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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SALES DE 2-METOXIMETIL-3-(3,4-DICLORO-FENIL)-8-AZABICICLO

(3.2.1)OCTAN TARTRATO

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DOMICILIO

BALLERUP, DINAMARCA

74. APODERADO

JUAN PABLO CADENA SARMIENTO

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1

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2

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Lugar de Constitución: Dinamarca

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IDENTIFICACION

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3

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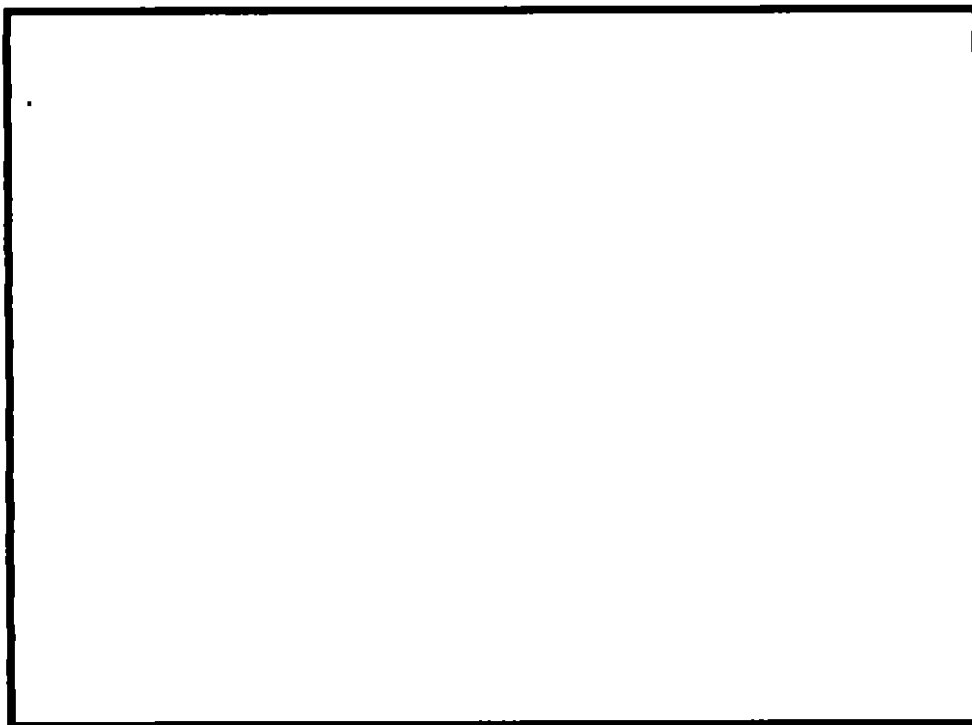
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$463.000
- ☒ Documento que acredite 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
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Tarjeta de propietarios.
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11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente

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3

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: 2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-AZABICYCLO[3.2.1]OCTANE TARTRATE SALTS

(57) Abstract: This invention relates to novel (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane
tartrate salts, such as L-tartrate monohydrates and anhydrites. The salts are useful as monoamine neurotransmitter re-uptake in-
hibitors. In other aspects the invention relates to the use of these salts in a method for therapy and to pharmaceutical compositions
comprising the salts of the invention.

WO 2005/011694 A1

**2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-AZABICYCLO[3.2.1]OCTANE
TARTRATE SALTS**

5

TECHNICAL FIELD

This invention relates to novel (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts, such as L-tartrate monohydrates and anhydrites. The salts are useful as monoamine neurotransmitter re-uptake inhibitors.

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

BACKGROUND ART

15 The compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane is disclosed in WO 97/30997 (NeuroSearch A/S). Therein, the citrate salt was prepared (Example 15).

For commercial use, however, it is important to have a physiologically acceptable salt with an optimal combination of stability, solubility, non-hygroscopicity, 20 bioavailability and good handling properties, such as a well defined melting point and a reproducible crystalline form.

SUMMARY OF THE INVENTION

25 In its first aspect, the invention provides a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a salt of the invention, together with at 30 least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a salt of the invention, 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 35 neurotransmitter re-uptake in the central nervous system.

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

nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a salt of the invention.

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

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate

In its first aspect the present invention provides a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

In one embodiment, the salt is selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

In a second embodiment, the salt is (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.

In a further embodiment, the salt is an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

In a still further embodiment, the salt is the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu K α)	20.29	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

In a further embodiment, the salt is the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.8	10.82	11.68	11.88	12.79	14.78	16.27	18.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

In a still further embodiment, the salt is the polymorphic form (form IV) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu Kα)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu Kα)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu Kα)	26.83	27.21								
d space (Å)	3.3	3.3								

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

10

Hydrated forms

The salt of the invention may be provided in anhydrous forms or hydrated forms. Hydrated forms include the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like.

15

Labelled Compounds

The salts of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the salt of interest that will allow easy quantitative detection of said salt.

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

Methods of Preparation

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

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

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

20 Biological Activity

Salts of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes eg such as described in WO 97/30997. Based on the balanced activity observed in these tests the salts 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 salts of the invention are considered useful for the treatment, prevention or alleviation of: mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress

X 10

disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, 5 rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofascial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, 10 stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourette's diseases.

15 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 100 mg API per day, more preferred of from about 0.1 to about 10 mg API per day, most preferred of from about 0.5 to about 5 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the 20 subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions 25 comprising a therapeutically effective amount of the salt of the invention.

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

30 In a preferred embodiment, the invention provides pharmaceutical compositions comprising the salt of the invention, together with one or more pharmaceutically acceptable carriers therefore, 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 35 recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonary, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or

those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the salt of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

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

The salt of the present invention can be administered in a wide variety of oral and parenteral dosage forms.

For preparing pharmaceutical compositions from a salt 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 homoge-

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neously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

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

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

The salt 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 salt 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

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glycerine or sucrose and acids; 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
5 In single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas.
10 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 salt in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP).
15 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-
20 nasal compositions, the active 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.

25 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
30 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 (Mack Publishing Co.,
35 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

tic index and may be expressed by the ratio LD_{50}/ED_{50} . Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

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

The actual dosage depend 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 10 mg of active ingredient per individual dose, preferably of from about 0.5 to about 5 mg, are suitable for therapeutic treatments.

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

20 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 salt of the invention.

Suitable dosage ranges are 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.

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Example 1**(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane citrate salt**

The citrate salt of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane was synthesized as described in WO 97/30897 (Example 15).

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane

The free base was obtained from dissolving the citrate salt in water and adjusting pH to 10-13 with aqueous base, followed with extraction with toluene. The toluene phase was collected, dried and evaporated to dryness. This left the free base as an oil.

Example 2**(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I)**

To a heated solution of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane (the free base) in aqueous ethanol was added L-tartaric acid. The warm mixture was treated with activated charcoal and filtered. The filtrate was cooled and (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane was isolated as the L-tartrate monohydrate.

Form I is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	12.05	14.21	16.37	17.4	18.34	19.29	19.58	20.27	23.3	23.75
d space (Å)	7.3	6.2	5.4	5.1	4.8	4.6	4.5	4.4	3.8	3.7
Peak	11	12	13	14	15	16	17			
2 Theta ° (Cu K α)	24.37	25.11	26.76	26.25	26.72	29.25	29.82			
d space (Å)	3.6	3.4	3.3	3.2	3.1	3.1	3.0			

Example 3**(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form II)**

The form was prepared thermal dehydration. (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I) was heated in a TGA AlO₂ crucible to 125°C, 10°C/min. The salt was allowed to cool before opening the TGA furnace. During heating and cooling the furnace was purged with 50ml/min dry nitrogen.

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Form II is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.25	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

5 Example 4

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form III)

- The form was prepared thermal dehydration. (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I) was heated
- 10 In a TGA AlO₂ crucible to 160°C, 10°C/min. The salt was allowed to cool before opening the TGA furnace. During heating and cooling the furnace was purged with 50ml/min dry nitrogen.

Form III is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

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Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.8	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	25.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

Example 5

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form IV)

- 20 The form was prepared by suspending a freshly prepared Form II in water free ethanol. Separation of the suspended matter was conducted after 24 hours and subsequent drying under vacuum.

Form IV can also be obtained from suspension of Form III by the same procedure as described using Form II.

Apparently Form IV was physically metastable. Successive preparations of Form IV turned out as mixtures of Form IV and Form III, indicating difficulties in producing Form IV

Form IV is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu K α)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu K α)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu K α)	26.83	27.21								
d space (Å)	3.3	3.3								

CLAIMS

1. A salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.
2. The salt of claim 1 being selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.
3. The salt of claim 1, being (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.
4. The salt of claim 1, being an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.
5. The salt of claim 4, being the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	10.36	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.6	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu K α)	20.29	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

6. The salt of claim 4, being the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.6	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu K α)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	26.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

7. The salt of claim 4, being the polymorphic form (form IV) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu K α)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu K α)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu K α)	26.83	27.21								
d space (Å)	3.3	3.3								

8. A pharmaceutical composition, comprising a therapeutically effective amount of a salt of any one of claims 1-7, together with at least one pharmaceutically acceptable carrier, excipient or diluent.
9. Use of a salt of any of claims 1-7 for the manufacture of a medicament.
10. The use according to claim 9, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.
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

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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
5 dementia complex, memory dysfunction in ageing, specific phobia, social phobia,
post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse,
cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism,
pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-
type headache, chronic tension-type headache, pain associated with depression,
10 fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain,
irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke
pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained
pain, trigeminal neuralgia, dental pain, myofascial pain, phantom-limb pain,
bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic
15 syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence,
urge incontinence, nocturnal incontinence, sexual dysfunction, premature
ejaculation, erectile difficulty, erectile dysfunction, eating disorders, anorexia
nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-
stroke depression, stroke-induced brain damage, stroke-induced neuronal
20 damage or Gilles de la Tourette's disease.

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
25 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
salt according to any one of the claims 1-7.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 03/045388 A (NEUROSEARCH AS ; ROENN LARS CHRISTIAN B (DK); SCHEEL-KRUEGER JOERGEN ()) 5 June 2003 (2003-06-05) abstract page 6, line 35 claims 6-10	1-12
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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(54) Título: SALES DE 2-METOXIMETIL-3-(3,4-DICLOROFENIL)-8-AZABICICLO[3.2.1] OCTAN TARTRATO

(57) Resumen: Esta invención se relaciona con sales novedosas de (1R, 2R, 3S, 5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3.2.1] octan tartrato, tales como monohidratos y anhídridos de L-tartrato. Las sales son útiles como inhibidores de la retoma de neurotransmisor de monoamina. En otros aspectos la invención se relaciona con el uso de estas sales en un método para terapia y a composiciones farmacéuticas que comprenden las sales de la invención.

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SALES DE TARTRATO DE 2-METOXIMETIL-3-(3,4-DICLOROFENIL)-8-AZABICICLO [3,2,1] OCTANO

CAMPO TECNICO

Este invento se relaciona con las novedosas sales de tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano, tales como las L-tartrato monohidratadas y anhidras. Las sales son útiles como inhibidores de re-captación de neurotransmisores monoamina.

En otros aspectos el invento se relaciona con el uso de estas sales en un método de terapia y con composiciones farmacéuticas que comprenden las sales del invento.

ANTECEDENTES

El compuesto (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1] octano es revelado en WO 97/30997 (NeuroSearch A/S), A partir de eso, se preparó la sal de citrato (Ejemplo 15).

Sin embargo, para uso comercial, es importante tener una sal fisiológicamente aceptable con una óptima combinación de estabilidad, solubilidad, no-higroscopicidad, biodisponibilidad y buenas propiedades de manejo, tales como un punto de fusión bien definido y una forma cristalina reproducible.

SÍNTESIS DEL INVENTO

En su primer aspecto, el invento proporciona una sal seleccionada de las formas anhidras e hidratadas de tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo [3,2,1] octano.

En su segundo aspecto, el invento proporciona una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de la sal del

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invento, junto con al menos un vehículo, excipiente o diluyente farmacéuticamente aceptable.

En otro aspecto, el invento proporciona el uso de la sal del invento, para la fabricación de una composición farmacéutica para el tratamiento, prevención o el alivio de una enfermedad o un desorden o una condición de un mamífero, incluyendo al ser humano, cuya enfermedad, desorden o condición responda a la inhibición de re-captación de neurotransmisores monoamina en el sistema nervioso central.

Más aún, el invento se relaciona con un método de tratamiento, prevención o alivio de la enfermedad, o el desorden o la condición de un cuerpo animal vivo, incluyendo al ser humano, cuyo desorden, enfermedad o condición responda a la inhibición de re-captación de neurotransmisores monoamina en el sistema nervioso central, cuyo método comprenda el paso de administrar al cuerpo animal vivo que lo necesite una cantidad terapéuticamente efectiva de la sal del invento.

Para la persona calificada en el área, otros objetos del invento serán evidentes a partir de la siguiente descripción detallada y ejemplos.

EXPOSICIÓN DETALLADA DEL INVENTO

Tartrato de (1R,2R,3S,5S)- 2-metoximetil- 3-(3,4-diclorofenil)- 8-azabicyclo [3,2,1] octano

En su primer aspecto el presente invento proporciona una sal seleccionada de las formas anhidras e hidratadas de tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano.

En una segunda organización, la sal es el L-tartrato monohidratado de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano.

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En otra organización más amplia, la sal es una forma anhidra del L-tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano,

En otra organización aún más amplia, la sal es la forma polimórfica (forma II) del L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1] octano caracterizada por los siguientes picos principales en su perfil de difracción de rayos X:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10,35	11,68	12,53	14,81	15	15,77	16,82	17,41	17,77	18,87
espacio d (Å)	8,5	7,6	7,1	6,0	5,9	5,6	5,3	5,1	5,0	4,7
Pico	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20,29	21,26	21,66	23,44	23,73	25,44	25,99	27,58	28,14	
espacio d (Å)	4,4	4,2	4,1	3,8	3,7	3,5	3,4	3,2	3,2	

En una organización más amplia, la sal es la forma polimórfica (forma III) del L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano caracterizada por los siguientes picos principales en su perfil de difracción de rayos X:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5,37	10,6	10,82	11,58	11,88	12,79	14,78	16,27	16,5	17,03
espacio d (Å)	16,4	8,3	8,2	7,6	7,4	6,9	6,0	5,4	5,4	5,2
Pico	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17,84	19,29	20,01	21,2	22,99	23,46	24,54	25,15	26,59	
espacio d(Å)	5,0	4,6	4,4	4,2	3,9	3,8	3,6	3,5	3,3	

En una organización aún más amplia, la sal es la forma polimórfica (forma IV) del L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano caracterizada por los siguientes principales picos en su perfil de difracción de rayos X:

Pico No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	5,31	10,19	11,23	12,13	12,35	12,69	14,31	14,55	14,77	16,43
espacio d (Å)	16,6	8,7	7,9	7,3	7,2	7,0	6,2	6,1	6,0	5,4
Pico	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu K α)	17,48	18,21	18,43	18,81	19,36	19,61	20,26	20,5	21,29	21,46
espacio d (Å)	5,1	4,9	4,8	4,7	4,6	4,5	4,4	4,3	4,2	4,1
Pico	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu K α)	21,95	22,53	22,77	23,38	23,59	23,9	24,45	25,02	25,56	26,19
espacio d (Å)	4,0	3,9	3,9	3,8	3,8	3,7	3,6	3,6	3,5	3,4
Pico	31	32								
2 Theta ° (Cu K α)	26,83	27,21								
espacio d (Å)	3,3	3,3								

Cualquier combinación de dos o más organizaciones, según las descriptas anteriormente, se considera dentro del alcance del presente invento.

Formas Hidratadas

La sal del invento puede ser provista tanto en formas anhidras o hidratadas. Las formas hidratadas incluyen la monohidratada, la dihidratada, la hemihidratada, la trihidratada, la tetrahidratada y similares.

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Compuestos Marcados

Las sales del invento pueden usarse en sus formas marcadas o no marcadas. En el contexto de este invento "marca" se refiere a la unión de un marcador a la sal de interés que permita la sencilla detección cuantitativa de dicha sal.

La sales marcadas del invento pueden ser útiles como herramientas de diagnóstico, radio-marcadores, o agentes de monitoreo en varios métodos de diagnóstico y para imágenes "in vivo" de receptores.

La sal marcada del invento contiene preferentemente al menos un radionucleido como marca. Los radionucleidos emisores de positrones son todos candidatos para este uso. En el contexto de este invento, el radionucleido se selecciona preferentemente entre ^2H (deuterio), ^3H (tritio), ^{13}C , y ^{14}C .

Métodos de Preparación

Las sales del invento pueden prepararse con los métodos convencionales de síntesis química, por ejemplo, aquellos descritos en los ejemplos de trabajo. Los materiales iniciales para los procesos descritos en la presente aplicación son conocidos o pueden prepararse fácilmente con los métodos convencionales a partir de productos químicos disponibles comercialmente.

También una sal del invento puede convertirse en otra sal del invento utilizando los métodos convencionales.

Los productos finales de las reacciones aquí descritas pueden ser aislados por medio de las técnicas convencionales, por ejemplo, por extracción, cristalización, destilación, cromatografía, etc.

Actividad Biológica

Las sales del invento pueden evaluarse por su habilidad para inhibir la recaptación de las monoaminas dopamina, noradrenalina y serotonina en sinaptosomas como ha sido descrito en WO 97/30997. En base a la actividad balanceada observada en estas pruebas, las sales del invento se consideran útiles para el tratamiento, la prevención o el alivio de una enfermedad, un desorden o una condición de un mamífero, incluyendo a los seres humanos, cuya enfermedad, desorden o condición respondan a la inhibición de re-captación de neurotransmisores monoamina en el sistema nervioso central.

En una organización especial, las sales del invento son consideradas útiles para el tratamiento, la prevención o alivio de los desórdenes de los estados de ánimo, depresión, depresión atípica, depresión secundaria al dolor, desorden depresivo mayor, desorden distémico, desorden bipolar, desorden bipolar I, desorden bipolar II, desorden ciclotímico, alteración del estado de ánimo debida a una condición médica general, alteración del estado de ánimo inducida por una sustancia, pseudodemencia, Síndrome de Ganser, desorden obsesivo compulsivo, desorden de pánico, desorden de pánico sin agorafobia, desorden de pánico con agorafobia, agorafobia sin antecedentes de desorden de pánico, ataque de pánico, déficit de la memoria, pérdida de la memoria, déficit de atención por hiperactividad, obesidad, ansiedad, desorden de ansiedad generalizado, desordenes de alimentación, enfermedad de Parkinson, parkinsonismo, demencia, demencia ocasionada por la edad, demencia senil, enfermedad de Alzheimer, complejo de demencia del síndrome de inmunodeficiencia adquirida, disfunción de la memoria ocasionada por la edad, fobia específica, fobia social, desorden de estrés postraumático, desorden agudo de estrés, adicción a las drogas, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso de tabaco, adicción al alcohol, alcoholismo, dolor, dolor crónico, dolor inflamatorio, dolor

neuropático, migraña, cefalea por tensión, cefalea crónica por tensión, dolor asociado con la depresión, fibromialgia, artritis, osteoartritis, artritis reumatoide, dolor de espalda, dolor de cáncer, dolor de colon irritable, síndrome de colon irritable, dolor posquirúrgico, dolor posapopléjico, neuropatía inducida por drogas, neuropatía diabética, dolor mantenido por el simpático, neuralgia trigeminal, dolor dental, dolor miofacial, dolor de extremidades fantasma, bulimia, síndrome premenstrual, síndrome de fase lútea tardía, síndrome postraumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia de apuro, incontinencia nocturna, disfunción sexual, eyaculación precoz, dificultad eréctil, disfunción eréctil, desórdenes alimentarios, anorexia nerviosa, desórdenes del sueño, autismo, mutismo, tricotilomanía, narcolepsia, depresión postapopléjica, daño cerebral inducido por apoplejia, daño neuronal inducido por apoplejía o enfermedad de Píllis de la Tourettes.

Actualmente se contempla que una dosificación apropiada de un ingrediente farmacéutico activo (API) se encuentra dentro del rango de alrededor de los 0,1 a 100 mg API por día, más preferentemente de alrededor de 0,1 a 10 mg API por día, más preferentemente alrededor de 0,5 mg a 5 mg API por día, dependiendo, sin embargo, del modo exacto de administración, la forma en la que se administra, la indicación considerada, el sujeto y en particular el peso del sujeto en cuestión, y más aún la preferencia y experiencia del médico o veterinario a cargo.

Composiciones Farmacéuticas

En otro aspecto el invento provee novedosas composiciones farmacéuticas que incluyen una cantidad terapéuticamente efectiva de la sal del invento.

Mientras que una sal del invento para uso terapéutico puede administrarse en forma de sal cruda, se prefiere introducir el ingrediente activo en una

composición farmacéutica junto con uno o más adyuvantes, excipientes, vehículos, buffers, diluyentes, y/o otros auxiliares farmacéuticos usualmente utilizados.

En la organización preferida, el invento provee composiciones farmacéuticas que comprenden la sal del invento, junto con uno o más vehículos farmacéuticamente aceptables y opcionalmente, otros ingredientes terapéuticos y/o profilácticos, conocidos y utilizados en el área. El/los vehículo(s) debe(n) ser "aceptable(s)": Esto significa que deben ser compatibles con los otros ingredientes de la formulación y no ser dañinos para el recipiente de la misma.

Las composiciones farmacéuticas del invento deben ser apropiadas para la administración oral, rectal, bronquial, nasal, pulmonar, tópica (incluyendo la bucal y sublingual), transdérmica, vaginal o parenteral (incluyendo cutánea, subcutánea, intramuscular, intraperitoneal, intravenosa, intrarterial, Intracerebral, inyección intraocular o infusión), o aquellas de una forma adecuada para la administración por inhalación o insuflación, incluyendo la administración en aerosol de polvos y líquidos, o por sistemas de liberación sostenida. Ejemplos apropiados de sistemas de liberación sostenida son las matrices semipermeables de polímeros hidrofóbicos sólidos conteniendo la sal del invento, cuyas matrices pueden presentarse como artículos formados, por ejemplo films o microcápsulas.

La sal del invento, junto con un adyuvante, vehículo o diluyente convencional, puede por lo tanto ser puesta en forma de composiciones farmacéuticas y de formas farmacéuticas unitarias. Dichas formas incluyen sólidos, y en particular tabletas, cápsulas rellenas, en forma de polvo y pellets, y líquida, en particular soluciones acuosas y no acuosas, suspensiones, emulsiones, elixires, y cápsulas rellenas con los mismos, todas para uso oral, supositorios para administración rectal y soluciones estériles inyectables para uso parenteral. Dichas composiciones farmacéuticas y las formas farmacéuticas

unitarias aquí mencionadas, pueden incluir ingredientes convencionales en proporciones convencionales, con o sin compuestos o principios activos adicionales, y dichas formas farmacéuticas unitarias pueden contener cualquier cantidad adecuadamente efectiva del ingrediente activo correspondiente al rango deseado de dosificación diario a ser empleado.

La sal del presente invento puede administrarse en una amplia variedad de formas orales y parenterales.

Para preparar las composiciones farmacéuticas de la sal del presente invento, los vehículos farmacéuticamente aceptables pueden ser sólidos o líquidos. Las preparaciones de forma sólida incluyen polvos, tabletas, píldoras, cápsulas, sellos, supositorios y gránulos dispersables. Un vehículo sólido puede ser una o más sustancias que puedan actuar también como diluyentes, agentes saborizantes, solubilizantes, lubricantes, agentes de suspensión, aglutinantes, conservantes, agentes desintegradores de tabletas o un material encapsulante.

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

En las tabletas, el componente activo está mezclado con el vehículo que tiene la necesaria capacidad de unión en proporciones adecuadas y compactadas en la forma y medida deseadas.

Los polvos y las tabletas contienen preferentemente desde entre cinco o diez y hasta el setenta por ciento de componente activo. Los vehículos adecuados son el carbonato de magnesio, estearato de magnesio, talco, azúcar, lactosa, pectina, dextrina, almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa sódica, cera de baja licuefacción, manteca de cacao, y otros. El término "preparación" está pensado para incluir la formulación del compuesto activo con el material encapsulante como vehículo, proporcionando una cápsula en la cual el componente

activo, con o sin vehículos, está rodeado de un vehículo que se encuentra por lo tanto en asociación con el mismo.

Del mismo modo, se incluyen los sellos y las pastillas, Las tabletas, polvos, cápsulas, píldoras, sellos y pastillas, pueden usarse como formas sólidas adecuadas para la administración oral.

Para preparar supositorios, se derrite primero una cera de baja licuefacción, como por ejemplo una mezcla de glicéridos de ácidos grasos o manteca de cacao, y luego allí dentro se mezcla de manera homogénea, puede ser revolviendo, el componente activo. La mezcla homogénea fundida se vuelca luego en moldes de la medida adecuada, que permitan el enfriado y así la solidificación.

Los compuestos adecuados para la administración vaginal pueden presentarse en pesarios, tampones, cremas, geles, pastas, espumas, o sprays que contengan además del ingrediente activo aquellos vehículos que se conozcan como apropiados en el área.

Los preparados líquidos incluyen soluciones, suspensiones y emulsiones, como por ejemplo soluciones acuosas o soluciones propilenglicol-agua. Por ejemplo, los preparados de inyecciones líquidas parenterales pueden formularse como soluciones en solución acuosa de polietilenglicol.

La sal de acuerdo con el presente invento puede por lo tanto formularse para administración parenteral (por inyección, por ejemplo inyección en bolus o infusión continua) y puede presentarse en forma de unidad de dosis de ampollas, jeringas pre-llenadas, infusión de poco volumen o en contenedores multi-dosis con agregado de conservante. Las composiciones pueden tomar la forma de suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizadores y/o agentes dispersantes. Alternativamente, el ingrediente activo puede estar en forma de polvo, obtenido por aislamiento aséptico del sólido estéril o por liofilización a partir

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de la solución, para reconstitución antes de su uso con un vehículo adecuado, por ejemplo agua estéril libre de pirógenos.

Las soluciones acuosas apropiadas para el uso oral pueden prepararse... disolviendo el componente activo en agua y agregando un colorante apropiado, saborizantes, agentes estabilizadores y espesantes, según se desee.

Las suspensiones acuosas apropiadas para el uso oral pueden prepararse dispersando el compuesto activo finamente dividido, en agua con material viscoso como gomas naturales o sintéticas, resinas, metilcelulosa, sodio, carboximetilcelulosa, o cualquier otro agente de suspensión conocido.

También están incluidas las preparaciones de forma sólida, destinadas a su conversión, inmediatamente antes de su uso a preparaciones de forma líquida para administración oral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones. Además del compuesto activo, tales preparados pueden incluir colorantes, saborizantes, estabilizadores, buffers, endulzantes artificiales y naturales, dispersantes, espesantes, agentes solubilizantes y otros similares.

Para la administración tópica en la epidermis, la sal del invento puede ser formulada como ungüentos, cremas o lociones o como parches transdérmicos. Los ungüentos y las cremas pueden, por ejemplo, formularse con una base acuosa u oleosa con el agregado de agentes espesantes y/o gelificantes apropiados. Las lociones pueden formularse con una base acuosa u oleosa y en general contienen uno o más agentes emulsionantes, agentes estabilizadores, agentes de dispersión, agentes de suspensión, agentes espesantes o agentes colorantes.

Las composiciones adecuadas para la administración tópica en la boca incluyen pastillas que contienen el compuesto activo sobre una base saborizada, usualmente sacarosa y goma arábiga o tragacanto; pastillas que contienen el ingrediente activo en una base inerte como ser gelatina y glicerina o sacarosa y

goma arábiga; y enjuagues bucales que contiene el ingrediente activo en un vehículo líquido apropiado.

Las soluciones o suspensiones se aplican directamente en la cavidad nasal... por medios convencionales, por ejemplo con un gotero, pipeta o spray. Las composiciones pueden proveerse en forma de dosis única o multi-dosis.

La administración para el tracto respiratorio puede lograrse también por medio de una formulación aerosolizada en la cual el ingrediente activo es provisto en un pack presurizado con un propelente adecuado como el clorofluorocarbono (CFC), por ejemplo, diclorotetrafluorometano, triclorofluorometano, o diclorofluorometano, dióxido de carbono o cualquier otro gas apropiado. El aerosol puede convenientemente contener también un surfactante como la lecitina. La dosis de la droga puede controlarse con la provisión de una válvula medidora.

Alternativamente, los ingredientes activos pueden proveerse en forma de polvo seco, por ejemplo, una mezcla de polvo de la sal en una base de polvo adecuada como la lactosa, el almidón, o derivados del almidón como la hidroxipropilmetil celulosa y la polivinilpirrolidona (PVP). Convenientemente, el vehículo en polvo formará un gel en la cavidad nasal. La composición en polvo puede presentarse en formas farmacéuticas unitarias, como por ejemplo en cápsulas o cartuchos de, por ejemplo, gelatina o blisters desde los cuales se pueda administrar el polvo por medio de un inhalador.

En composiciones que sean para la administración en el tracto respiratorio, incluyendo composiciones intranasales, el compuesto activo tendrá un pequeño tamaño de partícula por ejemplo del orden de los 5 micrones o menos. Tal tamaño de partícula puede obtenerse mediante medios conocidos en el área, por ejemplo la micronización.

Cuando se lo desee, se pueden utilizar composiciones adaptadas para brindar liberación sostenida del ingrediente activo.

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Preferentemente, las preparaciones farmacéuticas se encuentran en formas farmacéuticas unitarias. En tales formas la preparación se subdivide en unidades de dosis que contienen cantidades apropiadas del componente activo. La forma farmacéutica unitaria puede ser una preparación envasada, en un envase que contenga cantidades discretas de la preparación, como ser tabletas, cápsulas envasadas y polvos en viales o ampollas. También la forma farmacéutica unitaria puede ser una cápsula, tableta, sello o pastilla misma, o puede ser el número apropiado de cualquiera de ellos en forma envasada.

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

Se pueden hallar más detalles sobre las técnicas de formulación y administración en la última edición de Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

Una dosis terapéuticamente efectiva se refiere a la cantidad del ingrediente activo que mejora los síntomas o la condición. La eficacia terapéutica y la toxicidad, por ejemplo ED_{50} y LD_{50} , pueden determinarse por medio de procedimientos farmacológicos estándar en cultivos celulares o en animales de experimentación. La relación de dosis entre los efectos terapéuticos y tóxicos es el índice terapéutico y puede expresarse con la relación LD_{50}/ED_{50} . Se prefieren las composiciones farmacéuticas que exhiban amplios índices terapéuticos.

La dosis administrada debe ser, obviamente, cuidadosamente ajustada a la edad, peso y condición del individuo a tratar, así como también la ruta de administración, forma farmacéutica y régimen, y el resultado deseado, y la dosis exacta debe, por supuesto, estar determinada por el médico tratante.

La dosificación real depende de la naturaleza y severidad de la enfermedad a tratar, y se encuentra dentro de la discreción del médico y puede ser variada por titulación de la dosificación a las circunstancias particulares de este invento para

producir el efecto terapéutico deseado. Sin embargo, está actualmente contemplado que composiciones farmacéuticas que contengan entre 0,1 a 10 mg del ingrediente activo por dosis individual, preferentemente de 0,5 a 5 mg, son adecuadas para tratamientos terapéuticos.

El ingrediente activo puede administrarse en una o varias dosis por día. Se puede obtener un resultado satisfactorio, en ciertas circunstancias, con una dosificación tan baja como 0,1 µg/kg i.v. y 1 µg/kg p.o. El límite superior del rango de la dosis se considera, en la actualidad, en aproximadamente 10 mg/kg i.v. y 100 mg/kg p.o. los rangos preferidos son de aproximadamente 0,1 µg/kg a 10 mg/kg/día i.v., y desde aproximadamente 1 µg/kg a aproximadamente 100 mg/kg/día p.o.

Métodos de Terapia

En otro aspecto el invento proporciona un método para el tratamiento, la prevención o el alivio de una enfermedad o un desorden o una condición de un cuerpo animal vivo, incluido el ser humano, cuya enfermedad, desorden o condición responda a la inhibición de re-captación de neurotransmisores monoamina en el sistema nervioso central, y cuyos métodos comprendan la administración de una cantidad efectiva de la sal del invento, a dicho cuerpo animal vivo, incluido el ser humano.

Los rangos adecuados de las dosis dependen como siempre del modo exacto de administración, forma en la que se administra, la indicación para la que se la administra, el sujeto involucrado y el peso del cuerpo del mismo, y aún más, la preferencia y experiencia del médico o veterinario a cargo.

EJEMPLOS

El invento está ilustrado con relación a los siguientes ejemplos, los que no intentan de ninguna manera limitar el alcance del invento tal como se lo reivindica.

Ejemplo 1

Sal de citrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano

La sal de citrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1] octano fue sintetizada según se describe en WO 97/30997 (Ejemplo 15).

(1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano

La base libre se obtuvo disolviendo la sal de citrato en agua y ajustando el pH a 10-13 con una base acuosa, seguido de una extracción con tolueno. La fase de tolueno se recogió, secó y evaporó a sequedad. Esto dejó la base libre como un aceite.

Ejemplo 2

L-tartrato monohidratado de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano (Forma I)

A una solución caliente de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano (la base libre) en solución acuosa de etanol se le añadió ácido L-tartárico.

La mezcla templada fue tratada con carbón activado y filtrado. El filtrado se enfrió y se aisló el (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano como L-tartrato monohidratado.

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La forma I se caracteriza por los siguientes picos principales en su perfil de difracción de rayos X según se muestra a continuación:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	12,05	14,21	16,37	17,4	18,34	19,29	19,58	20,27	23,3	23,75
espacio d (Å)	7,3	6,2	5,4	5,1	4,8	4,6	4,5	4,4	3,8	3,7
Pico	11	12	13	14	15	16	17			
2 Theta ° (Cu Kα)	24,37	26,11	26,76	26,25	28,72	29,25	29,82			
espacio d (Å)	3,6	3,4	3,3	3,2	3,1	3,1	3,0			

Ejemplo 3

L-Tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1] octano (Forma II)

La forma se preparó por deshidratación térmica. El L-tartrato monohidratado (Forma I) de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano se calentó en un crisol TGA AlO₂ a 125°C, 10°C/min. Se dejó enfriar la sal antes de abrir el horno TGA. Durante el calentamiento y enfriado se purgó el horno con 50ml/min de nitrógeno seco.

La forma II se caracteriza por los siguientes picos principales en su perfil de difracción de rayos X según se muestra a continuación:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10,35	11,68	12,53	14,81	15	15,77	16,82	17,41	17,77	18,87
espacio d (Å)	8,5	7,6	7,1	6,0	5,9	5,6	5,3	5,1	5,0	4,7
Pico	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20,29	21,26	21,66	23,44	23,73	25,44	25,99	27,58	28,14	
espacio d (Å)	4,4	4,2	4,1	3,8	3,7	3,5	3,4	3,2	3,2	

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Ejemplo 4

L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabícclo[3,2,1] octano (Forma III)

La forma se preparó por deshidratación térmica. El L-tartrato monohidratado (Forma I) de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabícclo[3,2,1]octano se calentó en un crisol TGA AlO₂ a 160°C, 10°C/min. Se dejó enfriar la sal antes de abrir el horno TGA, Durante el calentamiento y enfriado se purgo el horno con 50ml/min de nitrógeno seco.

La forma III se caracteriza por los siguientes picos principales en su perfil de difracción de rayos X según se muestra a continuación:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5,37	10,8	10,82	11,58	11,88	12,79	14,78	16,27	16,5	17,03
espacio d (Å)	16,4	8,3	8,2	7,8	7,4	6,9	6,0	5,4	5,4	5,2
Pico	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17,84	19,29	20,01	21,2	22,99	23,46	24,54	25,15	26,59	
espacio d (Å)	5,0	4,6	4,4	4,2	3,9	3,8	3,6	3,5	3,3	

Ejemplo 5

L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabícclo[3,2,1] octano (Forma IV)

La forma se preparó suspendiendo un preparado fresco de la forma II en etanol libre de agua. La separación de la materia suspendida se llevó a cabo luego de 24 horas y el subsecuente secado bajo vacío.

La Forma IV puede obtenerse también a partir de la suspensión de la forma III por el mismo procedimiento descrito utilizando la Forma II.

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Aparentemente la forma IV fue físicamente metaestable. Los sucesivos preparados de la Forma IV resultaron mezclas de la forma IV y la forma III, indicando dificultades en producir la Forma IV.

La forma IV se caracteriza por los siguientes picos principales en su perfil de difracción de rayos X, según se muestra a continuación:

Pico No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	5,31	10,19	11,23	12,13	12,35	12,69	14,31	14,55	14,77	16,43
espacio d (Å)	16,6	8,7	7,9	7,3	7,2	7,0	6,2	6,1	6,0	5,4
Pico	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu K α)	17,48	18,21	18,43	18,81	19,36	19,61	20,26	20,5	21,29	21,46
espacio d (Å)	5,1	4,9	4,8	4,7	4,6	4,5	4,4	4,3	4,2	4,1
Pico	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu K α)	21,95	22,53	22,77	23,38	23,59	23,9	24,45	25,02	25,56	26,19
espacio d (Å)	4,0	3,9	3,9	3,8	3,8	3,7	3,6	3,6	3,5	3,4
Pico	31	32								
2 Theta ° (Cu K α)	26,83	27,21								
espacio d (Å)	3,3	3,3								

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REVINDICACIONES

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

1. Una sal seleccionada de las formas anhidras e hidratadas de tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano.

2. La sal de la reivindicación 1, seleccionada de las formas anhidras e hidratadas de L-tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano.

3. La sal de la reivindicación 1, que es L-tartrato monohidrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano.

4. La sal de la reivindicación 1, que es una forma anhidra de L-tartrato (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano.

5. La sal de la reivindicación 4, que es la forma polimórfica (forma II) de L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano caracterizado por los siguientes picos principales en su perfil de difracción de rayos X:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10,35	11,68	12,53	14,81	15	15,77	16,82	17,41	17,77	18,87
espacio d (Å)	8,5	7,6	7,1	6,0	5,9	5,6	5,3	5,1	5,0	4,7
Pico	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20,29	21,26	21,86	23,44	23,73	25,44	25,99	27,58	28,14	
espacio d (Å)	4,4	4,2	4,1	3,8	3,7	3,5	3,4	3,2	3,2	

6. La sal de la reivindicación 4, que es la forma polimórfica (forma III) de L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-

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azabicyclo[3,2,1] octano caracterizado por los siguientes picos principales en perfil de difracción de rayos X:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5,37	10,6	10,82	11,58	11,88	12,79	14,78	16,27	16,5	17,03
Espacio d (Å)	16,4	8,3	8,2	7,6	7,4	6,9	6,0	5,4	5,4	5,2
Pico	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17,84	19,29	20,01	21,2	22,98	23,46	24,54	25,15	26,59	
espacio d (Å)	5,0	4,6	4,4	4,2	3,9	3,8	3,6	3,5	3,3	

7. La sal de la reivindicación 4, que es la forma polimórfica (forma IV) de L-tartrato anhidro de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1] octano caracterizado por los siguientes picos principales en su perfil de difracción de rayos X:

Pico No,	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5,31	10,19	11,23	12,13	12,35	12,69	14,31	14,55	14,77	16,43
espacio d (Å)	16,6	8,7	7,9	7,3	7,2	7,0	6,2	6,1	6,0	5,4
Pico	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu Kα)	17,48	18,21	18,43	18,81	19,36	19,61	20,26	20,5	21,29	21,46
espacio d (Å)	5,1	4,9	4,8	4,7	4,6	4,5	4,4	4,3	4,2	4,1
Pico	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu Kα)	21,95	22,53	22,77	23,38	23,59	23,9	24,45	25,02	25,56	26,19
espacio d (Å)	4,0	3,9	3,9	3,8	3,8	3,7	3,6	3,6	3,5	3,4
Pico	31	32								
2 Theta ° (Cu Kα)	26,83	27,21								
espacio d (Å)	3,3	3,3								

8. Una composición farmacéutica, que incluye una cantidad terapéuticamente efectiva de una sal de cualquiera de las reivindicaciones 1-7, junto con al menos un vehículo, excipiente o diluyente farmacéuticamente aceptable.

9. El uso de una sal de cualquiera de las reivindicaciones 1-7 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 un desorden o una condición de un mamífero, incluyendo al ser humano, cuya enfermedad, desorden o condición respondan a la inhibición de recaptación de neurotransmisores monoamina en el sistema nervioso central.

11. El uso de acuerdo con la reivindicación 10, en que la enfermedad, desorden o condición sea alteración de los estados de ánimo, depresión, depresión atípica, depresión secundaria al dolor, desorden depresivo mayor, desorden distémico, desorden bipolar, desorden bipolar I, desorden bipolar II, desorden ciclotímico, alteración del estado de ánimo debido a una condición médica general, alteración del estado de ánimo inducida por una sustancia, pseudodemencia, Síndrome de Ganser, desorden obsesivo compulsivo, desorden de pánico, desorden de pánico sin agorafobia, desorden de pánico con agorafobia, agorafobia sin antecedentes de desorden de pánico, ataque de pánico, déficit de la memoria, pérdida de la memoria, déficit de atención por hiperactividad, obesidad, ansiedad, desorden de ansiedad generalizado, desordenes de alimentación, enfermedad de Parkinson, parkinsonismo, demencia, demencia ocasionada por la edad, demencia senil, enfermedad de Alzheimer, complejo de demencia del síndrome de inmunodeficiencia adquirida, disfunción de la memoria ocasionada por la edad, fobia específica, fobia social, desorden de estrés postraumático, desorden agudo de estrés, adicción a las

drogas, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso de tabaco, adicción al alcohol, alcoholismo, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, migraña, cefalea por tensión, cefalea crónica por tensión, dolor asociado con la depresión, fibromialgia, artritis, osteoartritis, artritis reumatoide, dolor de espalda, dolor de cáncer, dolor de colon irritable, síndrome de colon irritable, dolor posquirúrgico, dolor posapopléjico, neuropatía inducida por drogas, neuropatía diabética, dolor mantenido por el simpático, neuralgia trigeminal, dolor dental, dolor miofacial, dolor de extremidades fantasma, bulimia, síndrome premenstrual, síndrome de fase lútea tardía, síndrome postraumático, síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia de apuro, incontinencia nocturna, disfunción sexual, eyaculación precoz, dificultad eréctil, disfunción eréctil, desórdenes alimentarios, anorexia nerviosa, desórdenes del sueño, autismo, mutismo, tricotilomanía, narcolepsia, depresión postapopléjica, daño cerebral inducido por apoplejía, daño neuronal inducido por apoplejía o enfermedad de Píllas de la Tourettes.

12. Un método para el tratamiento, prevención o alivio de una enfermedad o un desorden o una condición de un cuerpo animal vivo, incluyendo al ser humano, cuyo desorden, enfermedad o condición responda a la inhibición de recaptación de neurotransmisores monoamina en el sistema nervioso central, cuyo método comprenda el paso de administrar a dicho cuerpo animal vivo que lo necesite, una cantidad terapéuticamente efectiva de la sal de acuerdo con cualquiera de las reivindicaciones 1-7.

p.: NEUROSEARCH A/S

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RESUMEN**SALES DE TARTRATO DE 2-METOXIMETIL-3-(3,4-DICLOROFENIL)-8-AZABICICLO [3,2,1] OCTANO**

Este invento se relaciona con las novedosas sales de tartrato de (1R,2R,3S,5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo[3,2,1]octano, tales como las L-tartrato monohidratadas y anhidras. Las sales son útiles como inhibidores de re-captación de neurotransmisores monoamina.

En otros aspectos el invento se relaciona con el uso de estas sales en un método de terapia y con composiciones farmacéuticas que incluyen las sales del invento.

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**AMENDED
CLAIMS**

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CLAIMS

1. A salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

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2. The salt of claim 1 being selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

10 3. The salt of claim 1, being (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.

4. The salt of claim 1, being an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

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5. The salt of claim 4, being the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

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Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.66	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

6. The salt of claim 4, being the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

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Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.86	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

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7. The salt of claim 4, being the polymorphic form (form IV) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu Kα)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu Kα)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu Kα)	26.83	27.21								
d space (Å)	3.3	3.3								

8. A pharmaceutical composition, comprising a therapeutically effective amount of a salt of any one of claims 1-7, together with at least one pharmaceutically acceptable carrier, excipient or diluent.
9. Use of a salt of any of claims 1-7 for the manufacture of a medicament.
10. The use according to claim 9, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.
11. The use according to claim 10, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, depression secondary to pain, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, 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

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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
5 dementia complex, memory dysfunction in ageing, specific phobia, social phobia,
post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse,
cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism,
pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-
type headache, chronic tension-type headache, pain associated with depression,
10 fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain,
irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke
pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained
pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain,
bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic
15 syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence,
urge incontinence, nocturnal incontinence, sexual dysfunction, premature
ejaculation, erectile difficulty, erectile dysfunction, eating disorders, anorexia
nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-
stroke depression, stroke-induced brain damage, stroke-induced neuronal
20 damage or Gilles de la Tourettes disease.

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
25 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
salt according to any one of the claims 1-7.

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**REIVINDICACIONES
MODIFICADAS**

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REIVINDICACIONES

1. Una sal seleccionada de las formas anhídrida e hidratada de tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(3,4-diclorofenil)-8-azabicyclo [3.2.1] octano.
2. La sal de la reivindicación 1 seleccionada de las formas anhídrida e hidratada de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano.
3. La sal de la reivindicación 1, que es monohidrato de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano.
4. La sal de la reivindicación 1, que es una forma anhídrida de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano.
5. La sal de la reivindicación 4, que es una forma polimórfica (forma II) de anhídrido de L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano caracterizada por los siguientes picos principales en el patrón de difracción de rayos X del polvo:

Pico N°	1	2	3	4	5	6	7	8	9	10
2Theta°(Cu Kα)	10,35	11,68	12,53	14,81	15	15,77	16,82	17,41	17,77	18,87
espacio d (Å)	8,5	7,8	7,1	6,0	5,9	5,6	5,3	5,1	5,0	4,7
Pico	11	12	13	14	15	16	17	18	19	
2Theta°(Cu Kα)	20,29	21,26	21,66	23,44	23,73	25,44	25,99	27,58	28,14	
espacio d (Å)	4,4	4,2	4,1	3,8	3,7	3,5	3,4	3,2	3,2	

6. La sal de la reivindicación 4, que es una forma polimórfica (forma III) del anhídrido del L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano caracterizada por los siguientes picos en el patrón de difracción de rayos X del polvo:

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Pico N°	1	2	3	4	5	6	7	8	9	10
2Theta°(Cu Kα)	5,37	10,6	10,82	11,58	11,88	12,79	14,78	16,57	16,5	17,03
espacio d (Å)	16,4	8,3	8,2	7,6	7,4	6,9	6,0	5,4	5,4	5,2
Pico	11	12	13	14	15	16	17	18	19	
2Theta°(Cu Kα)	17,84	19,29	20,01	21,2	22,99	23,46	24,54	25,15	26,59	
espacio d (Å)	5,0	4,6	4,4	4,2	3,9	3,8	3,6	3,5	3,3	

7. La sal de la reivindicación 4, que es una forma polimórfica (forma IV) del L-tartrato de (1R, 2R, 3S, 5S)-2-metoximetil-3-(4,3-diclorofenil)-8-azabicyclo[3.2.1] octano caracterizada por los siguientes picos en el patrón de difracción de rayos X del polvo:

Pico N°	1	2	3	4	5	6	7	8	9	10
2Theta°(Cu Kα)	5,31	10,19	11,23	12,13	12,35	12,69	14,31	14,55	14,77	16,43
espacio d (Å)	16,6	8,7	7,9	7,3	7,2	7,0	6,2	6,1	6,0	5,4
Pico	11	12	13	14	15	16	17	18	19	20
2Theta°(Cu Kα)	17,48	18,21	18,43	18,81	19,36	19,61	20,26	20,5	21,29	21,48
espacio d (Å)	5,1	4,9	4,8	4,7	4,6	4,5	4,4	4,3	4,2	4,1
Pico	21	22	23	24	25	26	27	28	29	30
2Theta°(Cu Kα)	21,59	22,53	22,77	23,38	23,59	23,9	24,45	25,02	25,56	26,19
espacio d (Å)	4,0	3,9	3,9	3,8	3,8	3,7	3,6	3,6	3,5	3,4
Pico	31	32								
2Theta°(Cu Kα)	26,83	27,21								
espacio d (Å)	3,3	3,3								

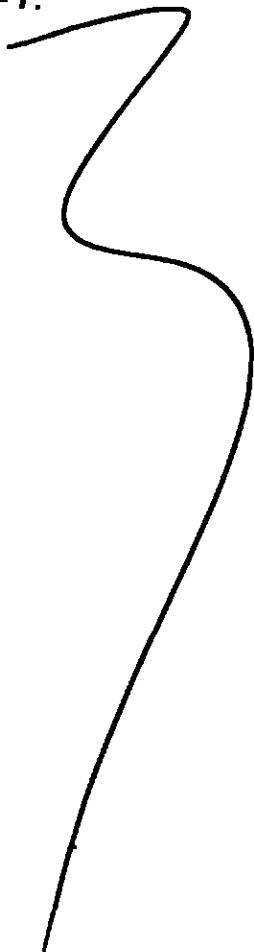
8. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de una sal de cualquiera de las reivindicaciones 1 – 7, junto con al menos un portador, excipiente o diluyente farmacéuticamente aceptable.
9. El uso de una sal de cualquiera de las reivindicaciones 1 – 7 para la fabricación de un medicamento.

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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 desorden o una condición de un mamífero, incluyendo un humano, enfermedad, desorden o condición que responde a la inhibición de la reabsorción del neurotransmisor de monoamina en el sistema nervioso central.
11. El uso de acuerdo con la reivindicación 10, en donde la enfermedad, desorden o condición es desorden del ánimo, depresión, depresión atípica, depresión secundaria al dolor, desorden depresivo importante, desorden distímico, desorden bipolar, desorden bipolar I, desorden bipolar II, desorden ciclotímico, desorden del ánimo debido a una condición médica general, desorden del ánimo inducido por sustancias, pseudodemencia, síndrome de Ganser, desorden obsesivo compulsivo, desorden de pánico, desorden de pánico sin agorafobia, desorden del pánico con agorafobia, agorafobia sin historial de desorden del pánico, ataque de pánico, déficit de memoria, pérdida de memoria, desorden de déficit de atención por hiperactividad, obesidad, ansiedad, desorden de ansiedad generalizada, desorden alimenticio, desorden de Parkinson, parkinsonismo, demencia, demencia del envejecimiento, demencia senil, enfermedad de Alzheimer, síndrome de inmunodeficiencia adquirido, complejo de demencia, disfunción de la memoria por envejecimiento, fobia específica, fobia social, desorden de estrés postraumático, desorden de estrés agudo, adicción a las drogas, abuso de drogas, abuso de cocaína, abuso de nicotina, abuso de tabaco, adicción al alcohol, alcoholismo, dolor, dolor crónico, dolor inflamatorio, dolor neuropático, dolor de migraña, dolor de cabeza del tipo tensión, dolor de cabeza del tipo tensión crónico, dolor asociado con la depresión, fibromialgia, artritis, osteoartritis, artritis reumatoidea, dolor de espalda, dolor por cáncer, dolor por intestino irritable, síndrome del intestino irritable, dolor postoperatorio, dolor postinfarto, neuropatía inducida por las drogas, neuropatía diabética, dolor mantenido por el simpático, neuralgia trigeminal, dolor dental, dolor miofacial, dolor del miembro fantasma, bulimia, síndrome premenstrual, síndrome de fase luteal tardía, síndrome postraumático,

síndrome de fatiga crónica, incontinencia urinaria, incontinencia por estrés, incontinencia por urgencia, incontinencia nocturna, disfunción sexual, eyaculación prematura, dificultad eréctil, disfunción eréctil, desórdenes alimenticios, anorexia nerviosa, desórdenes del sueño, autismo, mutismo, tricotilomanía, narcolepsia, depresión postinfarto, daño cerebral inducido por infarto, daño neuronal inducido por infarto o enfermedad de Gilles de la Tourettes.

12. Un método para el tratamiento, prevención o alivio de una enfermedad o desorden o una condición de un cuerpo animal vivo, incluyendo un humano, desorden, enfermedad o condición que responde a la inhibición de la reabsorción del neurotransmisor de monoamina en el sistema nervioso central, método que comprende el paso de administrar a cuerpo animal vivo en necesidad del mismo una cantidad terapéuticamente efectiva de una sal de acuerdo con una de las reivindicaciones 1 - 7.



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

10.100.026
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PCT

To:

NEUROSEARCH AS
Patent Department
93 Pederstrupvej
DK-2750 Ballerup
DANEMARK

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

23.05.2005

Applicant's or agent's file reference
264-204-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2004/051651

International filing date (day/month/year)
29.07.2004

Priority date (day/month/year)
31.07.2003

Applicant
NEUROSEARCH AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80286 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4485

Authorized Officer

Parriche, S

Tel. +49 89 2399-7890



PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 264-204-WO	FOR FURTHER ACTION See Form PCT/PEAA16	
International application No. PCT/EP2004/051651	International filing date (day/month/year) 29.07.2004	Priority date (day/month/year) 31.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/46, A61P25/00, C07D451/02		
Applicant NEUROSEARCH AS et al.		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☐ sent to the applicant and to the International Bureau) a total of sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).		
4. This report 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 Article 35(2) 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		
Date of submission of the demand 19.03.2005	Date of completion of this report 23.05.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80289 Munich Tel. +49 89 2399 - 0 Tx: 523856 apmu d Fax: +49 89 2399 - 4485	Authorized Officer Molina de Alba, J Telephone No. +49 89 2399-7823 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No. **59**
PCT/EP2004/051651

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-12 as originally filed

Claims, Numbers

1-12 received on 19.03.2005 with letter of 19.03.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify):*
 - ☐ any table(s) related to sequence listing *(specify):*
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify):*
 - ☐ any table(s) related to sequence listing *(specify):*

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No. 68
PCT/EP2004/051651

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	1-12
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	12?

2. Citations and explanations (Rule 70.7):

see separate sheet

1) Reference is made to the following document:

**D1: WO 97/30997 A (NEUROSEARCH AS ; SCHEEL KRUEGER JOERGEN (DK);
MOLDT PETER (DK); WAETJE) 28 August 1997 (1997-08-28)**

2) The present application relates to (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts and their use as monoamine neurotransmitter re-uptake inhibitors.

3) Re Item V

3.1 Novelty (Art. 33(2) PCT)

None of the cited documents discloses the particular compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate. The claimed subject-matter is therefore regarded as novel.

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

D1 is considered to be the closest state of the art. This document relates (cf. abstract and pg. 1, par. 1) to the preparation of particular tropane derivatives and their use as monoamine neurotransmitter re-uptake inhibitors in the treatment of disorders such as Parkinson's disease, depression, obsessive compulsive disorders, panic disorders, dementia, etc. For the preparation of the medicinal compositions, D1 suggests (cf. pg. 7, par. 1) as pharmaceutically acceptable salts a list of acid addition salts comprising tartrate. It is also mentioned (cf. pg. 8, par. 6), that the resolution of racemic mixtures may be carried out by fractional crystallization of D- or L-tartrates, mandelates, or camphorsulphonates. Example 15 of D1 discloses the preparation of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane and its citrate salt.

The subject-matter of the application differs from D1 in that the compound involved is a tartrate and not to a citrate. The Applicant has shown by means of comparative examples (filed on 19.03.2005) that the tartrate of the invention shows much better properties as regards hygroscopicity than its homologous citrate salt. The problem to be solved by the present

application may thus be regarded as providing less hygroscopic salts of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane.

Even though D1 mentions (see paragraphs indicated above) tartrates among the suitable pharmaceutical salts, this document is silent as to the hygroscopic properties of the resulting substances. Thus, there is no motivation in D1 for the skilled person to particularly select tartrates among other pharmaceutically acceptable salts. As this selection is accompanied by an unexpected effect (drastically low hygroscopic character) the claimed subject-matter involves an inventive step.

3.3 Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-11.

For the assessment of the present Claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States and the patentability can also be dependent upon the formulation of the claims.

TRATADO DE COOPERACIÓN DE PATENTES

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Remitante:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

NEUROSEARCH A/S
Patent Department
93 Pederstrupvej
DK-2750 Ballerup
DINAMARCA

PCT

NOTIFICACION DE TRANSMISION DEL INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

23.05.2005

No. de Expediente del Solicitante o Apoderado

264-204-WO

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

PCT/EP2004/051651

Fecha Internacional de Presentación (día/mes/año)

29.07.2004

Fecha de Prioridad (día/mes/año)

31.07.2003

Solicitante

NEUROSEARCH A/S y colaboradores

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.

2. Una copia del informe, en caso dado con los anexos correspondientes, se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.

3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4. RECORDATORIO

Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Nombre y dirección postal de la autoridad que realiza el examen preliminar internacional:

Oficina Europea de Patentes
D-80288 Munich
Tel. +49 89 2399 - 0 Tlx 523565 ampu d
Fax +49 89 2399 - 4465

Funcionario Autorizado

Perriche, S
Teléfono No. +49 89 2399-7890

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**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES**

PCT

**INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 PCT)**

No. de Expediente del Solicitante o Apoderado 264-204-WO	PROCEDIMIENTO POSTERIOR Véase Formulario PCT/IPEA/416
No. Solicitud Internacional PCT/EP2004/051651	Fecha Internacional de Presentación (día/mes/año) 29.07.2004
Fecha de Prioridad (día/mes/año) 31.07.2003	
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC A61K 31/46, A61P 25/00, C07D 451/02	
Solicitante NEIROSEARCH A/S y colaboradores	

1.	Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.
2.	Este INFORME comprende un total de 5 hojas, incluyendo esta portada
3.	Este INFORME también viene acompañado de ANEXOS que comprenden: a. ☐ (enviados al solicitante y a la Oficina Internacional) un total de _____ hojas, como sigue: ☐ hojas de la descripción, reivindicaciones y/o dibujos que han sido corregidas y son la base para este informe y/o hojas que contienen rectificaciones autorizadas por esta Autoridad (ver regla 70.16 y Sección 807 de las Instrucciones Administrativas) ☐ hojas que sustituyen hojas anteriores, pero las cuales esta Autoridad considera contienen una corrección que va más allá de lo divulgado en la solicitud internacional como se presentó, según se indica en el ítem 4 de la casilla I y la Casilla Suplementaria. b. ☐ (enviados solamente a la Oficina Internacional) un total de (Indique tipo y número de portador(es) electrónico(s)) _____, que contienen un listado de una secuencia y/o tablas relacionadas con el mismo, solo en forma legible por computador, como se indica en la casilla suplementaria Relacionada con el Listado de la Secuencia (ver Sección 802 de las Instrucciones Administrativas).
4.	Este informe contiene datos con respecto a los siguientes puntos: ☒ Casilla No. I Base del informe ☐ Casilla No. II Prioridad ☐ Casilla No. III Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial ☐ Casilla No. IV Uniformidad deficiente de la invención ☒ Casilla No. V Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración ☐ Casilla No. VI Ciertos documentos enumerados ☐ Casilla No. VII Ciertas deficiencias del registro internacional ☐ Casilla No. VIII Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 19.03.2005	Fecha de la preparación de este informe 23.05.2005
Nombre y dirección postal de la autoridad que realiza el examen preliminar internacional: Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523565 empu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Molina de Alba, J. Teléfono No. +49 89 2399-7823

Formulario PCT/IPEA/409 (hoja de portada) (Enero 2004)

**INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL
SOBRE PATENTABILIDAD**

Solicitud Internacional No.
PCT/EP2004/051651

Casilla No. I. Base para este informe.

1. Respecto al idioma, este informe se basa en la solicitud internacional en el idioma en el que fue presentada a menos que se indique lo contrario en este ítem.
 - ☐ Este informe se basa en traducciones del idioma original al siguiente idioma, el cual es el idioma de una traducción presentada con el propósito de:
 - ☐ la búsqueda internacional (bajo las Reglas 12.3 y 23.1 (b))
 - ☐ la publicación de la solicitud internacional (bajo la Regla 12.4)
 - ☐ el examen preliminar internacional (bajo las Reglas 55.2 y/o 55.3)
2. Respecto a los elementos* de la solicitud internacional, este informe se basa en *(hojas de reemplazo que han sido presentadas a la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se referencian en este informe como "presentadas originalmente" y no se anexan en este informe)*:

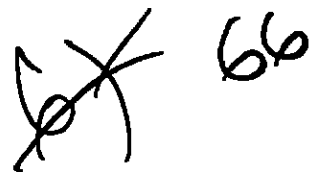
Descripción, páginas:

1 – 12 como se entregaron originalmente

Reivindicaciones, No.:

1 – 12 como se entregaron originalmente

- ☐ un listado de la secuencia y/o cualquier tabla relacionada – ver casilla suplementaria para el listado de la secuencia
3. ☐ Las correcciones han resultado en la cancelación de:
 - ☐ la descripción, páginas:
 - ☐ las reivindicaciones, Nos.
 - ☐ los dibujos, hojas/figuras
 - ☐ el listado de la secuencia (*especifique*):
 - ☐ cualquier tabla relacionada con el listado de la secuencia (*especifique*):
 4. ☐ Este informe se ha establecido como si (algunas de) las correcciones anexas a este informe y enumeradas debajo no hubieran sido hechas, ya que se ha considerado que van más allá de la divulgación como se presentó, como se indica en la casilla suplementaria (Regla 70.2(c)).
 - ☐ la descripción, páginas:
 - ☐ las reivindicaciones, Nos.
 - ☐ los dibujos, hojas/figuras
 - ☐ el listado de la secuencia (*especifique*):
 - ☐ cualquier tabla relacionada con el listado de la secuencia (*especifique*):
- * Si el ítem 4 aplica, alguna o todas estas hojas pueden ser marcadas "suprimida".



**INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL
SOBRE PATENTABILIDAD**

No de Solicitud Internacional
PCT/EP2004/051651

Casilla No. V. Declaración justificada bajo el Artículo 35(2) con respecto a la novedad, el nivel inventivo o la aplicabilidad industrial; las citas y explicaciones que sustentan dicha declaración.

1. DECLARACIÓN

Novedad (N)	Si:	Reivindicaciones	1 – 12
	No:	Reivindicaciones	
Nivel inventivo (IS)	Si:	Reivindicaciones	1 – 12
	No:	Reivindicaciones	
Aplicabilidad Industrial (IA)	Si:	Reivindicaciones	1 – 12
	No:	Reivindicaciones	

2. CITAS Y EXPLICACIONES

Ver hoja aparte

**INFORME DEL EXAMEN PRELIMINAR
INTERNACIONAL SOBRE PATENTABILIDAD
(HOJA APARTE)**

Solicitud internacional No.

PCT/EP2004/051651

1) Se hace referencia al siguiente documento:

D1: WO 97/30997 A (NEUROSEARCH AS; SCHEEL KRUEGER JOERGEN (DK); MOLDT PETER (DK); WAETJE) 28 de agosto de 1997 (1997-08-28)

2) La presente solicitud se relaciona con sales de tartrato de (1R, 2R, 3S, 5S)- 2-metoximetil.3-(3,4-diclorifenil)-8-azabicyclo [3.2.1] octano y su uso como inhibidores de la reabsorción del neurotransmisor de monoamina.

3) Re Ítem V

3.1 Novedad (Art. 33(2) del PCT)

Ninguno de los documentos citados divulga el compuesto particular tartrato de (1R, 2R, 3S, 5S)- 2-metoximetil.3-(3,4-diclorifenil)-8-azabicyclo [3.2.1] octano. La materia reivindicada es por lo tanto considerada novedosa.

3.2 Nivel Inventivo (Art. 33(3) del PCT)

D1 se considera como el arte previo más cercano. Este documento se relaciona con (ver el resumen y la página 1, párrafo 1) la preparación de derivados particulares de tropano y su uso como inhibidores de la reabsorción del neurotransmisor de monoamina en el tratamiento de desórdenes tales como la enfermedad de Parkinson, depresión, desórdenes obsesivos compulsivos, desórdenes de pánico, demencia, etc. Para la preparación de las composiciones médicas, D1 sugiere (ver página 7, párrafo 1) como sales farmacéuticamente aceptables una lista de sales de adición que comprenden tartrato. También se menciona (ver página 8, párrafo 6) que la resolución de mezclas racémicas puede llevarse a cabo por cristalización fraccional de D- o L-tartratos, mandelatos, o camforsulfonatos. El ejemplo 15 de D1 divulga la preparación de (1R, 2R, 3S, 5S)- 2-metoximetil.3-(3,4-diclorifenil)-8-azabicyclo [3.2.1] octano y su sal de citrato.

La materia de la solicitud difiere de D1 en que el compuesto involucrado en un tartrato y no un citrato. El solicitante ha demostrado por medio de ejemplos comparativos (presentados el 19.03.2005) que el tartrato de la invención muestra muchas mejores propiedades respecto a higroscopía que su sal homóloga de citrato. El problema a resolver por la presente

solicitud puede entonces considerarse como proporcionar sales menos higroscópicas de (1R, 2R, 3S, 5S)- 2-metoximetil.3-(3,4-diclorifenil)-8-azabicyclo [3.2.1] octano.

Aunque D1 menciona (ver los párrafos indicados arriba) tartratos entre las sales farmacéuticas aceptables, este documento es silente en cuanto a las propiedades higroscópicas de las sustancias resultantes. Por lo tanto, no hay una motivación en D1 para la persona con habilidad para seleccionar tartratos particulares entre otras sales farmacéuticamente aceptables. Ya que esta selección está acompañada por un efecto inesperado (caracter higroscópico drásticamente bajo) la materia reivindicada involucra nivel inventivo.

3.3 Aplicabilidad industrial (Art. 33(4) del PCT)

Se reconoce para las reivindicaciones 1 – 11.

Para la evaluación de la presente reivindicación 12 sobre la pregunta si es o no industrialmente aplicable, no hay un criterio unificado en los estados contratantes del PCT y la patentabilidad también puede depender de la formulación de las reivindicaciones.

PCT REQUEST

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X 69

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT Online Filing Version 3.50 (Build 0001.159)
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	264-204-WO
I	Title of invention	2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-ASABICYCLO[3.2.1]OCTANE TARTRATE SALTS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	NeuroSearch A/S
II-5	Address:	93 Pederstrupvej 2750 Ballerup Denmark
II-6	State of nationality	DK
II-7	State of residence	DK
II-8	Telephone No.	+45 4460 8000
II-9	Facsimile No.	+45 4460 8080
II-11	Applicant's registration No. with the Office	0.0

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X 20

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)	FRØSTRUP, Brian
III-1-6	Address:	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-1-8	State of nationality	DK
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)	WATJEN, Frank
III-2-6	Address:	c/o NeuroSearch A/S 93 Pederstrupvej 2750 Ballerup Denmark
III-2-8	State of nationality	DK
III-2-7	State of residence	DK
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	JENSEN, Klaus, Snej
III-3-6	Address:	Forchhammersvej 22, st.th. 1920 Frederiksberg C Denmark
III-3-8	State of nationality	DK
III-3-7	State of residence	DK

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 Føderstrupvej 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 4.2(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	31 July 2003 (31.07.2003)
VI-1-2	Number	PA 2003 01117
VI-1-3	Country	DK
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	12 August 2003 (12.08.2003)
VI-2-2	Number	60/494,090
VI-2-3	Country	US
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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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, FROSTRUP, Brian
VIII-2-1(i)		NeuroSearch A/S is entitled as employer of the inventor, WATJEN, Frank
VIII-2-1(i)		NeuroSearch A/S is entitled as employer of the inventor, JENSEN, Klaus, Snej
VIII-2-1(x)	This declaration is made for the purpose of:	all designations except the designation of the United States of America

PCT REQUEST

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X/74

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	12	-
IX-3	Claims	3	-
IX-4	Abstract	1	-
IX-5	Drawings	0	-
IX-7	TOTAL	22	
	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		
X-1-1	Name (LAST, First)		
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	IBA/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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2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-AZABICYCLO[3.2.1]OCTANE TARTRATE SALTS

5

TECHNICAL FIELD

This invention relates to novel (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts, such as L-tartrate monohydrates and anhydrides. The salts are useful as monoamine neurotransmitter re-uptake inhibitors.

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

15

BACKGROUND ART

The compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane is disclosed in WO 97/30997 (NeuroSearch A/S). Therein, the citrate salt was prepared (Example 15).

For commercial use, however, it is important to have a physiologically acceptable salt with an optimal combination of stability, solubility, non-hygroscopicity, bioavailability and good handling properties, such as a well defined melting point and a reproducible crystalline form.

25

SUMMARY OF THE INVENTION

In its first aspect, the invention provides a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a salt of the invention, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

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

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

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nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a salt of the invention.

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

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate

In its first aspect the present invention provides a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

In one embodiment, the salt is selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

In a second embodiment, the salt is (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.

In a further embodiment, the salt is an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

In a still further embodiment, the salt is the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.28	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

In a further embodiment, the salt is the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2

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Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.48	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

In a still further embodiment, the salt is the polymorphic form (form IV) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu Kα)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu Kα)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu Kα)	26.83	27.21								
d space (Å)	3.3	3.3								

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

10

Hydrated forms

The salt of the invention may be provided in anhydrous forms or hydrated forms. Hydrated forms include the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like.

15

Labelled Compounds

The salts of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the salt of interest that will allow easy quantitative detection of said salt.

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The labelled salts 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 salt of the invention preferably contains at least one radio-nuclide as a label. Positron emitting radionuclides are all candidates for usage. In

the context of this invention the radionuclide is preferably selected from ^2H (deuterium), ^3H (tritium), ^{13}C , and ^{14}C .

Methods of Preparation

- 5 The salts of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.
- 10 Also one salt of the invention can be converted to another salt of the invention using conventional methods.

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

15

Biological Activity

- Salts of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes eg such as described in WO 97/30997. Based on the balanced activity observed in these tests
- 20 the salts of the invention is considered useful for the treatment 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 salts of the invention are considered useful for
- 25 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
- 30 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
- 35 immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type
- 40 headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel

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syndrome, post-operative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourettes disease.

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 100 mg API per day, more preferred of from about 0.1 to about 10 mg API per day, most preferred of from about 0.5 to about 5 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.

Pharmaceutical Compositions

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

While a salt of the invention for use in therapy may be administered in the form of the raw salt, it is preferred to introduce the active ingredient, 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 salt of the invention, together with one or more pharmaceutically acceptable carriers therefore, 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 salt of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

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

The salt of the present invention can be administered in a wide variety of oral and parenteral dosage forms.

For preparing pharmaceutical compositions from a salt 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.

5 The salt 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
10 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
15 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
20 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
25 sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the salt 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
30 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
35 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
40 provided in single or multi-dose form.

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

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the salt 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 active compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

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

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

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

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

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

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

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The actual dosage depend 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

- 5 pharmaceutical compositions containing of from about 0.1 to about 10 mg of active ingredient per individual dose, preferably of from about 0.5 to about 5 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
10 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.

15 **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,
20 and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a salt of the invention.

Suitable dosage ranges are 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
25 involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

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

Example 1

35 **(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane citrate salt**

The citrate salt of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane was synthesized as described in WO 97/30997 (Example 15).

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(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane

The free base was obtained from dissolving the citrate salt in water and adjusting pH to 10-13 with aqueous base, followed with extraction with toluene. The toluene phase was collected, dried and evaporated to dryness. This left the free base as an oil.

Example 2

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I)

To a heated solution of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane (the free base) in aqueous ethanol was added L-tartaric acid. The warm mixture was treated with activated charcoal and filtered. The filtrate was cooled and (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane was isolated as the L-tartrate monohydrate.

Form I is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	12.05	14.21	16.37	17.4	18.34	19.29	19.58	20.27	23.3	23.75
d space (Å)	7.3	6.2	5.4	5.1	4.8	4.6	4.5	4.4	3.8	3.7
Peak	11	12	13	14	15	16	17			
2 Theta ° (Cu Kα)	24.37	26.11	26.76	28.25	28.72	29.25	29.82			
d space (Å)	3.6	3.4	3.3	3.2	3.1	3.1	3.0			

Example 3

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form II)

The form was prepared thermal dehydration. (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I) was heated in a TGA AlO₂ crucible to 125°C, 10°C/min. The salt was allowed to cool before opening the TGA furnace. During heating and cooling the furnace was purged with 50ml/min dry nitrogen.

Form II is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.88	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	

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2 Theta ° (Cu Kα)	20.28	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

Example 4

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form III)

5 The form was prepared thermal dehydration. (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I) was heated in a TGA AlO₂ crucible to 160°C, 10°C/min. The salt was allowed to cool before opening the TGA furnace. During heating and cooling the furnace was purged with 50ml/min dry nitrogen.

10 Form III is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

Example 5

15 (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form IV)

The form was prepared by suspending a freshly prepared Form II in water free ethanol. Separation of the suspended matter was conducted after 24 hours and subsequent drying under vacuum.

Form IV can also be obtained from suspension of Form III by the same procedure as described using Form II.

20 Apparently Form IV was physically metastable. Successive preparations of Form IV turned out as mixtures of Form IV and Form III, indicating difficulties in producing Form IV

Form IV is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

25

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20

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2 Theta ° (Cu Kα)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu Kα)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu Kα)	26.83	27.21								
d space (Å)	3.3	3.3								

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CLAIMS

1. A salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.
- 5
2. The salt of claim 1 being selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.
- 10
3. The salt of claim 1, being (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.
- 15
4. The salt of claim 1, being an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.
- 20
5. The salt of claim 4, being the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.28	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

6. The salt of claim 4, being the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:
- 25

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

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7. The salt of claim 4, being the polymorphic form (form IV) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

5

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu K α)	5.31	10.19	11.23	12.13	12.35	12.69	14.31	14.55	14.77	16.43
d space (Å)	16.6	8.7	7.9	7.3	7.2	7.0	6.2	6.1	6.0	5.4
Peak	11	12	13	14	15	16	17	18	19	20
2 Theta ° (Cu K α)	17.48	18.21	18.43	18.81	19.36	19.61	20.26	20.5	21.29	21.46
d space (Å)	5.1	4.9	4.8	4.7	4.6	4.5	4.4	4.3	4.2	4.1
Peak	21	22	23	24	25	26	27	28	29	30
2 Theta ° (Cu K α)	21.95	22.53	22.77	23.38	23.59	23.9	24.45	25.02	25.56	26.19
d space (Å)	4.0	3.9	3.9	3.8	3.8	3.7	3.6	3.6	3.5	3.4
Peak	31	32								
2 Theta ° (Cu K α)	26.83	27.21								
d space (Å)	3.3	3.3								

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

10

9. Use of a salt of any of claims 1-7 for the manufacture of a medicament.

10. The use according to claim 9, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

15

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,

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- parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, chronic pain, inflammatory pain, neuropathic pain, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofascial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, sexual dysfunction, premature ejaculation, erectile difficulty, erectile dysfunction, eating disorders, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourette's disease.
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 such a living animal body in need thereof a therapeutically effective amount of a salt according to any one of the claims 1-7.

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ABSTRACT**2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-AZABICYCLO[3.2.1]OCTANE TARTRATE SALTS**

This invention relates to novel (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts, such as L-tartrate monohydrates and anhydrides. The salts are useful as monoamine neurotransmitter re-uptake inhibitors.

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



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DK-2750 Bellerup, 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 enseñes, 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.

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 vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

A este efecto, lo(s) facuto(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 al descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

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

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

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

Otorgado y firmado en

Granted and signed in

hoy de de

this day of 200_

Firma

Nombre
Cargo

Name
Title



Peder Velling
Peder Velling
Head of Patents

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATE)

Hoy de 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

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

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

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

Estado de
con fecha

y que quien confiere el presente poder es su representante.

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.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Public Notary (Seal)

HENNING BROMAN
Notary Public
**NOTARIAL CERTIFICATE
NATURAL PERSON**

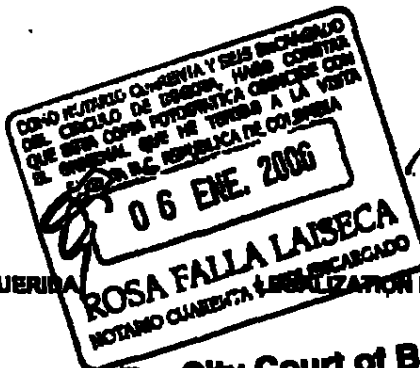
Hoy de de , compareció(eron) ante mí

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 firman el mismo para los fines y propósitos que en él

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

~~Henning Broman~~ 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
Notary Public

LEGALIZACION POR APOSTILLA ES REQUERIDA

The City Court of Ballerup
Blegdamsvej 6
2200 Copenhagen
Denmark

LEGALIZATION BY APOSTILLE IS REQUIRED.



THE TRUE SIGNATURE OF
Henning Broun
IS HEREBY CERTIFIED.
COPENHAGEN, 11 APR. 2005
FOR THE MINISTER FOR FOREIGN AFFAIRS.
B.A.

Henning

BIRGITTE THORELL

RECHERCHER
DERECHOS DE 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

.....
.....

Ole Waage Pedersen
CONSUL AD-HONOREM

NO SE ASUME
INCORRESPONSABILIDAD DEL TEXTO
2005 ABR 21 14:03:14
JOS
JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERNALES
355447
Ole Waage
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPAÑA
LAS FUNCIONES INDICADAS

CONO MIEMBRO CUARENTA Y SEIS ENCARGADO
DEL CUELLO DE FORTUNA, HAGO CONSTAR
QUE ESTA FIRMA FOTOGRÁFICA COINCIDE CON
EL ORIGINAL QUE ME TRUENO A LA VISTA
06 ENE. 2006
ROSA FALLA LAISECA
NOTARIO CUARENTA Y SEIS ENCARGADO

95 94

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.

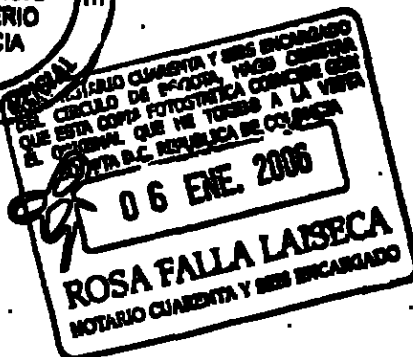
Y QUE QUIEN CONFIERE EL PRESENTE PODER ES SU REPRESENTANTE.

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



9/16 95

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, 1º 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 URIBE DE LEMOINE



97
96

SUPERINDUSTRIA Y COMERCIO
Radicación : 06081282 00000000 Folios: 96
Fecha (MD) 2006-01-05 16.06:48
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2829 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
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 se 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 o 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 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 de trazado	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	()	()
INCOMPLETA ()	()	()

Firma Responsable:

Fecha:

6 Feb / 06

92

98

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

2020
Bogotá D.C.,

Folio 97

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

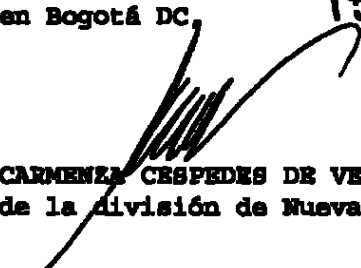
7

REFERENCIA	Radicación No.	06 1282
	Solicitud internacional	EP/2004/051651
	Fecha inicio fase nacional	28/02/2006
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	145
	Folios	1

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

Cumplase
Dado en Bogotá DC.

15 MAR. 2006


ALIX CARMEN CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

jramos