ shows 284.1275 Da. Calc. 284.128669 Da, dev. -4.1 ppm.

(100)

Method 4C**endo-8-Methyl-8-aza-bicyclo[3.2.1]oct-6-ene-3-ol (intermediate)**

- A mixture of zinc powder (10 g) and hydrochloric acid (10 ml, 1 M) was stirred for 1 minute and washed with hydrochloric acid (3 x 10 ml, 1 M) and water (5 x 10 ml) followed by aqueous copper sulphate (25 ml, 2%), water (5 x 10 ml), ethanol (10 ml, 96%) and diethylether (10 ml) followed by drying. The title compound was prepared from scopolamine hydrobromide trihydrate and zinc powder followed by hydrolysis by treatment with aqueous sodium hydroxide according to Tetrahedron Letters 42 (2001), p 1975.

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Method 5**exo-7-[(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yl)oxy]-3-bromo-chromen-2-one (intermediate)**

- Bromine (1.38 ml, 27.0 mmol) was added to a mixture of *exo*-7-(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one (7.8 g, 21.0 mmol), acetic acid (150 ml) and sodium acetate (5.2 g, 63.0 mmol). The mixture was stirred for 90 min at room-temperature. Water (100 ml) was added. The precipitation was filtered and washed with water (10 ml), methanol (5 ml) and diethylether (20 ml). Yield 7.5 g (79%).

- exo-3-(3-Chloro-2-oxo-2*H*-chromen-7-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl (intermediate)**

Was prepared according to method 5 from *exo*-7-(8-*tert*-butoxycarbonyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one and chlorine (instead of bromine), solved in acetic acid.

25

exo-3-(3-Bromo-2-oxo-2*H*-chromen-6-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (intermediate)

Was prepared according to method 5 from 3-(2-oxo-2*H*-chromen-6-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester.

30

exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one free base

- Was prepared according to method 5 from *exo*-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one. LC-ESI-HRMS of [M+H]⁺ shows 364.0547 Da. Calc. 364.054832 Da, dev. -0.4 ppm.

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**exo-3-Chloro-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one
hydrochloric acid salt**

Was prepared according to method 5 from *exo*-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one and chlorine (instead of bromine), solved in acetic acid. LC-ESI-
5 HRMS of [M+H]⁺ shows 320.1068 Da. Calc. 320.105347 Da, dev. 4.5 ppm.

Test Example**In vitro inhibition activity**

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

The test values are given as IC₅₀ (the concentration (μM) of the test substance which inhibits the specific binding of ³H-DA, ³H-NA, or ³H-5-HT by 50%).

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

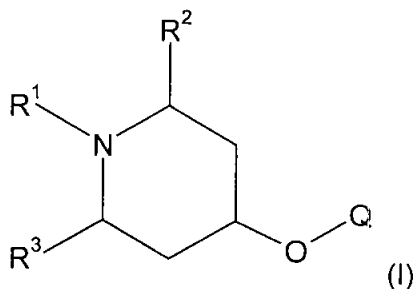
Table 1

Test compound	DA-uptake IC ₅₀ (μM)	NA-uptake IC ₅₀ (μM)	5-HT-uptake IC ₅₀ (μM)
<i>First compound of Method 2B:</i> <i>exo</i> -3-Bromo-7-(8-methyl-8-aza-bicyclo- [3.2.1]oct-3-yloxy)-chromen-2-one	0.044	0.017	0.0012
<i>Second last compound of Method 2B:</i> <i>exo</i> -7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3- chloro-chromen-2-one	0.054	0.014	0.00059
<i>First compound of Method 4B:</i> <i>exo</i> -7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6- en-3-yloxy)-chromen-2-one	0.70	0.72	0.036

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CLAIMS

1. A compound of Formula I:



- 5 any of its isomers or any mixture of its isomers,
or a pharmaceutically acceptable salt thereof,
wherein
Q represents a chromen-2-one group;
which chromen-2-one group is optionally substituted with one or more
10 substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro,
alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and
alkynyl;
R¹ represents hydrogen or alkyl;
15 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; and
20 R² and R³ together form $-(CH_2)-(CH_2)-$ or $-(CH)=(CH)-$.
2. The chemical compound of claim 1, wherein
R² and R³ together form $-(CH_2)-(CH_2)-$; and
R¹ is as defined in claim 1.
- 25 3. The chemical compound of claim 2, wherein
R¹ represents alkyl, alkenyl or alkoxyalkyl.
4. The chemical compound of claim 1, wherein
30 R² and R³ together form $-(CH)=(CH)-$; and
R¹ is as defined in claim 1.
5. The chemical compound of claim 4, wherein
R¹ represents hydrogen or alkyl.

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6. The chemical compound of any one of claims 1-5, wherein Q represents chromen-2-one-yl; which chromen-2-one-yl group is substituted in the 3-position with a substituent selected from the group consisting of:
- 5 halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.
7. The chemical compound of claim 1, which is
- 10 *exo*-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-2-oxo-2*H*-chromene-3-carbonitrile;
exo-6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-bromo-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-3-chloro-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-4-methyl-2-oxo-2*H*-chromene-3-carbonitrile;
- 15 *exo*-7-(8-Ethyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Isopropyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-(2-Methoxy-ethyl)-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Allyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-7-(8-Aza-bicyclo[3.2.1]oct-6-en-3-yl)oxy)-chromen-2-one;
- 20 *exo*-7-(8-Methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yloxy)-chromen-2-one;
exo-3-Bromo-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
exo-3-Chloro-7-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-chromen-2-one;
or a pharmaceutically acceptable salt thereof.
- 25 8. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-7, 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.
- 30 9. Use of the chemical compound of any of claims 1-7, any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.
10. The use according to claim 9, for the manufacture of a pharmaceutical
- 35 pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

11. The use according to claim 10, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, social anxiety disorder, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, kleptomania, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-mastectomy pain syndrome (PMPS), post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofascial pain, phantom-limb pain, bulimia, premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, premature female orgasm, restless leg syndrome, periodic limb movement disorder, eating disorders, anorexia nervosa, sleep disorders, pervasive developmental disorders, autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, learning disabilities, motor skills disorders, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage, Gilles de la Tourettes disease, tinnitus, tic disorders, body dysmorphic disorders, oppositional defiant disorder or post-stroke disabilities.
12. 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

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such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-7, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

ABSTRACT**NOVEL CHROMEN-2-ONE DERIVATIVES AND THEIR USE AS MONOAMINE
NEUROTRANSMITTER RE-UPTAKE INHIBITORS**

This invention relates to novel chromen-2-one derivatives useful as monoamine neurotransmitter re-uptake inhibitors.

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



AS: 96467
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Brigard & Castro
BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) NeuroSearch A/S

domiciliado(s) en

domiciled in 93 Pederstrupvej
DK-2750 Ballerup, Denmark

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

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

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

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

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

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

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

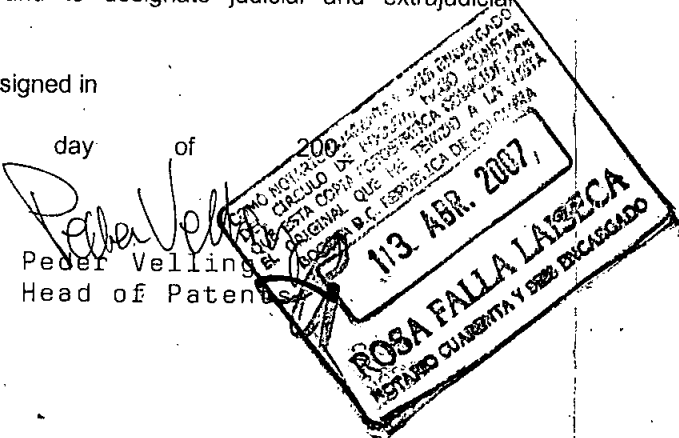
Granted and signed in

this day of

Signature

Name
Title

Peder Velling
Head of Patent



CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de
personalmente compareció ante mí

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

de

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

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

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

CERTIFICADO NOTARIAL
PERSONA NATURAL

Hoy de de , compareció(eron) ante mí

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



LEGALIZACION POR APOSTILLA ES REQUERIDA.

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

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

Head of patent department
of

Neurosearch A/S

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

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

State of Denmark
under date of 14th April 2005

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

Public Notary (Seal)

HENNING BROMAN
Reassessor
NOTARIAL CERTIFICATE
NATURAL PERSON

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

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

Notary Public (Seal)

HENNING BROMAN
Reassessor

LEGALIZATION BY APOSTILLE IS REQUIRED



The City Court of Ballerup
Blegdamsvej 6
2200 Copenhagen
Denmark



THE TRUE SIGNATURE OF
Henning Broman

IS HEREBY CERTIFIED.

COPENHAGEN, 17 APR. 2005
FOR THE MINISTER FOR FOREIGN AFFAIRS.

B.A.

Henning Broman

BIRGITTE THORELL

RECIBO
DE LA
COLOMBIA

EL CONSUL AD-HONOREM DE COLOMBIA EN
COPENHAGUE, DINAMARCA

Feca. 18 APR. 2005 No: 222

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

este consulado

Ole Waage Pedersen
CONSUL AD-HONOREM

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 ABR 27 A 10:14

nos
JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

355440

Ole Waage
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPLEA
LAS FUNCIONES INDICADAS



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TRADUCCION OFICIAL NO.364/2005-

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

FIRMADO: PEDER VELLING, DIRECTOR DE PATENTES

CERTIFICADO NOTARIAL (SOCIEDAD)

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

DINAMARCA, FECHADO EL 1° DE ABRIL DE 2005.

Y QUE QUIEN CONFIERE EL PRESENTE PODER ES SU REPRESENTANTE.

FIRMADO: HENNING BROMAN, NOTARIO.

HAY SELLO EN RELIEVE DEL NOTARIO.

CERTIFICADO NOTARIAL (PERSONA NATURAL)

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



110

TRADUCCION OFICIAL NO.364/2005-

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

FIRMADO: HENNING BROMAN, NOTARIO.

HAY SELLO EN RELIEVE DEL NOTARIO.

CORTE DE LA CIUDAD DE BALLERUP

BLEGDAMSVEL 6

2200 COPENHAGUEN, DINAMARCA

MINISTERIO DE RELACIONES EXTERIORES

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

POR EL MINISTERIO DE RELACIONES EXTERIORES

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

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

FIRMADO: OLE WAAGE PEDERSEN, CÓNSUL AD-HONOREM

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

LA TRADUCTORA OFICIAL

Helena Uribe de Lemoine

HELENA URIBÉ DE LEMOINE



2



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11

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-083690-00000-0000

Fecha: 2008-08-12 16:33:35 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 110

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

POT

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 []

Eduar Naranjo

Firma Responsable

Fecha 12-08-08

Carrera 13 No. 27-00 Piso 5, 7 y 10

Corrutador: 3 82 08 40

Fax: 350 52 20

E-mail: Info@slc.gov.co

www.slc.gov.co

Bogotá, D.C., Colombia