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☐ Capítulo I. ☒ Capítulo II.			
2 SOLICITANTE (71)	Nombre: H. LUNDBECK A/S sociedad constituida y existente bajo las leyes de Dinamarca. Dirección: 9 Ottliavej, DK-2500 Valby-Copenague, Dinamarca. Domicilio: Valby-Copenague, Dinamarca.	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: _____	
3 REPRESENTANTE O APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax:: 217 92 11 E-mail: <u>clientes@camvp.com.</u> Domicilio: Bogotá, Colombia.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: <u>438.018</u> T.P. <u>31.929</u>	
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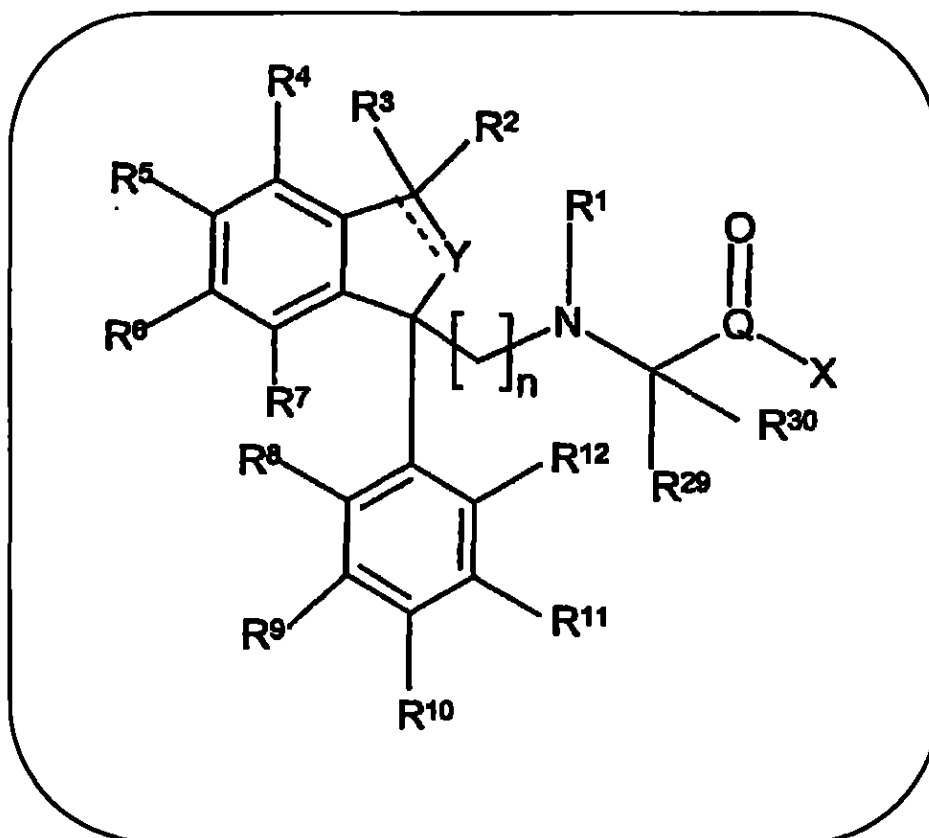
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 400.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ 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

11

FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

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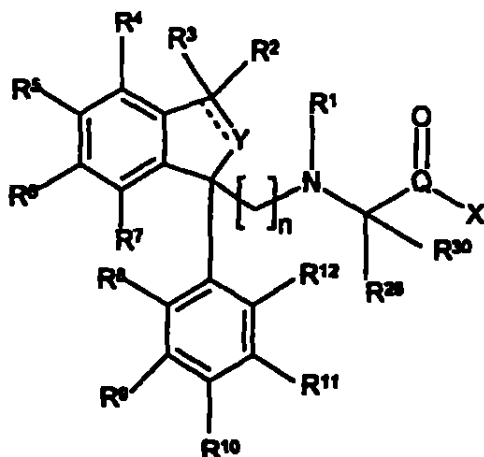
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL COMPOUNDS AND THEIR USE AS GLYCINE TRANSPORT INHIBITORS



(1)

(57) Abstract: The invention provides novel compounds of the formula I below: (I), wherein the meaning of each substituent is defined in the application. The compounds are useful as inhibitors of the glycine transporter and useful in the treatment of diseases responsive to the inhibition of the glycine transporter. The invention provides a pharmaceutical composition comprising a compound of Formula I as defined above and the use of compounds as above for the manufacture of medicaments for treatment of diseases responsive to ligands of the glycine transporter.

WO 02/08216 A1

Novel compounds and their use as glycine transport inhibitors

The present invention provides novel compounds of the general formula I, and their use as glycine transport inhibitors.

5

Background of the invention

Glutamic acid is the major excitatory amino acid in the mammalian central nervous system (CNS), and acts through two classes of receptors, the ionotropic and metabotropic receptors, 10 respectively. The ionotropic glutamate receptors are divided into three subtypes based on the affinities of agonists for these receptors, namely *N*-methyl-D-aspartate (NMDA), (*R,S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) and kainic acid (or kainate) receptors.

The NMDA receptor contains binding sites for modulatory compounds such as glycine and 15 polyamines. Binding of glycine to its receptor enhances the NMDA receptor activation. Such NMDA receptor activation may be a potential target for the treatment of schizophrenia and other diseases linked to NMDA receptor dysfunction. An activation can be achieved by an inhibitor of the glycine transporter.

Molecular cloning has revealed the existence of two types of glycine receptors, GlyT-1 and 20 GlyT-2, wherein GlyT-1 can be further subdivided into GlyT-1a, GlyT-1b and GlyT-1c.

The NMDA receptor is blocked by compounds such as phencyclidine which induce a psychotic state which resembles schizophrenia. Likewise, the NMDA antagonists, such as ketamine, induce negative and cognitive symptoms similar to schizophrenia. This indicates that NMDA receptor dysfunction is involved in the pathophysiology of schizophrenia.

25 The NMDA receptor has been associated with a number of diseases, such as pain (Yaksh *Pain* 1989, 37, 111-123), spasticity, myoclonus and epilepsy (Truong et. al. *Movement Disorders* 1988, 3, 77-87), learning and memory (Rison et. al. *Neurosci. Biobehav. Rev.* 1995, 19, 533-552,).

Thus, glycine transporter antagonistists or inhibitors are believed to be highly beneficial in the 30 treatment of schizophrenia, including both the positive and the negative symptoms of schizophrenia, other psychoses, dementia, and improving cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS

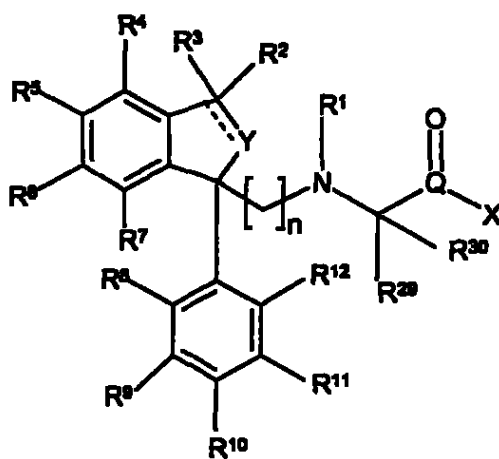
dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke.

Clinical trials with glycine have been reported (Javitt et. al. *Am. J. Psychiatry* 1994, 151, 1234-1236), (Leiderman et. al. *Biol. Psychiatry* 1996, 39, 213-215). The treatment with high-dose glycine is reported to improve the symptoms of schizophrenia. There is a need for more efficient compounds as ligands for the glycine transporter for the treatment of NMDA associated diseases.

The compounds of the present invention are potent ligands for the glycine transporter.

Summary of the invention

The invention provides novel compounds of the formula I below:



wherein

R^1 represents hydrogen, C_{1-6} -alkyl, cycloalkyl or cycloalkylalkyl;

R^2 and R^3 independently represent hydrogen, halogen, C_{1-6} -alkyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkyl- C_{1-6} -alkyl or R^2 and R^3 together form a C_{3-8} -cycloalkyl;

R^4 , R^5 , R^6 and R^7 independently represent hydrogen, halogen, CF_3 , NO_2 , CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, OH, SH, $NR^{14}R^{15}$, wherein R^{14} and R^{15} independently represent hydrogen or C_{1-6} -alkyl; $-COR^{16}$ wherein R^{16} represents OH, C_{1-6} -alkyl, C_{1-6} -alkoxy, $NR^{17}R^{18}$, wherein R^{17} and R^{18} independently represent hydrogen or C_{1-6} -alkyl; aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more

times with halogen, CF₃, OCF₃, CN, NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ thioalkyl, OH, SH or NR²⁴R²⁵, wherein R²⁴ and R²⁵ independently represent hydrogen or C₁₋₆-alkyl;

or R⁴ and R⁵, or R⁵ and R⁶, or R⁶, and R⁷ together form a fused, aromatic, saturated or partly

5 saturated ring which optionally contains one or more heteroatoms such as O, N or S;

R⁸, R⁹, R¹⁰, R¹¹ and R¹² independently represent hydrogen, halogen, CF₃, OCF₃, CN, NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆-alkylthio, OH, SH, NR¹⁹R²⁰, wherein R¹⁹ and R²⁰ independently represent hydrogen or C₁₋₆-alkyl; or R⁸, R⁹, R¹⁰, R¹¹ and R¹²

10 independently represent -COR²¹, wherein R²¹ represents OH, C₁₋₆-alkoxy, NR²²R²³, wherein R²² and R²³ independently represent hydrogen or C₁₋₆-alkyl; or R⁸, R⁹, R¹⁰, R¹¹, and R¹²

independently represent aryl or heteroaryl, wherein aryl and heteroaryl are optionally

substituted one or more times with halogen, CF₃, OCF₃, CN, NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkythio, OH, SH, COR²⁶, wherein R²⁶ represents

15 OH, C₁₋₆ alkoxy or C₁₋₆ alkyl; or NR³⁰R³¹, wherein R³⁰ and R³¹ independently represent hydrogen or C₁₋₆-alkyl;

R⁸ and R⁹, or R⁹ and R¹⁰, or R¹⁰ and R¹¹, or R¹¹ and R¹² together form a fused, aromatic, saturated or partly saturated ring which optionally contains one or more heteroatoms such as O, N, or S;

20 Y is O, S, CH₂ or CH, and when Y is CH then the dotted line is a bond;

n is 2, 3, 4, 5 or 6;

Q represents C, P-OR²⁹, or S=O, wherein R²⁹ represents hydrogen or C₁₋₆-alkyl;

X is OR¹³ or NR²⁷R²⁸, wherein R¹³, R²⁷, and R²⁸ independently represent hydrogen, C₁₋₆-alkyl, aryl or aryl-C₁₋₆-alkyl, wherein aryl may be substituted with halogen, CF₃, OCF₃, CN, NO₂, or

25 C₁₋₆ alkyl; optionally R²⁷ and R²⁸ together form a ring which may contain further nitrogen, oxygen or sulfur atoms and the ring may optionally be partly saturated;

R²⁹ and R³⁰ represent hydrogen, C₁₋₆-alkyl, cycloalkyl or cycloalkylalkyl

30 or a pharmaceutically acceptable addition salt thereof;

The compounds are useful as inhibitors of the glycine transporter and useful in treatment of diseases responsive to the inhibition of the glycine transporter.

Detailed description of the invention

5

In a preferred embodiment of the invention, Q is C;

Other preferred embodiments are wherein n is 2 or 3;

Another preferred embodiment is wherein R¹ is CH₃;

Yet another preferred embodiment is wherein X is OH or C₁₋₆-alkoxy, more preferred is

10 wherein X is OH, OCH₃, or OC₂H₅,

Other preferred embodiments are wherein R⁷ represent hydrogen, and R⁴, R⁵ or R⁶ represent hydrogen, CN, halogen, C₁₋₆-alkyl, CF₃, or phenyl optionally substituted one or more times

with halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, CF₃, or R⁴, R⁵ or R⁶ represent heteroaryl optionally

substituted one or more times with halogen, or wherein R⁴ and R⁵ or R⁵ and R⁶ together form

15 a fused aryl;

Another preferred embodiment of the invention is wherein R⁸, R⁹, R¹⁰, R¹¹ or R¹²

independently represent hydrogen, halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or R⁸ and R⁹ or R⁹ and R¹⁰ together form a fused aryl;

20

In an more preferred embodiment, one or two of R⁸, R⁹, R¹⁰, R¹¹ or R¹² represent halogen, C₁₋₆-alkyl, CF₃, or C₁₋₆-alkoxy;

In a more preferred embodiment of the invention R⁴, R⁶, R⁷, R⁸, R⁹ and R¹² are all hydrogen

25 and R⁵ represents halogen, CF₃, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy or -COR¹⁶, wherein R¹⁶ represents C₁₋₆-alkyl; and R¹⁰ and R¹¹ represent hydrogen, halogen, CF₃, or CN, provided that at least one of R¹⁰ and R¹¹ is not hydrogen;

R²⁹ and R³⁰ independently represent hydrogen or C₁₋₆-alkyl or R² and R³ together form a C₃₋₆-cycloalkyl;

30

Another preferred embodiment of the invention is wherein the compounds are the following

N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}glycine ethyl ester,

N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine ethyl ester,

5 N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}glycine,

N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[1-(3-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-

10 methylglycine,

N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine,

N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

15 N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine,

N-{3-[4-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

20 N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

N-{3-[6-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-

25 methylglycine,

N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

30 N-{3-[6-chloro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-fluoro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-fluoro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

5 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

10 N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-cyano-1-(4-cyanophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

15 N-{3-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine, N-{2-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]ethyl}-N-methylglycine,

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine,

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine,

20 N-{3-[3-cyclo-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylglycine,

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine,

25 N-{3-[1-(4-Fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methylglycine,

N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine,

30 N-[3-(3-methyl-1-phenyl-1*H*-inden-1-yl)-propyl]-N-methylglycine,

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylglycine,

- N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-glycine,
- N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,
- N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-glycine,
- N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methylalanine,
- N-[3-(3,3-Dimethyl-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methylalanine,
- N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methyl-(1-ethyl)glycine,
- N-[3-(3,3-Dimethyl-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methyl-(1-ethyl)glycine,
- N-[3-(3,3-Diethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,
- N-[3-(3,3-Diethyl-1-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,
- N-[3-(3,3-Diethyl-1-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylglycine,
- N-[3-(1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine,
- N-[3-[1-(4-Chloro-phenyl)-3,3-dimethyl-indan-1-yl]-propyl]-N-methylglycine,
- N-[3-[1-(4-Chloro-phenyl)-3,3-diethyl-1,3-dihydro-isobenzofuran-1-yl]-propyl]-N-methylalanine,
- N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine,
- N-[3-(1-phenyl-(1*H*)-inden-1-yl)-propyl]-N-methyl-alanine,
- N-[3-[1-(4-Fluoro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl]-N-methyl-glycine,
- N-[3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl]-N-methyl-glycine,
- N-[3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl]-N-methyl-alanine,
- N-[3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl]-N-methyl-glycine,
- N-[3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl]-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

5 N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

10 N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{2-[1-(4-Chloro-phenyl)-5-(5-chloro-thiophen-2-yl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

15 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

20 N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine ,

25 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

30 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

5 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-chloro-phenyl)-5-(2-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine ,

or a pharmaceutically acceptable addition salt thereof.

10

The invention provides a pharmaceutical composition comprising at least one compound of Formula I as defined above, or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

15

The invention also provides the use of compounds as above for the manufacture of medicaments for treatment of diseases responsive to ligands of the glycine transporter.

20

The invention provides a method for treatment of diseases responsive to ligands of the glycine transporter.

In preferred embodiments of the invention, the ligands are antagonists of the glycine transporter.

25

Pharmaceutically acceptable addition salts are those which form pharmacological acceptable anions such as maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-
30 halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The compound of the invention may be administered in any suitable way such as orally or parenterally, and it may be presented in any suitable form for such administration, for example in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the
5 compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art.
10 Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tableting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active
15 ingredients.

Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes
20 of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

25

Racemic forms can be resolved into the optical antipodes by known methods, for example by separation of diastereomeric salts thereof with an optically active acid and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active
30 matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g. by fractional crystallisation of d- or l- (tartrates, mandelates or

camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

Definition of substituents

Halogen means fluoro, chloro, bromo or iodo. Preferred halogens are F and Cl.

The term C_{1-6} -alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl. Preferred alkyls are methyl and ethyl.

Similarly, C_{2-6} -alkenyl and C_{2-6} -alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl.

The term C_{3-8} -cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C_{3-8} -cycloalkylalkyl designates a cycloalkyl as defined above and an alkyl as above.

The terms C_{1-6} -alkoxy and C_{1-6} -alkylthio designate such groups in which the alkyl group is C_{1-6} -alkyl as defined above.

The term aryl designates an aromatic hydrocarbon such as phenyl or naphthyl.

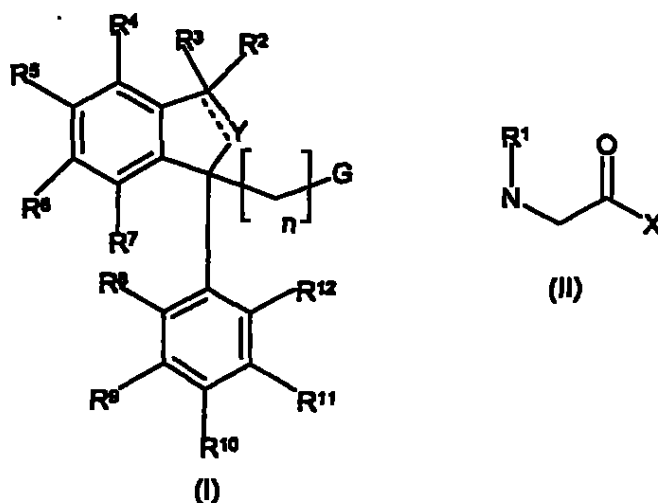
The term heteroaryl refers to a mono- or bicyclic heterocyclic aromatic group containing at least one N, S or O atom, such as furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrimidyl, tetrazolyl, benzofuranyl, benzothienyl, benzimidazolyl, indolyl. Preferred heteroaryls are monocyclic heteroaryls. Especially preferred is thienyl.

Preparatory examples

The compounds of the invention may be prepared as follows:

- 1) alkylating an amine of formula II with an alkylating agent of formula I

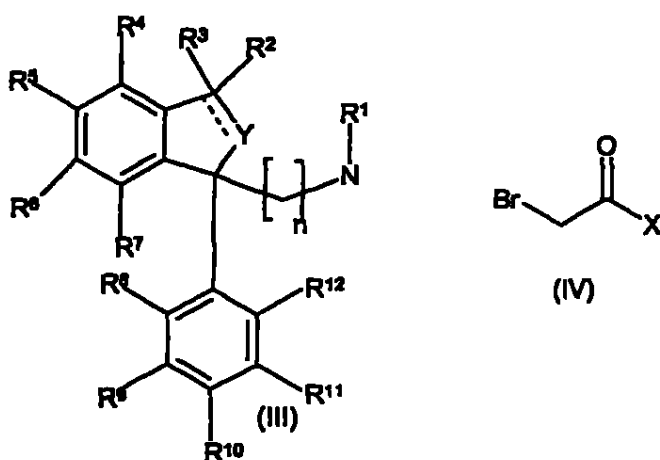
G is a suitable leaving group such as e.g. halogen or mesylate.



the substituents R¹-R¹², n, Y and X are as defined above;

- 2) alkylating an amine of formula III with an alkylating agent of formula IV

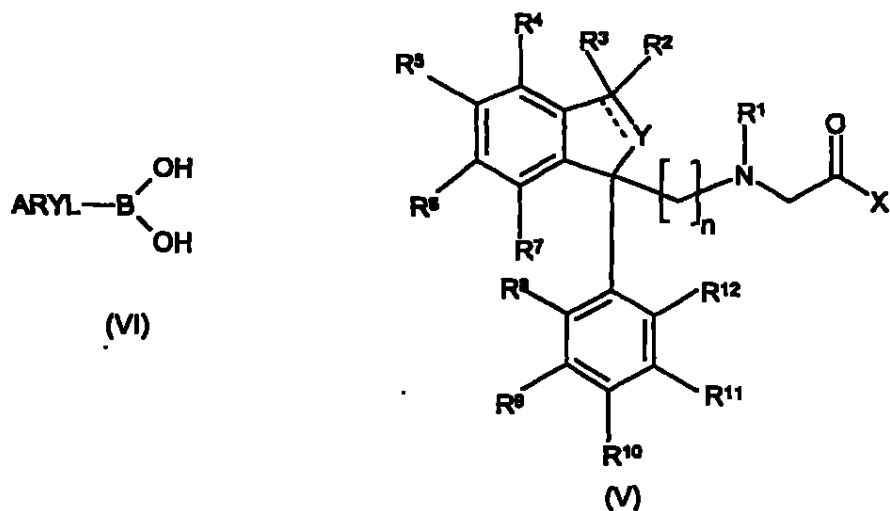
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wherein the substituents R^1 - R^{12} , n , Y and X are as defined above;

5

3) Coupling of an aryl substituent of formula VI to the aryl bromide derivative of formula V wherein the substituents R^4 - R^7 are halogens, R^1 - R^3 and R^8 - R^{12} , n , Y and X are as defined above

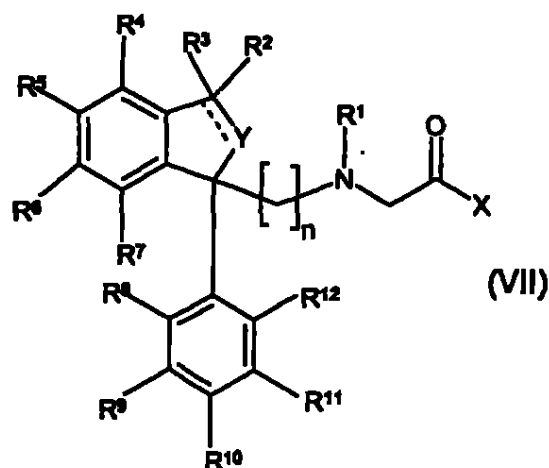


10

4) hydrolysing the ester group of a compound of formula VII to obtain the corresponding carboxylic acid derivative

15

14



the substituents R^1 - R^{12} , n , and Y are as defined above and X is OH in the final product.

The alkylations according to methods 1 and 2 are conveniently carried out in an inert solvent
 5 such as a suitably boiling alcohol or ketone or in tetrahydrofuran, preferably in the presence of
 an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at
 reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature
 which is different from the boiling point in one of the above-mentioned solvents or in
 dimethylformamide, dimethylsulfoxide or *N*-methylpyrrolidin-2-one, preferably in the
 10 presence of a base.

Reagents of formula I are prepared by methods described in the literature, see. e.g. US
 3,549,656, GB 1166711 and Dykstra et al. *J. Med. Chem.* 1967, 10(3), 418-28.

Glycine derivatives of formula II are well described in the literature.

15 Amines of formula III are prepared as described by Bigler et. al. *Eur. J. Med. Chem.* 1977, 12,
 289.

Biaryl derivatives of formula IV are prepared by Suzuki type coupling of an aryl boronic acid
 with the desired halide in dimethoxyethane, tetrahydrofuran or toluene containing an
 inorganic base such as sodium carbonate and a palladium catalyst at a temperature between
 20 room temperature and the boiling point of the solvent.

The hydrolysis according to method 4 is conveniently performed in a suitably boiling alcohol
 in the presence of an aqueous base such as e.g. sodium hydroxide at ambient temperature. The
 starting materials of formula V are prepared by methods 1 or 2.

Experimental

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (50 X 4.6 mm YMC ODS-A with 5 µm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times, R_p , are expressed in minutes.

Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion, MH^+ , was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100V).

Preparative LC-MS-separation was performed on the same instrument. The LC conditions (50 X 20 mm YMC ODS-A with 5 µm particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^1H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard.

Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet, b=broad singlet. NMR signals corresponding to acidic protons are generally omitted.

Content of water in crystalline compounds was determined by Karl Fischer titration. Standard workup procedures refer to extraction with the indicated organic solvent from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$ or Na_2SO_4), filtering and evaporation of the solvent *in vacuo*. For column chromatography, silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography, SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. No. 220776 was used. Prior use of the SCX-columns was pre-conditioned with 10 % solution of acetic acid in methanol (3 mL).

The following examples will illustrate the invention further. They are, however, not to be construed as limiting. **Example 1**

1a, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)glycine.ethyl ester.

A stirred mixture of 3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl amine (1.5 g), potassium carbonate (1.3 g) and ethanol (15 mL) was treated dropwise with a solution of ethyl bromoacetate (0.75 g) in ethanol (15 mL) at room temperature. After reflux for 1.5 h, the mixture was cooled and concentrated *in vacuo*. Standard work-up with ethyl acetate gave an oil which was purified by flash chromatography (eluent heptane/ethyl acetate/triethylamine 26:70:4). The title compound was obtained as a clear oil (0.77 g). LC/MS (m/z) 383 (MH⁺), purity (UV): >99%.

Example 2

2a, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)-N-methylglycine.ethyl ester.

A stirred mixture of 3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl iodide (3.1 g), ethyl N-methylglycinate (4.4 g) and diethylisopropylamine (4.4 g) in tetrahydrofuran (50 mL) was refluxed for 16 h. Standard work-up with ethyl acetate gave an oil which was purified by flash chromatography (eluent heptane/ethyl acetate/triethylamine 64:32:4) giving the title compound as a clear oil (1.4 g). LC/MS (m/z) 397 (MH⁺), purity (UV): >99%

Example 3

3a, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)glycine hydrochloride

A mixture of N-(3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)glycineethyl ester (0.7 g), methanol (6 mL) and 6 M sodium hydroxide (2 mL) was

stirred at room temperature for 2 h. Adjustment of pH to < 6.5 with dilute hydrochloric acid followed by standard work-up with ethyl acetate gave the title compound as an oil (0.2 g).
LC/MS (m/z) 355 (MH⁺), purity (UV): >90%

5 In a similar manner, the following compound were prepared:

3b, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)-N-methylglycine hydrochloride.

LC/MS (m/z) 369 (MH⁺), purity (UV): >90%

10 3c, Example 4:

N-{3-[1-(3-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 360 (MH⁺), purity (UV 90%)

3d, Example 5:

15 N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 394 (MH⁺), purity (UV 79%)

3e, Example 6:

20 N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine hydrochloride

LC/MS (m/z) 422 (MH⁺), purity (UV 79%)

3f, Example 7:

N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

25 LC/MS (m/z) 378 (MH⁺), purity (UV 91%)

3g, Example 8:

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 344 (MH⁺), purity (UV 81%)

30 3h, Example 9

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 358 (MH⁺), purity (UV 81%)

3i, Example 10

5 N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine hydrochloride

LC/MS (m/z) 372 (MH⁺), purity (UV 86%)

3j, Example 11

10 N-{3-[4-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 392 (MH⁺), purity (UV 86%)

3k, Example 12

N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

15 LC/MS (m/z) 394 (MH⁺), purity (UV 98%)

3l, Example 13

N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 408 (MH⁺), purity (UV 85%)

20 3m, Example 14

N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 394 (MH⁺), purity (UV 99%)

3n, Example 15

25 N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 374 (MH⁺), purity (UV 76%)

3o, Example 16

30 N-{3-[6-chloro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 390 (MH⁺), purity (UV 98%).

3p, Example 17

N-{3-[5-fluoro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 378 (MH⁺), purity (UV 85%).

3q, Example 18

N-{3-[5-fluoro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 378 (MH⁺), purity (UV 99%).

3r, Example 19

10 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 412 (MH⁺), purity (UV 81%)

3s, Example 20.

15 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 426 (MH⁺), purity (UV 98%).

3t, Example 21

N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

20 LC/MS (m/z) 383 (MH⁺), purity (UV 83%).

3u, Example 22

N-{3-[5-cyano-1-(4-cyanophenyl)-indan-1-yl]-1-propyl}-N-methylalanine hydrochloride.

LC/MS (m/z) 388 (MH⁺), purity (UV 80%).

3v, Example 23

25 N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 381 (MH⁺), purity (UV 81%)..

3x, Example 24

30 N-{3-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 369 (MH⁺), purity (UV 98%)

3y, Example 25

N-{2-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]ethyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 355 (MH⁺), purity (UV 94%)

3z, Example 26

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 392 (MH⁺), purity (UV 98%)

3aa, Example 27

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 406 (MH⁺), purity (UV 95%)

3ab, Example 28

N-{3-[3-spirocyclopentyl-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

3ac, Example 29

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylglycine hydrochloride

3ad, Example 30

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine

LC/MS (m/z) 370 purity (UV 96%)

3ae, Example 32

N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine

LC/MS (m/z) 440 (MH⁺), purity (ELSD 93%)

3af, Example 33

N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine

LC/MS (m/z) 374 (MH⁺), purity (UV 72%)

3ag, Example 34

N-[3-(3-methyl-1-phenyl-1*H*-inden-1-yl)-propyl]-N-methylglycine

LC/MS (m/z) 336 (MH⁺), purity (UV 85%)

3ah, Example 35

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine
LC/MS (m/z) 380 (MH⁺), purity (UV 85%)

3ai, Example 36

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-
glycine

LC/MS (m/z) 394 (MH⁺), purity (UV 80%)

3aj, Example 37

N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine

LC/MS (m/z) 354 (MH⁺), purity (UV 78%)

3ak, Example 38

N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine

LC/MS (m/z) 451, purity (UV 92%)

3al, Example 39

N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-
methyl-glycine

Example 4

4a, N-{3-[5-Bromo-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-ethyl}-N-methylglycine ethyl ester (226mg, 0.5mmol) was dissolved in a 1:1 mixture of tetrahydrofuran and dimethoxyethane (3 mL) containing tetrakis (triphenylphosphine)palladium under nitrogen. To the reaction was added 4-chlorophenyl boronic acid (102mg, 0.75 mmol) and 0.5M aqueous sodium carbonate solution (2 mL, 1mmol) and the reaction was heated to 65 °C for 18 hours. The solution was diluted with water (5 mL) and ethyl acetate (7 mL). The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (5 mL). The organic extractions were combined and washed with saturated brine solution (7 mL) before being evaporated in the presence of 1g of silica gel. The crude product absorbed on silica gel was poured on top of a 20g silica gel cartridge and eluted with a gradient solvent system eluting from heptane to heptane/ethyl

acatet (1:1) over 37 minutes. The product was isolated as a light oil (135 mg, 64%). LC/MS 479.

The compound was hydrolysed as described for Experimental 3a to give the N-methylglycine hydrochloride derivative.

5 LC/MS (m/z) 436, purity (UV 92%)

In an analogous fashion, the following compounds were prepared:

4b, Example 40

N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

10 LC/MS (m/z) 452, purity (UV 94%)

4c, Example 41

N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 428, purity (UV 96%)

15 4d, Example 42

N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 450, purity 91%

4e, Example 43

20 N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 466, purity (UV 95%)

4f, Example 44

N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

25 LC/MS (m/z) 504, purity (UV 89%)

4g, Example 45

N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

30 LC/MS (m/z) 456, purity 96%

4h, Example 46

N-{2-[1-(4-Chloro-phenyl)-5-(5-chloro-thiophen-2-yl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 462, purity 74%

4i, Example 47

5 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 436, purity UV 94 %

4j, Example 48

10 N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 436, purity (UV 91%)

4k, Example 49

N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

15 LC/MS (m/z) 490, purity 94%

4l, Example 50

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 490, purity 89%

20 4m, Example 51

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 506, purity 91%

4n, Example 52

25 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 490, purity 89%

4o, Example 53

30 N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 470, purity (UV 94%)

4p, Example 54

N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 450, purity 96%

5 4q, Example 55

N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 450, purity 93%

4r, Example 56

10 N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 506, purity 91%

4s, Example 57

N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-

15 N-methyl-glycine

LC/MS (m/z) 504, purity 95%

4t, Example 58

N-{3-[1-(4-chloro-phenyl)-5-(2-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

20 LC/MS (m/z) 504, purity 78%

Pharmacological Testing

The compounds of the invention were tested in a well-recognised and reliable test measuring
25 glycine uptake:

[³H]-Glycine uptake

Cells transfected with the human GlyT-1b were seeded in 96 well plates. Prior to the
30 experiment the cells were washed twice in HBS (10 mM Hepes-tris (pH 7,4), 2,5 mM KCl, 1

mM CaCl₂, 2,5 mM MgSO₄) and pre-incubated with test compound for 6 minutes.

Afterwards, 10 nM ³H-glycine was added to each well and the incubation was continued for 15 minutes. The cells were washed twice in HBS. Scintillation fluid was added and the Plates were counted on a Trilux (Wallac) scintillation counter.

5

The test results were as follows:

Inhibition of Glycine Transport by hGlyT-

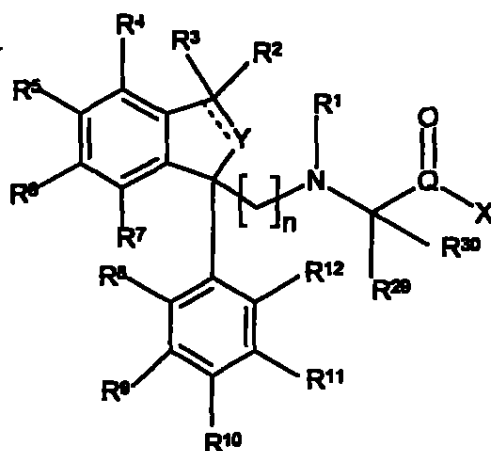
Compound	Compound Name	IC ₅₀ GlyT-1b
3f	N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	5400
3k	N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	4100
3l	N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine	5500
3m	N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	7200
3n	N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	9600
3t	N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	5700
3v	N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine	8600
3z	N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine	1100
3aa	N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine	470
3ac	N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine	4000

3af	N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine	3500
3ak	N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine	2200
3al	N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	2200
4c	N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	1200
4d	N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine	1500
4j	N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	710
4k	N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	950

The above results demonstrate that the compounds of the invention are able to inhibit glycine uptake into synaptosomes in micromolar concentrations

Claims:

1. A compound represented by the general formula I



wherein

R^1 represents hydrogen, C_{1-6} -alkyl, cycloalkyl or cycloalkylalkyl;

R^2 and R^3 independently represent hydrogen, halogen, C_{1-6} -alkyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkyl- C_{1-6} -alkyl or R^2 and R^3 together form a C_{3-6} cycloalkyl;

R^4 , R^5 , R^6 and R^7 independently represent hydrogen, halogen, CF_3 , NO_2 , CN , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, OH, SH, $NR^{14}R^{15}$, wherein R^{14} and R^{15} independently represent hydrogen or C_{1-6} -alkyl; $-COR^{16}$ wherein R^{16} represents OH, C_{1-6} -alkyl, C_{1-6} -alkoxy, $NR^{17}R^{18}$, wherein R^{17} and R^{18} independently represent hydrogen or C_{1-6} -alkyl; aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with halogen, CF_3 , OCF_3 , CN , NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, OH, SH or $NR^{24}R^{25}$, wherein R^{24} and R^{25} independently represent hydrogen or C_{1-6} -alkyl;

or R^4 and R^5 , or R^5 and R^6 , or R^6 and R^7 together form a fused, aromatic, saturated or partly saturated ring which optionally contains one or more heteroatoms such as O, N or S;

R^8 , R^9 , R^{10} , R^{11} , and R^{12} independently represent hydrogen, halogen, CF_3 , OCF_3 , CN , NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} -alkylthio, OH, SH, $NR^{19}R^{20}$, wherein R^{19} and R^{20} independently represent hydrogen or C_{1-6} -alkyl; or R^8 , R^9 , R^{10} , R^{11} and R^{12} independently represent $-COR^{21}$, wherein R^{21} represents OH, C_{1-6} -alkoxy, $NR^{22}R^{23}$ wherein R^{22}

and R²³ independently represent hydrogen or C₁₋₆-alkyl; or R⁸, R⁹, R¹⁰, R¹¹ and R¹² independently represent aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with halogen, CF₃, OCF₃, CN, NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, OH, SH, COR²⁶, wherein R²⁶ represents OH, C₁₋₆ alkoxy or C₁₋₆ alkyl; or NR³⁰R³¹, wherein R³⁰ and R³¹ independently represent hydrogen or C₁₋₆-alkyl; R⁸ and R⁹, or R⁹ and R¹⁰, or R¹⁰ and R¹¹, or R¹¹ and R¹² together form a fused, aromatic, saturated or partly saturated ring which optionally contains one or more heteroatoms such as O, N or S;

- 10 Y is O, S, CH₂ or CH, and when Y is CH then the dotted line is a bond;
n is 2, 3, 4, 5 or 6;

Q represents C, P-OR²⁹ or S=O, wherein R²⁹ represents hydrogen or C₁₋₆-alkyl;

X is OR¹³ or NR²⁷R²⁸, wherein R¹³, R²⁷, and R²⁸ independently represent hydrogen, C₁₋₆-alkyl, aryl or aryl-C₁₋₆-alkyl, wherein aryl may be substituted with halogen, CF₃, OCF₃, CN, NO₂, or

- 15 C₁₋₆ alkyl; Optionally R²⁷ and R²⁸ together form a ring which may contain further nitrogen, oxygen or sulfur atoms and the ring may optionally be partly saturated,
R²⁹ and R³⁰ represent hydrogen, C₁₋₆-alkyl, cycloalkyl or cycloalkylalkyl;

or a pharmaceutically acceptable addition salt thereof.

20

2. The compound according to any of the preceding claims, wherein n is 2 or 3.
3. The compound according to any of the preceding claims, wherein R¹ is CH₃.
4. The compound according to any of the preceding claims, wherein Q is C.
5. The compound according to any of the preceding claims, wherein X is OH or C₁₋₆-alkoxy.
- 25 6. The compound according to any of the preceding claims, wherein R⁷ represents hydrogen, and R⁴, R⁵ or R⁶ represent hydrogen, C₁₋₆-alkyl, CN, halogen, CF₃, or phenyl optionally substituted one or more times with halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, CF₃, or R⁴, R⁵ or R⁶ represent heteroaryl optionally substituted one or more times with halogen or wherein R⁴ and R⁵, or R⁵ and R⁶ together form a fused aryl.

7. The compound according to any of the preceding claims wherein R⁸, R⁹, R¹⁰, R¹¹ or R¹² independently represent hydrogen, halogen, alkyl, alkoxy, or R⁸ and R⁹, or R⁹ and R¹⁰ together form a fused aryl.
8. The compound according to any of the preceding claims wherein R⁸, R⁹, R¹⁰, R¹¹ or R¹² independently represent halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy.
9. A pharmaceutical composition comprising at least one compound according to any of the preceding claims, or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.
10. The use of a compound according to claims 1-8, for the manufacture of a medicament for the treatment of diseases responsive to modulation of the glycine transporter.
11. The use according to claim 10 wherein the disease is responsive to antagonism of the glycine transporter;
12. The use according to claims 10 and 11, wherein the disease is selected from the group consisting of the positive and the negative symptoms of schizophrenia, psychoses, dementia, pain, improving cognition, Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke.
13. A method for the treatment of a disease responsive to modulation of the glycine transporter by administering to a patient in need thereof, an effective amount of a compound according to claims 1-8.
14. The method according to claim 13 wherein the diseases are responsive to antagonism of the glycine transporter.
15. The method according to claims 13 and 14, wherein the diseases to be treated are selected from the group consisting of the positive and the negative symptoms of schizophrenia, psychoses, dementia, pain, improving cognition, Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00510

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87, C07D 333/72, C07C 229/02, C07C 211/03, A61K 31/343, A61K 31/381, A61K 31/198, A61P 25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, C07C

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1166711 A (KEFALAS A/S), 8 October 1969 (08.10.69), the claims, the examples --	1-15
X	STN International, file CAPLUS, CAPLUS accession no 1970:90271, document no 72:90271, Kefalas A/S: "Antidepressant thiophthalanes", & ZA,6800199,19690711 --	1-15
X	WO 0034263 A1 (H. LUNDBECK A/S), 15 June 2000 (15.06.00) --	1-15
X	US 4136193 A (BOGESO ET AL), 23 January 1979 (23.01.79) --	1-15

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

29 October 2001

Date of mailing of the international search report

30 -10- 2001

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00510

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Journal of Analytical Toxicology, Vol 24, No 5, 2000, Hans H. Maurer et al. "Screening Procedure for Detection of Antidepressants of the Selective Serotonin Reuptake Inhibitor Type and their Metabolites in Urine as Part of a Modified Systematic Toxicological Analysis Procedure using Gas Chromatography-Mass Spectrometry", pages 340-347, page 343, A-G --	1-15
X	Acta Pharmacologica et toxicologica, Vol 32, (1973): 3-4, pages 278-284, B. Fjalland et al: "Anti-Nociceptive Activity of Some Thiophthalanes with Morphine-like Properties" --	1-15
X	J. Org. Chem., Vol 36, No 5, 1971, W.L. Matier et al: "Novel Cyclizations and Ring-Opening Reactions of 3-Phenylindene Derivatives" pages 650-654, page 650, left column, first paragraph, page 651, compound 10, page 653, right column --	1-8
P,A	WO 0103694 A1 (H. LUNDBECK A/S), 18 January 2001 (18.01.01) --	1-15
A	J. Chem. Soc.(C), Vol 10, 1971, M.V. Bhatt et al: "Aspects of Tautomerism. Part II Reactions of the Pseudo-acid Chloride of o-Benzoylbenzoic Acid with Nucleophiles", page 1772-1777, page 1776 - page 1777, RN 32524-77-9, 32557-56-5 -- -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00510

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-15
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00510

Claims 13-15 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised in the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.

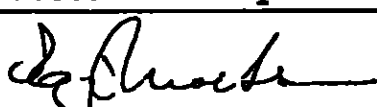
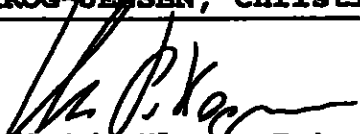
PCT/DK 01/00510

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				FI	48458 B	01/07/74
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WO	0103694	A1	18/01/01	AU	5806100 A	30/01/01 -

PCT REQUEST

332 WO

Original (for SUBMISSION) - printed on 19.07.2001 02:39:08 PM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	26	-
IX-3	Claims	3	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	35	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
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	LUNDBECK A/S	
X-1-2	Name of signatory	MEIDAHN PETERSEN, John	
X-1-3	Capacity	Director of Corporate Patents	
X-2	Signature of applicant, agent or common representative		
X-2-1	Name (LAST, First)	MOLTZEN, Ejner, Knud	
X-3	Signature of applicant, agent or common representative		
X-3-1	Name (LAST, First)	SMITH, Garrick, Paul	
X-4	Signature of applicant, agent or common representative		
X-4-1	Name (LAST, First)	KROGH-JENSEN, Christian	
X-5	Signature of applicant, agent or common representative		
X-5-1	Name (LAST, First)	BOGESØ, Klaus, Peter	

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	

24

PCT REQUEST

332 WO

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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-EASY Version 2.92 (updated 01.03.2001)
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)	Danish Patent and Trademark Office (RO/DK)
0-7	Applicant's or agent's file reference	332 WO
I	Title of invention	NOVEL COMPOUNDS AND THEIR USE AS GLYCINE TRANSPORTER INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	H. LUNDBECK A/S
II-5	Address:	Ottiliavej 9 DK-2500 Valby-Copenhagen Denmark
II-6	State of nationality	DK
II-7	State of residence	DK
II-8	Telephone No.	+45 36 30 13 11
II-9	Facsimile No.	+45 36 44 45 32
III-1	Applicant and/or inventor	
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III-1-2	Applicant for	US only
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III-1-5	Address:	Toftekarsvej 29 DK-2820 Gentofte Denmark
III-1-6	State of nationality	DK
III-1-7	State of residence	DK

PCT REQUEST

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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)	SMITH, Garrick, Paul
III-2-5	Address:	Eblehaven 10 DK-2500 Valby Denmark
III-2-6	State of nationality	GB
III-2-7	State of residence	DK
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	KROG-JENSEN, Christian
III-3-5	Address:	Hornemansgade 23 DK-2100 Copenhagen Ø Denmark
III-3-6	State of nationality	SE
III-3-7	State of residence	DK
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	BØGESØ, Klaus, Peter
III-4-5	Address:	Hørsholm Park 16, 2 tv DK-2970 Hørsholm Denmark
III-4-6	State of nationality	DK
III-4-7	State of residence	DK
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT (patent and utility model) AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ (patent and utility model) DE (patent and utility model) DK (patent and utility model) DM DZ EC EE (patent and utility model) ES FI (patent and utility model) GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ N NZ PL PT RO RU SD SE SG SI SK (patent and utility model) SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW	
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	21 July 2000 (21.07.2000)	
VI-1-2	Number	PA200001124	
VI-1-3	Country	DK	
VII-1	International Searching Authority Chosen	Swedish Patent Office (ISA/SE)	
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	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

PCT REQUEST

332 WO

Original (for SUBMISSION) - printed on 19.07.2001 02:39:06 PM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	--
IX-2	Description	26	--
IX-3	Claims	3	--
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	--
IX-7	TOTAL	35	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	--
IX-13	Priority document(s)	Item(s) VI-1	--
IX-17	PCT-EASY diskette	--	Diskette
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	LUNDBECK A/S	
X-1-2	Name of signatory	MEIDAHN PETERSEN, John	
X-1-3	Capacity	Director of Corporate Patents	
X-2	Signature of applicant, agent or common representative		
X-2-1	Name (LAST, First)	MOLTZEN, Ejner, Knud	
X-3	Signature of applicant, agent or common representative		
X-3-1	Name (LAST, First)	SMITH, Garrick, Paul	
X-4	Signature of applicant, agent or common representative		
X-4-1	Name (LAST, First)	KROG-JENSEN, Christian	
X-5	Signature of applicant, agent or common representative		
X-5-1	Name (LAST, First)	BØGESØ, Klaus, Peter	

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	

PCT REQUEST

332 WO

Original (for SUBMISSION) - printed on 19.07.2001 02:39:06 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/SE
10-8	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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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MEIDAHL PETERSEN, John
H. LUNDBECK A/S
Otteliavej 9
DK-2500 Valby-Copenhagen
DANEMARK

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 21.08.2002

Applicant's or agent's file reference
332 WO

IMPORTANT NOTIFICATION

International application No.
PCT/DK01/00510

International filing date (day/month/year)
19/07/2001

Priority date (day/month/year)
21/07/2000

Applicant
H. LUNDBECK A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report 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 examination report. 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.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/



European Patent Office
D-80286 Munich
Tel. +49 89 2399 - 0 Tx: 523856 epmu d
Fax: +49 89 2399 - 4485

Authorized officer

Brell, S

Tel. +49 89 2399-7271



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 332 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/DK01/00510	International filing date (day/month/year) 19/07/2001	Priority date (day/month/year) 21/07/2000
International Patent Classification (IPC) or national classification and IPC C07D307/87		
Applicant H. LUNDBECK A/S et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 8 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: - I ☒ Basis of the report - II ☐ Priority - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability - IV ☐ Lack of unity of invention - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement - VI ☐ Certain documents cited - VII ☐ Certain defects in the international application - VIII ☐ Certain observations on the international application		
Date of submission of the demand 16/01/2002	Date of completion of this report 21.08.2002	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax: +49 89 2399 - 4485	Authorized officer Ousset, J-B Telephone No. +49 89 2399 8271 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/DK01/00511

31

I. Basis of the report

1. With regard to the elements of the international application (*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 since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-26 as originally filed

Claims, No.:

1-15 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/DK01/0051

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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

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

- ☐ the entire international application.
- ☒ claims Nos. 13-15.

because:

- ☒ the said international application, or the said claims Nos. 13-15 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

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
	No:	Claims 1-12
Industrial applicability (IA)	Yes:	Claims 1-12

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/DK01/0051

No: Claims

2. Citations and explanations
see separate sheet

SECTION III

1). Claims 13-15 relate to the treatment of human and/or animal bodies. According to Rule 67(1)(iv) an examination is not required for such claims.

SECTION V

1). Relevant prior art is represented by:

D1: GB-A-1166711

D2: ZA-A-6800199

D3: WO-A1-0034263

D4: US-A-4136193

D5: WO-A1-0103694

D6: 'Antidepressant thiophthalanes',", 'CAPLUS', 'KEFALAS A/S', DOC. NO. 72:90271,

D7: 'Screening procedure for detection of antidepressants of the selective serotonin reuptake inhibitor type and their metabolites in urine as part of a modified systematic toxicological analysis procedure using gas chromatography-mass spectrometry', 'HANS H. MAURER ET AL.', 'JOURNAL OF ANALYTICAL TOXICOLOGY',", 24/5/00-00-2000, 340-347,

2). The claimed matter is regarded as novel, since the cited documents differ mainly from the content of the present application in that there is either no oxygen linked by a double bond to the chain attached at the position 1 of the core heterocycle or no carbon atom between the nitrogen atom and the carbonyl group in this chain.

Novelty is acknowledged.

3). D3 represents the structurally closest prior art, since it discloses compounds which also can be used against schizophrenia (see page 2, line 2). The compounds of D3 differ from the ones of the present application in that there is no group "Q(O)" between the nitrogen atom and the terminal group on the lateral chain attached at the position 1 of the core moiety.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/DK01/00510

Thus, the problem underlying the current application appears to be the provision of further heterocyclic compounds used to treat schizophrenia.

Due to the data provided by the applicant in his description on pages 41-43, the problem is regarded as being solved.

None of the other cited document gives a hint to the skilled person, seeking to make available further compounds to treat schizophrenia, to modify the lateral chain to arrive at the claimed compounds without inventive effort.

Thus an inventive step can be acknowledged for the tested compounds.

However, in view of the state of the art and the different alternatives tested by the applicant, it is not clear for which reason, the same skilled person would consider the claimed generalisation as obvious in view of the tested compounds. In other words, for which reason would this same skilled person expect that the compounds falling within the scope of the claims would retain the claimed activity.

Inventive step on the whole scope is not acknowledged.

4). No objection with regard to industrial applicability.

PCT

From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

H. LUNDBECK A/S
Ottiliavej 9
DK-2500 Valby-Copenhagen
DANEMARK

Date of mailing (day/month/year)

31 January 2002 (31.01.02)

Applicant's or agent's file reference

332 WO

IMPORTANT NOTICE

International application No.

PCT/DK01/00510

International filing date (day/month/year)

19 July 2001 (19.07.01)

Priority date (day/month/year)

21 July 2000 (21.07.00)

Applicant

H. LUNDBECK A/S et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
- KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 31 January 2002 (31.01.02) under No. WO 02/08216

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 18 months from the priority date.

It is the applicant's sole responsibility to monitor the 18-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.91.11

PATENT COOPERATION TREATY

37

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

H. LUNDBECK A/S
Ottiliavej 9
DK-2500 Valby-Copenhagen
DANEMARK

Date of mailing (day/month/year)

18 February 2002 (18.02.02)

Applicant's or agent's file reference

332 WO

IMPORTANT INFORMATION

International application No.

PCT/DK01/00510

International filing date (day/month/year)

19 July 2001 (19.07.01)

Priority date (day/month/year)

21 July 2000 (21.07.00)

Applicant

H. LUNDBECK A/S et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

National : AU, BG, CA, CN, CZ, DE, GB, IL, JP, KP, KR, MN, NO, NZ, PL, RO, RU, SE, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, PT, SD, SG, SI, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 38(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

ALI SOLEIMAN

Telephone No. (41-22) 338.83.38



FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Royal
Technologies S.A.
Autopromoción y Desarrollo S.A.

38

Expediente No		03003680	No de Follo
Item		No de unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	1	
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		
Observaciones: <i>Arte Final</i>			

240 00
For patents, utility models, industrial designs,
trademarks, commercial names, trade emblems,
slogans.

39

Para patentes, modelos de utilidad, diseños
industriales, marcas de fábrica, nombres
comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned / Yo (nosotros), abajo firmado (s)
H. LUNDBECK A/S

03003

06049

of/domiciliado (s) en 9. Ottiliavej, DK-2500,
-Copenhagen, DENMARK

por el presente nombramos a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; y LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistír, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both, of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights. b) Actions of unfair competition, protection of consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this/Dado y firmado hoy
11 June 1998

in/en Copenhagen

H. Lundbeck A/S

John Mejdahl Petersen
Signature
John Mejdahl Petersen
Patent Department

Firma

CAVELIER ABOGADOS
WPPODERE-1 (MINUTA N° 12.1.1.2.5)

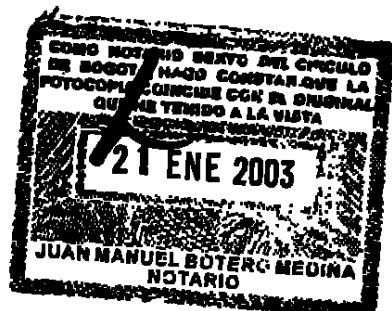
164033 06 0001.2101 12.06.98 RA
60100-02364/98 200.00 K

LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate*, on the legal existence of the company which grants the Power-of-Authority, (2) that it is in actual exercise of its company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

La suscrita Ilse Greby, notario público de Copenhague, Dinamarca, certifica que el señor

John Meidahl Petersen,

que en la fecha de hoy ha firmado ante mí el presente documento, está autorizado, según documentos justificativos que juzgo suficientes, para usar la firma de la sociedad denominada

H. LUNBECK A/S,

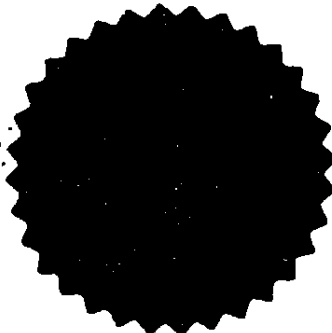
domiciliada en 9, Ottiliavej, DK-2500 Copenhague, Dinamarca, y que legalmente existe y actualmente ejerce su objeto social de acuerdo con las leyes del Dinamarca.

En fé de lo cual pongo mi firma y el sello notarial.

Notaría de Copenhague, a 11 de Junio de 1998.

Ilse Greby
Ilse Greby

notario público



Derechos: 200,- DKK.



SE LEGALIZA LA FIRMA QUE ANTECEDE DE

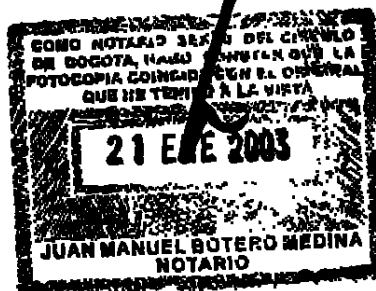
ILSE GREBY

COPENHAGUE, EL

11 JUN 1998

POR EL MINISTRO DE RELACIONES EXTERIORES
P.A.

Inger Regaard
INGER REGAARD



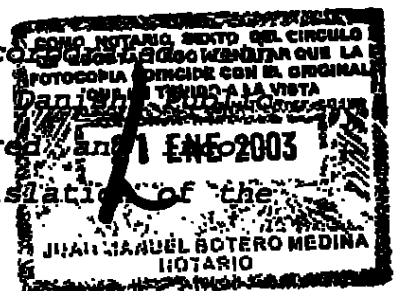
Notary public of Colombia
Denmark



The Danish Commerce and Companies Agency
certifies and attests that

"H. LUNDBECK A/S"
Ottiliavej 7-9
DK-2500 Valby
Denmark

of the municipality of Copenhagen
which company was established 14th October 1950
under registration number A/S 22.472
in the Danish Commerce and Companies Agency incorporated
limited liability, is legally existing as a Danish
Company, limited by shares, and duly registered and
incorporated under the provisions of the Company Legislation of the
Kingdom of Denmark.



Copenhagen, 11th May 1998

Pia Sødequist

THE TRUE SIGNATURE OF

P. R. SØDEQUIST

18 MAY 1998

FOR THE MINISTRY OF FOREIGN AFFAIRS

E.A.

ENGELHART

42

CONSULADO DE COLOMBIA

No 33-98

El suscrito, Cónsul de Colombia en Copenhague, Dinamarca, vistos los documentos presentados por los interesados,

CERTIFICA:

Que la Sra. Inger Elgaard quien autoriza el documento adjunto, ejercía legalmente, en la fecha allí expresada, sus funciones como Funcionario del Ministerio de Relaciones Exteriores de Dinamarca, y que su firma y sellos corresponden a los registrados en este Consulado.

Que la firma H. LUNDBECK A/S. existe legalmente, que ejerce su objeto social de acuerdo a las leyes danesas y que el Sr. John Meidahl Petersen está autorizado para firmar el documento, de acuerdo al Resumen expedido por la Dirección de Industrias y Comercio Nr. A/S 22472, cuya copia se adjunta.

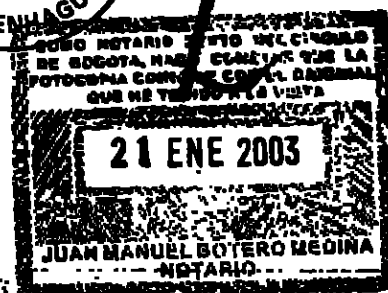
El suscrito Cónsul de Colombia no asume responsabilidad por el contenido del documento.

"Se pagarán en Colombia los impuestos de Timbre que se ocasionen al ejecutar en Colombia las obligaciones emanadas del presente documento de conformidad con el artículo 519 del Estatuto tributario."

Copenhague, Junio 23 de 1.998.

CARLOS ARTURO MORALES
Cónsul de Colombia

Pagado : Impuesto Timbre USD. 6.00
Derechos Consulares USD: 100.00



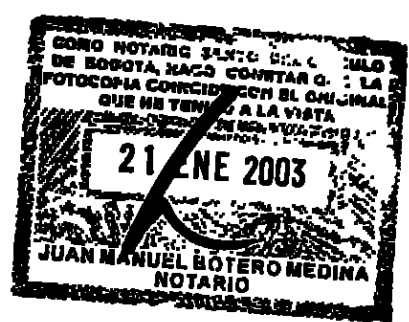
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

90 JUL -1 PM 2:40

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERIORES

651248
Cuba Pinales
CUMPLIMIENTO DE SEMEJERA
LAS FUNCIONES INDICADAS

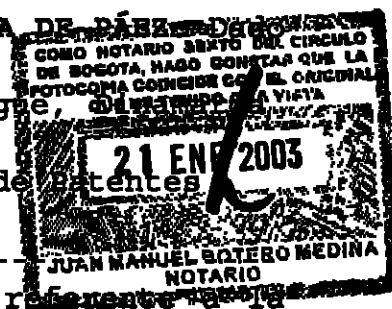


TRADUCCIÓN OFICIAL N° 0807981 al español de un documento escrito en inglés, preparada por Jaime Armando Garavito Burgos, Traductor Oficial debidamente reconocido por el Ministerio de Relaciones Exteriores y aprobado por el Ministerio de Justicia de la República de Colombia mediante Resolución N° 034 de enero 11 de 1983

(En la parte superior central de las tres primeras páginas aparece sello redondo en relieve de la Embajada de Colombia en Copenhague, Dinamarca)

(Adherido en la esquina superior izquierda de las dos primeras hojas del documento aparece sello rojo de oblea, junto con sello en tinta del Notario Público de Copenhague, Dinamarca)

Documento escrito en inglés y español por medio del cual H. LUNDBECK A/S, otorga poder a favor de GERMÁN CAVELIER, GONZALO PERDOMO, EMILIO FERRERO y LUZ CLEMENCIA DE PÁEZ y firmado el 11 de junio de 1998 en Copenhague, Dinamarca (firmado) John Meidahl Petersen, Departamento de Patentes



CERTIFICACIÓN NOTARIAL (SOCIEDAD) en español referente a la existencia legal de la sociedad H. LUNDBECK A/S y su representante autorizado John Meidahn Petersen, expedida el 11 de junio de 1998 en Copenhague, Dinamarca. (firmado) Ilse Greby, Notario Público (Aparece adherido sello notarial rojo de oblea)

24

2

El Ministerio de Relaciones Exteriores en Copenhague,
Dinamarca legaliza la firma de Ilse Greby, Notario Público el
19 de junio de 1998. (firmado) INGER ELGAARD

ERHVERVS- OG SELSKABSSTYRELSEN
ERHVERVSMINISTERIET

(Aparece un símbolo)

La Agencia Danesa de comercio y Compañías certifica y

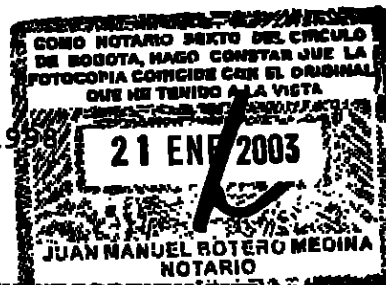
atestigua que

"H. LUNDBECK A/S"
Ottiliavej 7-9
DK-2500 Valby
Dinamarca

del municipio de Copenhague, compañía que fue establecida el
14 de octubre de 1950 bajo el número de registro A/S 22.472
en la Agencia Danesa de Comercio y de Compañías constituida
con responsabilidad limitada, existe legalmente como una
Compañía Pública Danesa, limitada por acciones y debidamente
registrada y constituida bajo las disposiciones de la
Legislación de Compañías del Reino de Dinamarca.

(Aparece copia de sello de oblea)

Copenhague, mayo 11, 1998
(firmado)
Pia Sødequist



EL MINISTERIO DE RELACIONES EXTERIORES EN COPENHAGUE,
DINAMARCA CERTIFICA LA FIRMA DE PIA SØDEQUIST el 14 de mayo
de 1998. (firmado) INGER ELGAARD

N° 33-98. EL CONSULADO GENERAL DE COLOMBIA en Copenhague,
Dinamarca, certifica las funciones y firma de Inger Elgaard,
el 23 de junio de 1988. Pagado impuesto de timbre y derechos

VJ

consulares. (firmado) CARLOS ARTURO MORALES, Cónsul de Colombia

EL MINISTERIO DE RELACIONES EXTERIORES en Santafé de Bogotá, D.C. certifica la firma y las funciones de Carlos Morales, el 1 de julio de 1998. N° 051248. (firmado) Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santafé de Bogotá, D.C., julio 8 de 1998

COLO: 3003-801-001-0
WPCL3003- ID # 19

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

98 JUL 14 PM 12:18

JEFE DE LEGALIZACIONES
SANTAFÉ DE BOGOTÁ D.C.

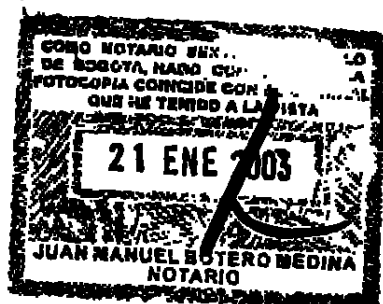
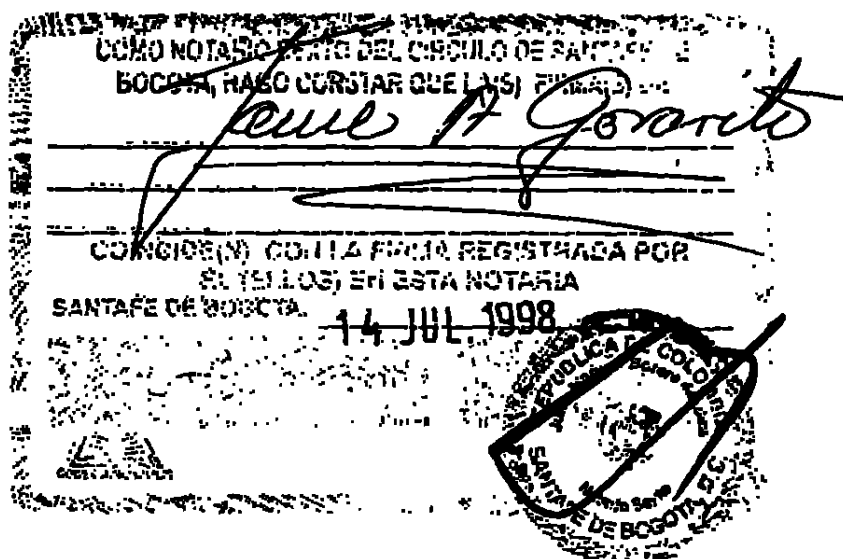
MINISTERIO DE RELACIONES
EXTERIORES

054833

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

Jaime A. Garavito B.
JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Bo. 034 de Enero 11 de 1993
MINISTERIO DE JUSTICIA

COMO NOTARIO EN UNO DEL CIRCULO
DE BOGOTÁ, HAGO CONSTAR QUE LA
FOTOCOPIA CONCORDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
21 JUN 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO



RECEIVED
2003 JAN 21 10:24 AM
NOTARY PUBLIC
JUAN MANUEL BOTERO MEDINA

46

CAVELIER
ABOGADOS

WEB SITE: www.caveller-abogados.com
E-MAIL: caveller@colomat.net.co

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTÁ 8, COLOMBIA

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: H. LUNDBECK A/S

Poder conferido el: 11-06-98

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que los otros sustitutos faltan en este momento.

Señor Jefe,

GERMAN CAVELIER

T.P.A. No. 832

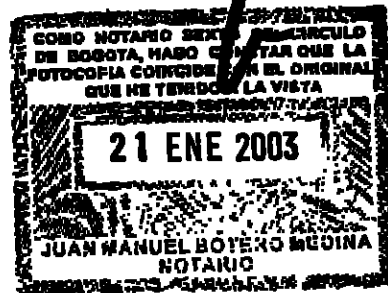
C.C. No. 2.877.924 de Bogotá

Acepto:

EMILIO FERRERO

T.P.A. No. 31.929

C.C. No. 438.019 de Usaquén



2e-780-2

NOTARIA SEXTA DE ECOGOTA

RECONOCIMIENTO Y PRESENTACIÓN PERSONAL

Bogotá, D. C. 14 AGO. 1998

Ante Mí, PABLO MENDEZ BARAJAS S.

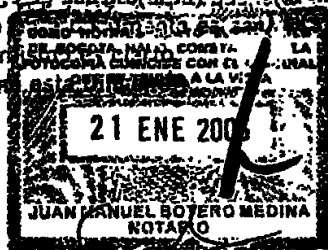
NOTARIO SEXTO ENCARGADO DEL CIRCULO DE BOGOTÁ

Comparecís (eros)

[Firma]
[Firma]
C. en (ad) ext. 016 (eros) C. en (ad) 2897424
438079

C. en (ad) ext. 016 (eros) C. en (ad) 832-31429

El/los compareciente(s) en Bogotá ha/s declaró(n) que la(s) firma(s) que
aparecen(n) en el presente documento es/s de su/s. *[Firma]*
que el contenido del mismo es verídico y que se firmó en presencia de la vida
En consecuencia se firmó este documento a la vista



[Firma]
[Firma]
[Firma]



VIT : 800176000-2

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03003600 00000000

Folios: 47

Fecha (AMD): 2003-01-21 16:27:32

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 03 - 114
FECHA : ENERO 2 DE 2003

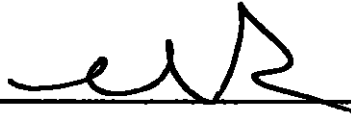
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	3136954	02/01/2003	34,706,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	7 .TRANITES DE SOL. DE DISEÑOS INDUS	400,000.00
	TOTAL :	\$ 400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 03003-841-002-0

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
Indicacion de que se solicita la concesion de una patente.	X	()
Datos de Identificacion del solicitante o de la persona que se presenta la solicitud	X	()
Descripcion de la Invencion.	X	()
Diligencias de ser estas pertinentes.	X	()
Comprobante de Pago de las tasas establecidas		()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
Indicacion de que se solicita el registro de Diseño Industrial	()	()
Datos de Identificación del solicitante o de la persona que presenta la solicitud	()	()
Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
Indicacion 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 *Audrea Posseu*