

342
340

Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-019948- -00003-0000

Fecha: 2008-01-16 16:25:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 3

Referencia: Expediente No. 06.019.948

Solicitud de Patente de Invención titulada: "Derivado de (TIO) carbamoil-
ciclohexano como antagonistas de los receptores D3/D2"

Solicitante: Richter Gedeon Vegyészeti Gyár RT.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISIÓN
486. GACETA NO. 579

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad arriba mencionada, solicito que se examine la invención de la referencia según los requisitos de patentabilidad previstos en la Decisión 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto recibo de caja por valor de \$210.000 para cubrir la tasa correspondiente según la Resolución 44372 del 26 de diciembre de 2007.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

Anexo: Recibo de caja por valor de \$210.000

2

00000014
341

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CERTIFICACION DE EXCEDENTE : 07 - 53,078
FECHA : JUNIO 29 DE 2007

Act. 2004-01-10-23-04 Dep. 1 de CONCILIACION
Eje. 11 PATENTEYI Eje. 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 3

***** CONSIGNACION *****

POSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	49375977	29/06/2007	64,444,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	8,000.00
		TOTAL :	\$ 8,000.00

SON: OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

344
342

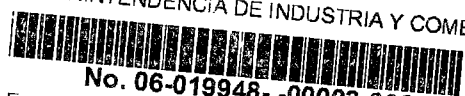
00000020

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 82,090
FECHA : OCTUBRE 5 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-019948- -00003-0000

Fecha: 2008-01-16 16:25:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Evs: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 3

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	69421920	05/10/2007	51,962,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	202,000.00
		TOTAL :	\$ 202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

305
343

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-19948

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **579** DE

FECHA **31 DE AGOSTO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE NOVIEMBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
10 April 2003 (10.04.2003)

PCT

(10) International Publication Number
WO 03/029233 A1(51) International Patent Classification⁷: C07D 295/12,
A61K 31/445, 31/495

(21) International Application Number: PCT/HU02/00093

(22) International Filing Date:
25 September 2002 (25.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PO1 03988 28 September 2001 (28.09.2001) HU(71) Applicant (for all designated States except US):
RICHTER GEDEON VEGYÉSZETI GYÁR RT.
[HU/HU]; Gyömrői út 19-21, H-1103 Budapest (HU).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GH, GM,
GN, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GALAMBOS,
János [HU/HU]; Cserkút u. 40., H-1162 Budapest
(HU). NÓGRÁDI, Katalin [HU/HU]; Kossuth Lajos u.
145/a, H-1182 Budapest (HU). ÁGAINÉ CSONGOR,
Éva [HU/HU]; Rozália u. 35., H-1031 Budapest (HU).
KESERÚ, György, Miklós [HU/HU]; Berkenye u. 9.,
H-2089 Telki (HU). VÁGÓ, István [HU/HU]; Denevér
Út 64., H-1121 Budapest (HU). DOMÁNY, György
[HU/HU]; Fő u. 2/G, H-7695 Óbánya (HU). KISS, Béla
[HU/HU]; Nemeske u. 16/C, H-1182 Budapest (HU). GY-
ERTYÁN, István [HU/HU]; Koronafűt u. 33, H-1165
Budapest (HU). LASZLOVSKY, István [HU/HU];
Bartók B. u. 16., H-1111 Budapest (HU). LASZY, Judit
[HU/HU]; Madách tér 1., H-2094 Nagykovácsi (HU).(74) Common Representative: RICHTER GEDEON VEG-
YÉSZETI GYÁR RT.; Gyömrői út 19-21, H-1103 Bu-
dapest (HU).

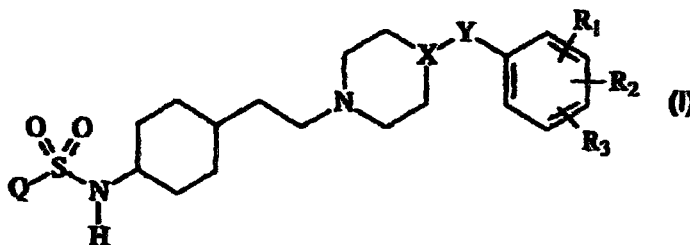
Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, 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, NO, NZ, OM, PH, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG)

Published:

with international search report

[Continued on next page]

(54) Title: NEW SULFONAMIDE DERIVATIVES AS D₃-RECEPTOR AGONISTS(57) Abstract: The present invention
relates to new D₃ dopamine receptor
subtype selective ligands of formula
(I) to pharmacological compositions
containing the same and to their use in
therapy and/or prevention of psychoses
(e.g. schizophrenia, schizo-affective
disorders, etc), drug (e.g. alcohol,
cocaine and nicotine, opioids etc.) abuse,
cognitive impairment accompanying
schizophrenia, mild-to-moderate cognitivedeficits, amnesia, eating disorders (e.g. bulimia nervosa, etc.), attention deficit disorders, hyperactivity disorders in children,
psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders (e.g. Parkinson's diseases, neuroleptic
induced Parkinson's diseases, tardive dyskinesias) anxiety, sexual dysfunction, sleep disorders, emesis, aggression, autism, pain
ophthalmological diseases (e.g. glaucoma etc.).

WO 03/029233 A1

347
345

- 12 -

disease and drug abuse. The effect of dopamine is mediated via at least five distinct dopamine receptors belonging to the D₁- (D₁, D₅) or the D₂- (D₂, D₃, D₄) families. D₃ receptors have been shown to have characteristic distribution in the cerebral dopaminergic systems. Namely, high densities were found in certain limbic structures such as nucleus accumbens and islands of Calleja. Therefore, selective targeting of the D₃ receptors may be a promising approach for more selective modulation of dopaminergic functions and consequently for successful therapeutic intervention in several abnormalities, such as schizophrenia, emotional or cognitive dysfunctions and addiction (Sokoloff, P. et al: Nature, 1990, 347, 146; Schwartz, J.-C. et al.: Clin. Neuropharmacol., 1993, 16, 295; Levant, B.: Pharmacol. Rev., 1997, 49, 231.), addiction (Pilla, C. et al: Nature, 1999, 400, 371) and Parkinson's disease (Levant, B. et al.: CNS Drugs, 1999, 12, 391) or pain (Levant, B. et al.: Neurosci. Lett., 2001, 303, 9). Dopamine D₃ receptors are also implicated in regulation of intraocular pressure and agonists at these receptors are capable of decreasing the intraocular pressure (Chu, E. et al: J. Pharmacol. Exp. Ther., 2000, 292, 710), thus D₃ receptors agonists can be useful for the treatment of glaucoma.

Certain compounds of formula (I) have been found to be dopamine D₃ receptor antagonist, others may be agonists or partial agonists.

In a further aspect of the present invention provides a method of treating conditions which require modulation of dopamine D₃ receptors, for example psychoses, for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, depression, anxiety, memory disorders, sexual dysfunction, drug dependency and ophthalmological disorders which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

The invention also provides the use of a compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the

manufacture of a medicament for the treatment of conditions which require modulation of dopamine D₃ receptors.

A preferred use for D₃ agonists or partial agonists according to the present invention is in the treatment of drug abuse (such as cocaine abuse etc.) and eye
5 diseases (such as glaucoma).

A preferred use for D₃ antagonists according to the present invention is in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders, dyskinetic disorders such as Parkinson's disease, neuroleptic induced parkinsonism, depression, anxiety, memory disorders,
10 sexual dysfunction, drug abuse, pain.

For use in medicine, the compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further
15 aspect pharmaceutical compositions comprising a new compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and one or more physiologically acceptable carrier(s).

The compounds of formula (I) and/or geometric isomers and/or
20 stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof may be administered by any convenient method, for example by oral, parental, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and/or geometric isomers and/or
25 stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and the physiologically acceptable salts thereof which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation of the compounds of formula (I) and/or geometric isomers
30 and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof generally consists of a suspension or solution of the compound of formula (I) or physiologically acceptable salts thereof in

dose between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof calculated as the free base. The compound of the present invention can be administered 1 to 4 times per day. The compound of the present invention can suitably be administered for a period of continuous therapy, for example for a week or more.

10

Receptor binding assays

1. D₃ receptor binding

15

Binding study was carried out on rat recombinant D₃ receptors expressed in Sf9 cells using [³H]-spiperone (0.4 nM) as ligand and haloperidol (10 μM) for determination of non-specific binding. The assay was performed according to Research Biochemical International assay protocol for rD₃ receptor (Cat. No. D-181).

20

2. D₂ receptor binding

Binding of [³H]-spiperone (0.5 nM) to rat striatal tissue was measured according to the method of Seeman (J. Neurochem., 1984, 43 221-235). The non-specific binding was determined in the presence of (±)-sulpiride (10 μM).

D₃ and D₂ receptor binding data of compounds of the present invention are listed in Table 1.

30

code	D3-IC ₅₀ (nM)	D2-IC ₅₀ (nM)
70001485	5,5	2586
70001488	4,3	245
70001492	2,0	65
70001588	2,5	102
70001589	3,0	16
70001596	0,6	110
70001766	5,3	128
70001788	1,5	290
70001934	1,0	109
70001935	0,3	29
70001686	3,9	345
70001875	2,8	66

Table 1

The most prominent side effects of the first generation antipsychotic compounds (e.g. chlorpromazine and haloperidol) with preferential blockade at dopamine D₂ and alpha-1 receptors, are the tardive dyskinesia and orthostatic hypotension. The former one is the result of blockade of D₂ receptors in the basal ganglia whereas the latter is the consequence of antagonism of alpha-1 receptors.

Compounds in Table 1 are potent ligands at D₃ receptors (IC₅₀ values are between 0.3 and 5.5 nM) and show 5 to 470 fold selectivity over D₂ receptors. Moreover, the compounds have beneficial profile in terms of potency on D₃ receptors and selectivity towards D₂. It is therefore anticipated that no or greatly diminished adverse effects related to D₂ receptors will occur in the course of therapeutical application of compounds of the present invention.

The invention is further illustrated by the following non-limiting examples.

Example 1

1-(3-cyano-5-trifluoromethyl-phenyl)-piperazine

2.42 g (13 mmol) 3-fluoro-5-trifluoromethyl-benzonitrile and 6.0 g (70 mmol) piperazine was dissolved in 50 ml dimethylsulfoxide and the solution was refluxed for one day. The mixture was poured into 200 ml of water and extracted with diethylether (3 x 100 ml). The organic layers were washed with saturated sodium

chloride solution, then dried and evaporated to dryness in vacuo giving 2.96 g (yield 89.2 %) of the title compound, melting at 85-7 °C.

Example 1

5 ***Trans*-(4-{2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester**

0.63 g (2.5 mmol) of 1-(3-cyano-5-trifluoromethyl-phenyl)-piperazine and 0.6 g (2.5 mmol) of *trans*-2-[1-[4-(*N*-*tert*-butoxycarbonyl)amino]cyclohexyl]-acetaldehyde were dissolved in dichloroethane (35 ml), 0.79 g (3.7 mmol) sodium triacetoxyborohydride was added portionswise and the reaction mixture was stirred
10 for 20 hours at ambient temperature, then 20 % potassium carbonate solution in water (20 ml) was added. The organic layer was separated, dried and evaporated to dryness in vacuo. The precipitate was recrystallized from acetonitrile to give the title compound 1.03 g (yield 85.8 %), m.p.: 139-140 °C.

15

The following compounds were prepared in a similar manner to Example 1:

Trans-(4-{2-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 171-2 °C

20 *Trans*-(4-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 130-2 °C

Trans-(4-{2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 144-5 °C

Trans-(4-{2-[4-(3-trifluoromethyl-phenylmethyl)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 107 °C

25 *Trans*-(4-{2-[4-(3-fluoro-phenylmethyl)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 128 °C

Trans-(4-{2-[4-(3-cyano-phenylmethyl)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 115-6 °C

30 *Trans*-(4-{2-[4-(3-trifluoromethyl-phenylamino)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 112-3 °C

Trans-(4-{2-[4-(3-trifluoromethyl-phenylmethoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester, m.p.: 107 °C

Trans-4-[2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl]-cyclohexyl)-carbamic acid tert-butyl ester, m.p.: 118-9 °C

Example 2

5 ***Trans*-3-[4-[2-(4-amino-cyclohexyl)-ethyl]-piperazin-1-yl]-5-trifluoromethyl-benzonitrile**

1.03 g (2.1 mmol) *trans*-4-[2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl]-cyclohexyl)-carbamic acid tert-butyl ester was deprotected at 10 °C using 10 ml ethylacetate saturated with gaseous hydrochloric acid, the precipitate was
10 filtered giving 0.94 g (yield 98 %) dihydrochloride salt of the title compound, melting above 260 °C.

The following compounds were prepared in a similar manner to Example 2:

15 *Trans*-4-[2-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: > 280 °C

Trans-4-[2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 280 °C

Trans-4-[2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 264-5 °C

20 *Trans*-4-[2-[4-(3-trifluoromethyl-phenylmethyl)-piperidin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 268 °C

Trans-4-[2-[4-(3-fluoro-phenylmethyl)-piperidin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 286-7 °C

25 *Trans*-4-[2-[4-(3-cyano-phenylmethyl)-piperidin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 257-8 °C

Trans-4-[2-[4-(3-trifluoromethyl-phenylamino)-piperidin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 260-4 °C

Trans-4-[2-[4-(3-trifluoromethyl-phenylmethoxy)-piperidin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 262 °C

30 *Trans*-4-[2-[4-(3-trifluoromethyl-phenoxy)-piperidin-1-yl]-ethyl]-cyclohexylamine dihydrochloride, m.p.: 294 °C

383
351

- 20 -

Example 3***Trans-N-(4-{2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-pyridine-3-sulfonamide (70001503)***

0.38 g (1 mmol) of *trans*-3-{4-[2-(4-amino-cyclohexyl)-ethyl]-piperazin-1-yl}-5-trifluoromethyl-benzonitrile was dissolved in dichloromethane (30 ml), 0.42 ml (3 mmol) triethylamine was then added followed by 0.24 g (1.1 mmol) of pyridine-3-sulfochloride hydrochloride. The mixture was stirred for 24 hours, washed twice with 10 % sodium bicarbonate solution, dried and evaporated to dryness in vacuo. The residue was purified on silica gel eluting with 10% ethanol/chloroform, then converted to the dihydrochloride salt of the title compound. 0.32 g (yield 54 %), melting at 194-5 °C.

The following compounds were prepared in a similar manner to Example 3:

Trans-N'-(4-{2-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-N,N-dimethyl-sulfamide hydrochloride, m.p.: 243-6 °C (70001488)

Trans-4-chloro-N-(4-{2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-benzenesulfonamide hydrochloride, m.p.: 260-2 °C (70001492)

Trans-4-chloro-N-(4-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-benzenesulfonamide hydrochloride, m.p.: 223 °C (70001552)

Trans-N-(4-{2-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-pyridinesulfonamide dihydrochloride, m.p.: 219 °C (70001737)

Trans-5-chloro-N-(4-{2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-2-thiophenesulfonamide hydrochloride, m.p.: 181 °C (70001766)

Trans-N'-(4-{2-[4-(3-cyano-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-N,N-dimethyl-sulfamide, m.p.: 83-5 °C (70001788)

Trans-N-(4-{2-[4-(3-methoxy-biphenyl-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-buthanesulfonamide hydrochloride, m.p.: 215-8 °C (70001485)

Trans-N-(4-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-buthanesulfonamide hydrochloride, m.p.: 228-9 °C (70001596)

Trans-N-(4-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-4-morpholinepropanesulfonamide dihydrochloride, m.p.: 218-20 °C (70001934)

continued from the previous page

80001238	N-(4-{2-[4-(5-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-4-fluoro-benzenesulfonamide	510,1	510,5	3,52 1
80001239	N-[4-(4-{2-[4-(3-Chloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)sulfamoyl]-phenyl]-acetamide	519,1	519,6	3,27 3
80001252	Biphenyl-4-sulfonic acid (4-{2-[4-(2-fluoro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-amide	521,7	522,6	3,98 5
80001255	N-(4-{2-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-4-methoxy-benzenesulfonamide	475,6	476,6	3,32 5
80001262	N-(4-{2-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-4-methyl-benzenesulfonamide	459,6	460,5	3,47 6
80001264	N-(4-{2-[4-(5-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-trifluoromethyl-benzenesulfonamide	560,1	560,5	3,80 4
80001271	N-(4-{2-[4-(4-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3,4-dimethoxy-benzenesulfonamide	552,1	552,6	3,37 4
80001276	N-(4-{2-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-nitro-benzenesulfonamide	490,6	491,5	3,44 2
80001280	N-(4-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3,4-dimethoxy-benzenesulfonamide	556,5	557,5	3,71 3
80001294	N-(4-{2-[4-(4-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-ethyl}-cyclohexyl)-4-methyl-benzenesulfonamide	506,1	506,5	3,69 8

Table 2

5

Example 10**Pharmaceutical formulation**10 a) Intravenous injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml

b) Bolus injection

15 Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-solvent	to 5 ml

Buffer: suitable buffers include e.g. citrate, phosphate, sodium hydroxide/hydrochloric acid.

384
352

255
353

- 26 -

Solvent: typically water but may also include cyclodextrins (1-100 mg) and co-solvents, such as propylene glycol, polyethylene glycol and alcohol.

c) Tablet

5	Compound of formula (I)	1-40 mg
	Diluent/Filter(may also include cyclodextrins)	50-250 mg
	Binder	5-25 mg
	Disintegrant (may also include cyclodextrins)	5-50 mg
	Lubricant	1-5 mg
10	Cyclodextrin	1-100 mg

Diluent: *e.g.* microcrystalline cellulose, lactose starch.

Binder: *e.g.* polyvinylpyrrolidone, hydroxypropylmethylcellulose.

Disintegrant: *e.g.* sodium starch glycolate, crospovidone.

Lubricant: *e.g.* magnesium stearate, sodium stearyl fumarate

15 d) Oral suspension

	Compound of formula (I)	1-40 mg
	Suspending agent	0.1-10 mg
	Diluent	20-60 mg
	Preservative	0.01-1.0 mg
20	Buffer	to pH ca 5-8
	Co-solvent	0-40 mg
	Flavour	0.01-1.0 mg
	Colourant	0.001-0.1 mg

25 Suspending agent: *e.g.* xanthan gum, microcrystalline cellulose.

Diluent: *e.g.* sorbitol solution, typically water.

Preservative: *e.g.* sodium benzoate.

Buffer: *e.g.* citrate.

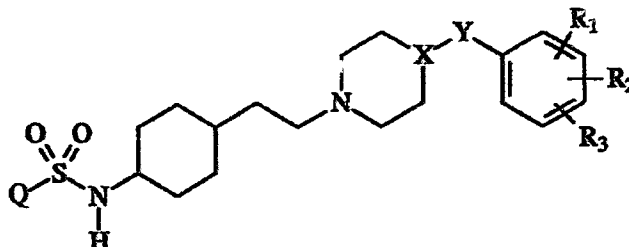
30 Co-solvent: *e.g.* alcohol, propylene glycol, polyethylene glycol, cyclodextrin.

856
354

- 27 -

What we claim:

1. A compound of formula (I)



(I)

5 - wherein

- X represents a nitrogen atom or CH group;
- Y represents a bond when X stands for nitrogen, or an oxygen atom or NH or CH₂ or OCH₂ group when X stands for CH group;
- R₁, R₂, R₃ may be the same or different and represent independently a
 10 substituent selected from hydrogen, halogen, C₁₋₆-alkyl, C₁₋₆ alkoxy, cyano, hydroxy, trifluoromethyl, C₁₋₆-alkylsulfonyloxy, trifluoromethanesulfonyloxy, C₁₋₆-alkanoyloxy, amino, alkylamino, alkanoylamino, alkylsulfonylamino, arylsulfonylamino, aminocarbonyl, carboxy, N-hydroxycarbonylamidoyl, carbamimidoyl, hydroxycarbonyl,
 15 thiocarbonyl, sulfamoyl, mono or bicyclic heterocyclic group or optionally substituted phenyl, or two adjacent groups of R₁, R₂ and R₃ may combine to form an optionally substituted fused mono or bicyclic heterocyclic group;
- Q represents an optionally substituted alkyl, aryl, aralkyl or heteroaralkyl
 20 group

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

2. A compound of formula (I) as claimed in claim 1 wherein

- X represents a nitrogen atom or CH group;
- Y represents a bond when X stands for nitrogen, or an oxygen atom or NH or CH₂ or OCH₂ group when X stands for CH group;

~~357~~
355

- 28 -

- 5
- R₁, R₂, R₃ may be the same or different and represent independently hydrogen, alkyl, alkoxy, halogen, cyano, aminocarbonyl, trifluoromethyl or optionally substituted phenyl or two adjacent groups of R₁, R₂ and R₃ may combine to form an optionally substituted fused mono or bicyclic heterocyclic group;
 - Q represents dialkylamino, optionally substituted phenyl, biphenyl, pyridyl, thienyl, alkyl or quinoliny

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

10

3. A compound of formula (I) as claimed in claim 1 wherein

- X represents a nitrogen atom or CH group;
- Y represents a bond when X stands for nitrogen, or CH₂ group when X stands for CH group;
- 15 - R₁, R₂, R₃ may be the same or different and represent independently hydrogen, fluorine, bromine, chlorine atoms or cyano, trifluoromethyl, methyl, methoxy, ethoxy, optionally substituted phenyl or aminocarbonyl groups or two adjacent groups of R₁, R₂ and R₃ may combine to form an optionally substituted fused mono or bicyclic heterocyclic group;
- 20 - Q represents C₁₋₄ alkyl, dimethylamino, biphenyl, alkylphenyl, alkoxyphenyl, halophenyl, nitrophenyl, trifluoromethylphenyl or aminocarbonylmethylphenyl, pyridyl, or quinoliny

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof.

25

4. A process for preparing compounds of formula (I) as claimed in any of claims 1-3 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or salts and/or hydrates and/or solvates thereof which comprises reacting a
30 compound of formula (II) or a derivative thereof

- i) a compound of formula (VI), wherein R_6 represents hydrogen or a protecting group, was attached to a polystyrene resin of formula (V), wherein R_4 and R_5 can be the same or different and represent hydrogen or methoxy group with the exception $R_4=R_5=H$, by reductive amination with a reducing agent;
- 5 ii) halogenation, preferably bromination, of the terminal hydroxy group of a compound of formula (VII), wherein the meaning of R_6 is as described above for formula (VI), with a halogenation agent, or if it was protected, the protecting group had been removed before the halogenation, which results a solid phase compound of formula (VIII) wherein Z represents halogen and the meaning of R_4 and R_5 is as described above for formula (V);
- 10 iii) sulfonylation a compound of formula (VIII) with a sulfochloride of formula (II) wherein the meaning of Q is as described above for formula (I);
- 15 iv) alkylation with a compound of formula (IX) wherein the meaning of Z, R_4 and R_5 are as described above for the formula (VIII) and the meaning of Q is as described above for formula (I) of a secondary amine of formula (IV) wherein the meaning of R_1 , R_2 , R_3 , X and Y are as described above for the formula (I);
- 20 v) releasing the products of formula (I) from the solid-phase compound of formula (X) wherein the meaning of Q, R_1 , R_2 , R_3 , R_4 , R_5 , X and Y are as described above for the formula (I) by acidic cleavage.

7. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of claims 1-3 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof and one or more physiologically acceptable carrier(s).

25

8. The use of a compound of formula (I) as claimed in any of claims 1-3 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof in the

30

389
357

- 31 -

manufacture of a medicament for the treatment and/or prevention of a condition which requires modulation of a dopamine receptor.

9. Use according to claim 8 wherein the dopamine receptor is a
5 dopamine D₃ receptor.

10. A method of treating and/or preventing a condition which requires modulation of a dopamine receptor which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in any of
10 claims 1-3 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or physiologically acceptable salts and/or hydrates and/or solvates thereof.

11. A method of treating and/or preventing a condition as claimed in claim
10 wherein the dopamine receptor is a dopamine D₃ receptor.

15

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
ALVARO CORREA ORDOÑEZ
Apoderado

ASUNTO	Radicación	06-19948
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	551
	Folios	002

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederán de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ... b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera; ... Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente".

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- GLASE S A ET AL : « 4-bromo-1-methoxy-N-'2-(4-aryl-1-piperazinyI) ethyl l-2-naphthalenecarb oxamide s : selective dopamine D3 receptro partial agonists » BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 12, 18-06-1996, pages 1361-1366, XP004134841, ISSN : 0960-894X

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha_____

CONCEPTO TÉCNICO Nº: 01	EXAMINADOR TÉCNICO Código Nº: 202087	EXAMINADOR JURÍDICO Código Nº:
----------------------------	---	-----------------------------------

360
~~362~~

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
ALVARO CORREA ORDOÑEZ
Apoderado

ASUNTO	Radicación	06-19948
	Trámite	011
	Evento	379
	Actuación	430 550
	Oficio	
	Folios	365

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional	PCT/HU2004/000056		
Fecha de Presentación Internal.	2004/05/21		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 74 a 123

Reivindicaciones: Folios 124 a 173 como se radicó inicialmente.
Folios 208 a 248 reivindicaciones corregidas.
Folios 291 a 331 nuevo capítulo modificado.

Prioridad: Fecha: 2003/08/04, país: HU, número: P0302451

2. Objeto de la invención

- Título de la solicitud: Derivados de (tio) carbamoil- ciclohexano como antagonistas de los receptores D₃/D₂. Número de folio: 1

El problema planteado en esta solicitud es la necesidad de compuestos para trastornos psiquiátricos, que muestren la manifestación simultánea de los efectos benéficos de la modulación de ambos receptores D₃ y D₂ de la dopamina con preferencia D₃, sin la aparición de desventajas por cada receptor individual y con selectividad aún mucho mas alta que otros receptores como los alfa-1.

EXP 2006 19948

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados de ciclohexano con cadenas laterales de (tio) carbamoilo, ligandos del tipo del receptor de dopamina D₃ y D₂ de fórmula (I).

Clasificación Internacional de Patentes (IPC.): A61K31/495

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Reivindicación 1: Se requiere al solicitante delimitar la materia reivindicada en cuanto a los sustituyentes **alquilo, alquenilo, arilo, cicloalquilo, arilo** ya que no se está determinando su **tamaño** lo cual implica que se usan de forma especulativa como términos genéricos que no definen inequívocamente una estructura específica.
- Reivindicación 5: Selecciona una serie de compuestos que no se sabe si provienen de la misma molécula general reivindicada (1) o pertenecen a otro grupo independiente e indefinido.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)

Reivindicaciones 20 - 24: Se refiere a un método para tratar y/o prevenir una condición que requiere modulación de receptores de dopamina por lo tanto están exceptuadas de patentabilidad según la legislación vigente.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Reivindicaciones 15 - 19: Se refieren a usos de compuestos de fórmula (I) para la fabricación de medicamentos por lo tanto están exceptuadas de patentabilidad según la legislación vigente.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2003/08/04

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

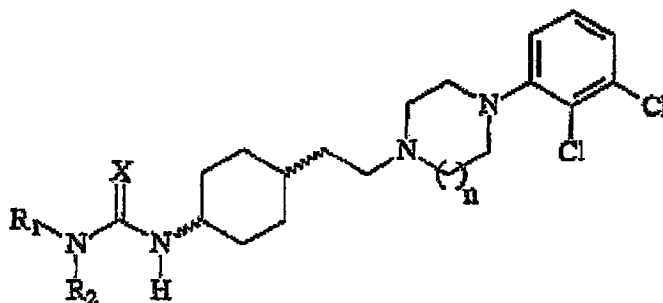
Nº	Documento	Título	Fecha de publicación
D ₁	WO 03/029233	NEW SULFONAMIDE DERIVATIVES AS D3-RECEPTOR AGONISTS	2003/04/10

7. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica:

Reivindicaciones 1 - 5: Compuesto de fórmula (I).

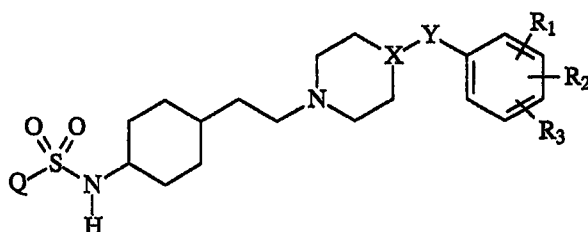


Reivindicación 14: Composición que comprende:

- Compuesto (I)
- Portadores fisiológicamente aceptables.

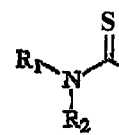
Dicho compuesto está afectado por el siguiente documento más cercano del Estado de la Técnica:

D₁ que enseña compuestos de fórmula (I) donde se preparan aminas y aminoácidos por reacción de una amina, un derivado carbonilo y un compuesto organoboron bajo condiciones moderadas (Ver folios: 303-305).



(I)

La única diferencia con D₁ es que esta solicitud posee un grupo



y la

anterioridad en igual posición el grupo es pero esta diferencia no parece conceder una ventaja excepcional.

No puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada ya que a pesar de realizarse ensayos de enlace con cada receptor mostrando valores IC₅₀ (nM), no puede evidenciarse que exista una superioridad contra la anterioridad ya que los datos mostrados por D₁ son muy semejantes a los de la solicitud del orden nM (folios 277-278 vs 349-350).

El Problema Técnico Objetivo se puede definir en como lograr **compuestos alternativos a los previamente conocidos.**

Por consiguiente resultaría obvio el diseño de este tipo de fármacos y compuestos para un experto en la materia que conozca el estado de la técnica ya que a partir de los efectos de los compuestos de la anterioridad es posible deducir los posibles efectos de lo reivindicado en la propuesta de la presente solicitud.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	WO 03/029233	1-5, 14	NIVEL INVENTIVO

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

_____ 22 ENE. 2011

CONCEPTO TÉCNICO No. 01	EXAMINADOR TÉCNICO Código No. 202087
-----------------------------------	--