

LLOREDA & CIA. S. A.

A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-039712- -00002-0000

Fecha: 2008-04-21 17:03:06 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 538 PETICION Folios: 2

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de
Invención en Fase Nacional PCT para "DERIVADOS DE
BENZODIAZEPINA SUSTITUIDA POR HALOGENO".-Clase C07D
487/14.-Expediente número 07-039.712.-

1. Me refiero a mi memorial de 25 de Septiembre de 2007.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **581** de 31 de Octubre de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo II.
4. Anexo me permito acompañar recibo número 08-28.384, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176085

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No 07-039712- -00002-0000

Dep. 2020 NUECREACIONE
Eve: 379 FASENACIONALII
Folios: 2

RECIBO OFICIAL DE CAJA : 08 - 28,384
FECHA : ABRIL 8 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLORED A Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	2756065	08/04/2008	11,999,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
		TOTAL :	\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-39712

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **581** DE

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

LEY EXPIRA EL **31 DE ENERO DE 2008**

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

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40487 A2(51) International Patent Classification⁷: **C07D 487/14**,
A61K 31/55, A61P 25/00 // (C07D 487/14, 243:00,
235:00, 235:00)

(21) International Application Number: PCT/EP01/12887

(22) International Filing Date:
8 November 2001 (08.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00124332.8 16 November 2000 (16.11.2000) EP(71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH];
Grenzacherstrasse 124, CH-4070 Basle (CH).(72) Inventors: **MASCIADRI, Raffaello**; 228 Klybeckstrasse,
CH-4057 Basle (CH). **THOMAS, Andrew, William**; 5
Zwinglistrasse, CH-4127 Birsfelden (CH). **WICHMANN,**
Juergen; 32 Im Wolfischbuehl, 79585 Steinen (DE).(74) Agent: **POPPE, Regina**; Grenzacherstrasse 124,
CH-4070 Basle (CH).(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, 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, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA,
ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SI, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).**Published:***without international search report and to be republished
upon receipt of that report**For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*(54) Title: **BENZODIAZEPINE DERIVATIVES AS GABA A RECEPTOR MODULATORS**

(57) Abstract: The present invention relates to compounds of formula (I) wherein R¹ is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, cyano, trifluoromethyl, trifluoromethoxy or lower alkylthio; R² is C(O)O-lower alkyl, isoxazol, 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl, which rings may be substituted by lower alkyl, trifluoromethyl or cycloalkyl; R³ is hydrogen, lower alkyl, -(CH₂)_n-cycloalkyl, -(CH₂)_n-halogen, -(CH₂)_n-pyridin-4-yl, or -(CH₂)_n-phenyl, wherein the phenyl ring may be substituted by one or two substituents selected from the group consisting of lower alkoxy, halogen, -SO₂CH₃, phenyl, OCF₃, nitro, CF₃, -NR₂, or is -(CH₂)_n-indolyl, optionally substituted by lower alkyl or lower alkoxy, or is pyrrolidinyl-5-oxo, -C(O)-NR₂, -(CH₂)_n-OH, -(CH₂)_n-NR₂ or -(CH₂)_n-benzo[1,3]dioxole; R is hydrogen or lower alkyl; and is 0, 1, 2 or 3; and to their pharmaceutically acceptable acid addition salts, with the exception of the following compounds: Ethyl 9H-imidazo[1,5-a][1,2,4]triazolo[3,4-d][1,4]benzodiazepine-10-carboxylate, 10-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-9H-imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]benzodiazepine, ethyl 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[3,4-d][1,4]benzodiazepine-10-carboxylate, 10-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[3,4-d][1,4]benzodiazepine, ethyl 3-chloro-9H-imidazo[1,5-a][1,2,4]triazolo[3,4-d][1,4]benzodiazepine-10-carboxylate and 3-chloro-10-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-9H-imidazo[1,5-a][1,2,4]triazolo[3,4-d][1,4]benzodiazepine. These compounds have a good affinity to the GABA α₅ receptor and they are therefore useful for the treatment of diseases, related to this receptor.

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the present invention are ligands for GABA A receptors containing the $\alpha 5$ subunit and are therefore useful in the therapy where cognition enhancement is required.

The compounds were investigated in accordance with the test given hereinafter.

Membrane preparation and binding assay

- 5 The affinity of compounds at GABA A receptor subtypes was measured by competition for [^3H]flumazenil (85 Ci/mmol; Amersham) binding to SF9 cells expressing rat receptors of composition $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 2$ and $\alpha 5\beta 3\gamma 2$.

- . Cellpellets were suspended in Krebs-tris buffer (4.8 mM KCl, 1.2 mM CaCl_2 , 1.2 mM MgCl_2 , 120 mM NaCl, 15 mM Tris; pH 7.5; binding assay buffer), homogenized by
10 polytron for ca. 15 sec on ice and centrifuged in UZ for 30 min at 4°C (100000 g; rotor: TFT 4594 = 300000 rpm). The cellpellets were resuspended in Krebs-tris buffer and homogenized by polytron for ca. 15 sec on ice. Aliquots of 1 ml were prepared, protein was measured (Bradford method) and the resulting membrane aliquots were stored at -70 °C.

- Radioligand binding assays were carried out in a volume of 200 μL (96-well plates)
15 which contained 100 μL of cells, [^3H]flumazenil at a concentration of 1 nM for $\alpha 1\alpha 2\alpha 3$ subunits and 0.5 nM for $\alpha 5$ subunits and the test compound in the range of 10^{-10} – 3×10^{-6} M. Nonspecific binding was defined by 10^{-5} M diazepam and typically represented less than 5 % of the total binding. Assays were incubated to equilibrium for 1 hour at 4 °C and harvested onto GF/C uni-filters (Packard) by filtration using a Packard
20 harvester and washing with ice-cold wash buffer (50 mM Tris; pH 7.5). After drying, filter-retained radioactivity was detected by liquid scintillation counting. K_i values were calculated using Excel-Fit (Microsoft) and are the means of two determinations.

- The compounds of the accompanying examples were tested in the above described assay, and all were found to possess a K_i value for displacement of [^3H]flumazenil from $\alpha 5$
25 subunits of the rat GABA A receptor of 100 nM or less. In a preferred embodiment the compounds of the invention are binding selective for the $\alpha 5$ subunit relative to the $\alpha 1$, $\alpha 2$ and $\alpha 3$ subunit.

In the table below it is shown the activity data of some preferred compounds:

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Example No.	Ki[nM] ra1	Ki[nM] ra2	Ki[nM] ra3	Ki[nM] ra5
1	30.6	57.6	39.2	1.3
6	407.8	361.5	148.8	10.8
13	34.9	55.5	23.7	1.2
19	480.9	500.1	482.3	14.5
20	802.7	283.9	190.9	10.7
25	95.3	122.8	107.4	5.9
37	295.8	266.1	162.0	8.2
47	694.5	224.6	100.3	13.1
50	1002.9	409.4	220.1	14.4
54	64.6	148.0	108.2	12.9
69	359.8	308.4	158.1	7.0
61	67.3	53.0	18.9	1.3
63	12.5	10.7	5.6	0.6

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

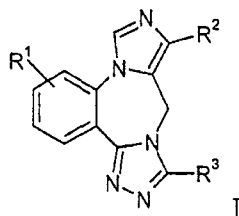
The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragées and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients for tablets, dragées and hard gelatine capsules. Suitable excipients for soft gelatine

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Claims

1. A compound of the general formula

5



wherein

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, cyano, trifluoromethyl, trifluoromethoxy or lower alkylthio;

10 R^2 is $-C(O)O$ -lower alkyl, isoxazol, 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl, which rings may be substituted by lower alkyl, trifluoromethyl or cycloalkyl;

R^3 is hydrogen, lower alkyl, $-(CH_2)_n$ -cycloalkyl, $-(CH_2)_n$ -halogen, $-(CH_2)_n$ -pyridin-4-yl, or $-(CH_2)_n$ -phenyl, wherein the phenyl ring may be substituted by one or two substituents selected from the group consisting of lower alkoxy, halogen, $-SO_2CH_3$, phenyl, OCF_3 , nitro, CF_3 , $-NR_2$, or is $-(CH_2)_n$ -indolyl, optionally substituted by lower
15 alkyl or lower alkoxy, or is pyrrolidinyl-5-oxo, $-C(O)-NR_2$, $-(CH_2)_n-OH$, $-(CH_2)_n-NR_2$ or $-(CH_2)_n$ -benzo[1,3]dioxole;

R is hydrogen or lower alkyl; and

n is 0, 1, 2 or 3;

20 and their pharmaceutically acceptable acid addition salts,

with the exception of the following compounds:

Ethyl 9H-imidazo[1,5-a][1,2,4]triazolo[3,4-d][1,4]benzodiazepine-10-carboxylate,
10-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-9H-imidazo[1,5-a][1,2,4]triazolo[4,3-
d][1,4]benzodiazepine,

25 ethyl 3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]benzodiazepine-10-carboxylate,

10-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[4,3-