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COLOMBIA

252
ESCOBAR - URIBE ASOCIADOS
Intellectual Property

As. 2907/PCT.

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

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



NO 06-008093- -00003-0000

Ref.: Expediente No. **06-008.093**
Solicitud de Patente a nombre de
Altana Pharma AG.

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Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Altana Pharma AG.**, con domicilio en Konstanz, Alemania, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 08 - 1,891 de 8 de enero de 2008, por la suma de \$420.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68.228

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-008093- -00003-0000

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DIA 14 ENE 2008 Linea 378 FASENACIONAL
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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FECHA : ENERO 8 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
MARKET MODET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	2662954	08/01/2008	40,235,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
TOTAL :			\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-08093

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **578** DE

FECHA **31 DE JULIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **26 DE OCTUBRE 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.

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(71) Applicants (for all designated States except US): **BAYER CORPORATION** [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). **BAYER AKTIENGESellschaft** [DE/DE]; 51368 Leverkusen (DE).

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(72) Inventors; and

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(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, 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).

Declarations 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)

— 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)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

[Continued on next page]

(54) Title: 3-SUBSTITUTED PYRROLO[2.1-A]ISOQUINOLINE DERIVATIVES

(57) Abstract: The present invention relates to 3-substituted pyrrolo[2.1-a]dihydroisoquinolines which are in-hibitors of phosphodiesterase 10a and can be used for combating cancer.

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wherein R^9 to R^{11} independently from each other denote C_{1-4} -alkyl;

or

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ii) naphthyl optionally containing one further OH group;

or

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iii) indolyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

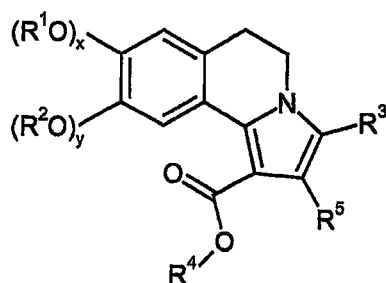
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and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

A bond with a dotted line thereunder, $\cdots$ denotes a bond which alternatively is a single bond or a double bond.

20

Compounds (I) wherein the radicals $(R^1O)_x$ and $(R^2O)_y$ are attached to the phenyl ring in the following positions, are particularly preferred:



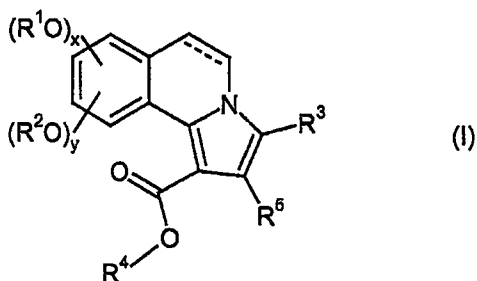
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We claim:

1. A compound of the formula



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wherein

x and y independently from each other denote zero or 1 and x+y is 1 or 2;

10

R^1 and R^2 independently from each other denote hydrogen, C_{1-4} -alkyl or CF_3 , or R^1 and R^2 together form a C_{1-4} -alkylene bridge;

15

R^3 denotes hydrogen, formyl, $(C_{1-4}$ -alkyl)-carbonyl, $(C_{1-4}$ -alkoxy)-carbonyl, NO_2 , NR^6R^7 , C_{1-4} -alkyl- NR^6R^7 , C_{1-4} -alkyl- OR^8 , C_{1-4} -alkyl- $COOR^8$, C_{6-10} -aryl- C_{1-4} -alkyl wherein the aryl moiety is optionally substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4} -alkyl, and C_{1-4} -alkoxy;

wherein

20

R^6 and R^7 independently from each other denote hydrogen, C_{1-4} -alkyl, C_{3-8} -cycloalkyl, or C_{6-10} -aryl- C_{1-4} -alkyl wherein the aryl moiety is optionally substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4} -alkyl and C_{1-4} -alkoxy;

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or

5 R⁶ and R⁷ together with the nitrogen atom to which they are attached
form a 5- to 7-membered heterocyclyl which may contain up to 2
further hetero atoms selected from the group consisting of N, O, and
S, which heterocyclyl can further be substituted with 1 to 3 radicals
selected from the group consisting of OH, C₁₋₄-alkyl, C₁₋₄-alkoxy, C₆₋₁₀-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero
atoms selected from the group consisting of N, O and S;

10

R⁸ denotes hydrogen or C₁₋₄-alkyl;

R⁴ denotes C₁₋₄-alkyl;

15

R⁵ is

i) C₆₋₁₄-aryl optionally containing 1 to 3 further substituents
selected from the group consisting of

20

halogen;

C₁₋₆-alkyl which can be further substituted with one or more
radicals selected from the group consisting of C₁₋₆-alkoxy, OH
and NH₂;

25

C₁₋₆-alkoxy which can be further substituted with one or more
radicals selected from the group consisting of C₁₋₆-alkoxy, OH,
and NH₂;

30

C₆₋₁₀-aryloxy-C₁₋₆-alkoxy;

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- 5 OH;
 NO₂;
 CN;
 CF₃;
 OCF₃;
 NR⁹R¹⁰;
 CONR⁹R¹⁰;
 COOR¹¹;
10 SR¹¹;
 SOR¹¹;
 SO₂R¹¹;
 OSO₂R¹¹;
- 15 -O-(CH₂)₁₋₄-O- wherein the oxygen atoms are bound to the aryl
 moiety in ortho-position to each other;
- 20 phenyloxy or benzyloxy wherein the phenyl moieties can
 contain one further substituent selected from the group
 consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen and NO₂;
- phenyl optionally substituted with CN;
- 25 aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero
 atoms selected from the group consisting of N, O and S;
- and
- 30 saturated 5- to 7-membered nitrogen-containing heterocyclyl
 which is bound to the C₆₋₁₀-aryl moiety via the nitrogen atom

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and may contain up to 2 further heteroatoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with one or more radicals selected from the group consisting of C₁₋₆-alkoxy, OH and NH₂;

wherein

R⁹ and R¹⁰ independently from each other denote hydrogen, C₁₋₆-alkyl, (C₁₋₆-alkyl)-carbonyl, (C₁₋₆-alkoxy)-carbonyl, C₁₋₆-alkylsulfonyl, (C₁₋₆-alkylamino)-carbonylamino, (C₆₋₁₀-aryl-amino)-carbonylamino,

or

R⁹ and R¹⁰ together with the nitrogen atom to which they are attached, form a 5- to 7-membered saturated, partially unsaturated or aromatic heterocyclyl which can contain up to 3 further hetero atoms selected from the group consisting of N, O and S, and which heterocyclyl can contain 1 to 3 substituents selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, C₆₋₁₀-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

R¹¹ is hydrogen, C₁₋₆-alkyl or C₆₋₁₀-aryl;

or

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- 5 ii) C₁₋₁₂-alkyl which can contain 1 to 3 substituents selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, C₆₋₁₀-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;
- or
- 10 iii) C₃₋₈-cycloalkyl which can contain 1 to 3 substituents selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, COOR¹¹ wherein R¹¹ is as defined above, C₆₋₁₀-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;
- or
- 15 iv) aromatic C₂₋₉-heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S which aromatic heterocyclyl can contain 1 to 3 further substituents selected from the group consisting of OH, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₆₋₁₀-aryl which can contain 1 to 3 halogen radicals, COR¹¹ or COOR¹¹ wherein R¹¹ is as defined above, halogen, CN, and saturated 5- to 7-membered nitrogen-containing heterocyclyl which is bound to the C₆₋₁₀-aryl moiety via the nitrogen atom and can contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with one or more radicals selected from the group consisting of C₁₋₆-alkoxy, OH and NH₂;
- 20
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with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

5 and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

10 x and y independently from each other denote zero or 1 and x+y is 1 or 2;

R¹ and R² independently from each other denote C₁₋₄-alkyl or CF₃;

15 R³ denotes hydrogen, formyl, (C₁₋₄-alkyl)-carbonyl, (C₁₋₄-alkoxy)-carbonyl, NO₂, NR₆R₇, C₁₋₄-alkyl-NR⁶R⁷, C₁₋₄-alkyl-OR⁸, C₁₋₄-alkyl-COOR⁸, or C₆₋₁₀-aryl-C₁₋₄-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C₁₋₄-alkyl, and C₁₋₄-alkoxy;

wherein

20 R⁶ and R⁷ independently from each other denote hydrogen, C₁₋₄-alkyl, C₃₋₈-cycloalkyl, or C₆₋₁₀-aryl-C₁₋₄-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C₁₋₄-alkyl, and C₁₋₄-alkoxy;

25 or

30 R⁶ and R⁷ together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O, and S and which heterocyclyl can be further substituted with 1 to 3 radicals

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(71) Applicant (for all designated States except US): **BAYER AKTIENGESELLSCHAFT** [DE/DE]; 51368 Leverkusen (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NIEWÖHNER, Ulrich** [DE/DE]; Gartenstrasse 3, 42929 Wermelskirchen (DE). **BAUSER, Marcus** [DE/DE]; Claudiusweg 3, 42115 Wuppertal (DE). **ERGÜDEN, Jens-Kerim** [DE/DE]; Bertolt-Brecht-Strasse 2, 42489 Wülfrath (DE). **FLUBACHER, Dietmar** [DE/DE]; Schongauer Weg 57, 79110 Freiburg (DE). **NAAß, Paul** [DE/DE]; Amalienstrasse 29, 42287 Wuppertal (DE). **REPP, Thorsten-Oliver** [DE/DE]; In der Flecht 10, 50389 Wesseling (DE). **STOLTEFUSS, Jürgen** [DE/DE]; Parkstrasse 20, 42781 Haan (DE). **BURKHARDT, Nils** [DE/DE]; Hügelstrasse 53, 40589 Düsseldorf (DE). **SEWING, Andrea** [DE/GB]; 2 Gladstone Road, Broadstairs, CT 10 2HZ (US). **SCHAUER, Michael** [DE/DE]; Falkenberg 28, 42113 Wuppertal (DE). **SCHLEMMER, Karl-Heinz** [DE/DE]; Wildsteig 22a, 42113 Wuppertal

(DE). **WEBER, Olaf** [DE/US]; 400 Morgan Lane, West Haven, CT 06516-4175 (US). **BOYER, Stephen, J.** [US/US]; 233 Colony Street, Fairfield, CT 06430 (US). **MIGLARESE, Mark** [US/US]; 15 Rosewood Lane, Ivorytown, CT 06442 (US).

(74) Common Representative: **BAYER AKTIENGESELLSCHAFT**; 51368 Leverkusen (DE).

(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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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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.

WO 02/48144 A1

(54) Title: PYRROLO (2.1-A) DIHYDROISOQUINOLINES AND THEIR USE AS PHOSPHODIESTERASE 10A INHIBITORS

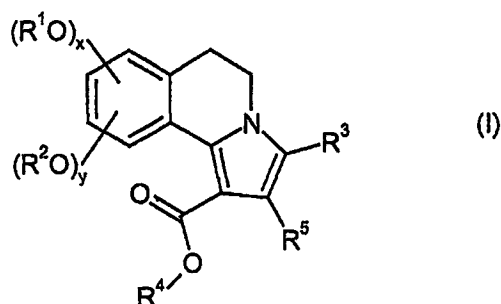
(57) Abstract: The present invention relates to pyrrolo[2.1-a]dihydroisoquinolines which are inhibitors of phosphodiesterase 10a and can be used for combating cancer.

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The compounds (B) are described as having anti-tumor activity due to their ability to intercalate into DNA. It is not mentioned that these compounds have any PDE 10a inhibitory activity.

- 5 Surprisingly, it has been found that the pyrrolo[2.1-a]dihydroisoquinolines of the present invention inhibit PDE 10a and exhibit an antiproliferative activity.

The present invention relates to compounds of the formula



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wherein

x and y independently from each other denote zero or 1 with the proviso that $x+y = 1$ or 2;

15

R^1 and R^2 independently from each other denote hydrogen, C_{1-4} -alkyl or CF_3 or

R^1 and R^2 together form a C_{1-4} -alkylene bridge;

20

R^3 and R^4 independently from each other denote C_{1-4} -alkyl;

R^5 denotes C_{6-14} -aryl, optionally having 1 to 3 further substituents selected from the group consisting of

25

halogen;

385
785

C₁₋₆-alkyl which can be further substituted with one or more radicals selected from the group consisting of OH, halogen, NH₂ and C₁₋₆-alkoxy;

5 C₁₋₆-alkoxy which can be further substituted with one or more radicals selected from the group consisting of OH, halogen, NH₂, C₁₋₆-alkoxy and C₆₋₁₀-aryloxy;

OH;

NO₂;

10 CN;

CF₃;

OCF₃;

NR⁶R⁷;

SR⁸;

15

-O-(CH₂)₁₋₄-O- wherein the oxygen atoms are bound to the aryl moiety in ortho-position to each other;

20 phenyloxy or benzyloxy wherein the phenyl moieties optionally contain one further substituent selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, and NO₂;

phenyl, optionally substituted with CN; and

25 4- to 9-membered aromatic heterocyclyl containing 1 to 4 hetero atoms selected from the group consisting of N, O, and S;

30 R⁶ and R⁷ independently from each other denote hydrogen, C₁₋₆-alkyl or, together with the nitrogen atom to which they are attached, form a 5- to 7-membered saturated, partially unsaturated or aromatic ring which can contain up to 3 further hetero atoms selected from the group consisting of N, O, and S, and

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which ring can contain 1 to 3 substituents selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, C₆₋₁₀-aryl, and 4- to 9-membered aromatic heterocyclyl containing 1 to 4 hetero atoms selected from the group consisting of N, O, and S; and

5

R⁸ denotes hydrogen, C₁₋₆-alkyl or C₆₋₁₀-aryl-C₁₋₆-alkyl

with the proviso that 8,9-dimethoxy-3-methyl-2-phenyl-5,6-dihydro-pyrrolo-[2.1-a]-isoquinoline-1-carboxylic acid ethyl ester is excluded,

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and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

An alternative embodiment of the present invention relates to compounds of formula (I), wherein

15

x and y independently from each other denote zero or 1 with the proviso that x+y = 1 or 2;

20 R¹ and R² independently from each other denote hydrogen, C₁₋₄-alkyl or CF₃ or

R¹ and R² together form a C₁₋₄-alkylene bridge;

R³ and R⁴ independently from each other denote C₁₋₄-alkyl;

25

R⁵ denote (i) phenyl, optionally having 1 to 3 further substituents selected from the group consisting of

F, Cl, Br;

30

C₁₋₆-alkyl;

C₁₋₆-alkoxy;

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- 5 C₆₋₁₀-aryloxy-C₁₋₆-alkoxy;
OH;
NO₂;
CN;
CF₃;
OCF₃;
NR⁶R⁷;
SR⁸;
- 10 -O-(CH₂)₂₋₃-O- wherein the oxygen atoms are bound to the phenyl moiety in
ortho-position to each other;
- 15 phenyloxy or benzyloxy wherein the phenyl moieties optionally contain one
further substituent selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alk-
oxy, F, Cl, Br, and NO₂;
- phenyl, optionally substituted with CN; and
- 20 benzoxazolyl;
- (ii) naphthyl, optionally having 1 to 3 further substituents selected from the
group consisting of
F, Cl, Br,
C₁₋₆-alkyl;
25 C₁₋₆-alkoxy;
CF₃; and
NR⁶R⁷ (wherein R⁶ and R⁷ are as defined above); or
- (iii) phenanthrenyl;
- 30

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R⁶ and R⁷ independently from each other denote hydrogen, C₁₋₆-alkyl or, together with the nitrogen atom to which they are attached, form a 5- to 7-membered saturated heterocyclyl which can contain up to 3 further hetero atoms selected from the group consisting of N, O, and S, and which saturated heterocyclyl
5 can contain 1 to 3 substituents selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, C₆₋₁₀-aryl and 4- to 9-membered aromatic heterocyclyl containing 1 to 4 hetero atoms selected from the group consisting of N, O, and S; and

10 R⁸ denotes hydrogen, C₁₋₆-alkyl or C₆₋₁₀-aryl-C₁₋₆-alkyl

with the proviso that 8,9-dimethoxy-3-methyl-2-phenyl-5,6-dihydro-pyrrolo-[2.1-a]-isoquinoline-1-carboxylic acid ethyl ester is excluded,

15 and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

A further alternative embodiment of the present invention relates to compounds of formula (I), wherein

20

x and y independently from each other denote zero or 1 with the proviso that x+y = 1 or 2;

R¹ and R² independently from each other denote hydrogen, C₁₋₄-alkyl or CF₃ or

25

R¹ and R² together form a methylene bridge;

R³ and R⁴ independently from each other denote C₁₋₄-alkyl;

30

R⁵ denotes

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- 9 -

- (i) phenyl, optionally having 1 to 3 further substituents selected from the group consisting of
- 5 F, Cl, Br;
CH₃, C₂H₅, i-C₃H₇;
OCH₃, OC₂H₅, i-OC₃H₇;
phenyloxy-C₁₋₄-alkoxy;
OH;
NO₂;
CN;
10 CF₃;
OCF₃;
NR⁶R⁷;
SR⁸;
-O-(CH₂)₂₋₃-O- wherein the oxygen atoms are bound to the phenyl
15 moiety in ortho-position to each other;
- phenyloxy or benzyloxy wherein the phenyl moieties optionally contain one further substituent selected from the group consisting of C₁₋₄-alkyl, C₁₋₄-alkoxy, F, Cl, Br, and NO₂;
- 20 phenyl, optionally substituted with CN; and
- benzoxazolyl;
- 25 (ii) naphthyl, optionally having 1 to 3 further substituents selected from the group consisting of
- F, Cl, Br;
C₁₋₄-alkoxy;
CF₃; and
30 NR⁶R⁷ (wherein R⁶ and R⁷ are as defined above); or

(iii) phenanthrenyl;

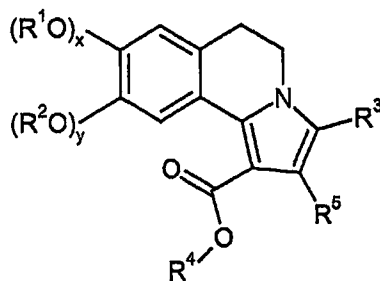
5 R^6 and R^7 independently from each other denote hydrogen, C_{1-6} -alkyl or, together with the nitrogen atom to which they are attached, form a 5- to 7-membered saturated heterocyclyl; and

R^8 denotes hydrogen, C_{1-4} -alkyl or phenyl- C_{1-4} -alkyl

10 with the proviso that 8,9-dimethoxy-3-methyl-2-phenyl-5,6-dihydro-pyrrolo-[2.1-a]isoquinoline-1-carboxylic acid ethyl ester is excluded,

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

15 Compounds (I) wherein the radicals $(R^1O)_x$ and $(R^2O)_y$ are attached to the phenyl ring in the following positions, are particularly preferred:



20 Pharmaceutically acceptable salts according to the invention are non-toxic salts which in general are accessible by reaction of the compounds (I) with an inorganic or organic base or acid conventionally used for this purpose. Non-limiting examples of pharmaceutically acceptable salts of compounds (I) include the alkali metal salts, e.g. lithium, potassium and sodium salts, the alkaline earth metal salts such as the magne-
25 sium and calcium salts, the quaternary ammonium salts such as, for example, the triethyl ammonium salts, acetates, benzene sulphonates, benzoates, dicarbonates,

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

2020
Bogotá, D.C.

Abogado
JIMENA ESCOBAR URIBE

ASUNTO	Radicación	06-8093
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	6978
	Folios	021

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional	<u>PCT/EP2004/051307</u>		
Fecha de Presentación Internal.	<u>30-06-2004</u>		

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

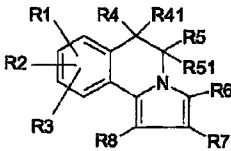
<u>Descripción:</u>	Folios <u>11-179</u> como se radicó inicialmente
<u>Reivindicaciones:</u>	Folios <u>180-216</u> como se radicó inicialmente
<u>Prioridad:</u>	Folio <u>1</u> EP, 30-06-2003, 03014424.0

2. Objeto de la invención

Título de la solicitud: PIRROLODIHIDROISOQUINOLINAS COMO INHIBIDORES DE PDE10 (folio 1)

El problema técnico planteado en esta solicitud esta relacionado con la necesidad de obtener otros compuestos derivados de pirrolo dihidroisoquinolina, como inhibidores de PDE10, útiles en el tratamiento de desordenes neurológicos y psiquiátricos tales como ansiedad, adiciones a drogas, trastornos del movimiento o de deficiencia cognitiva (folios 13-14; pág. 1-2).

Para solucionar este problema técnico la solicitud en estudio proporciona en: Reivindicaciones 1-15: un compuesto de fórmula I y sus sales, estereoisómeros, hidratos e hidratos de sus sales.



(I)

Reivindicaciones 16: uso de un compuesto.

Reivindicación 17: una composición farmacéutica que comprende por lo menos un compuesto de fórmula (I).

Reivindicaciones 18-20: relacionadas con un método de tratamiento.

Clasificación Internacional de Patentes (IPC): C07D471/04, A61K31/4745, A61P25/00

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

En reivindicaciones 1-15 se solicita un compuesto de fórmula I y sus sales, estereoisómeros, hidratos e hidratos de sus sales, fórmula con radicales con radicales R^1 - R^8 , R^{41} , R^{51} ; No obstante, se encuentra que existe falta de claridad, concisión, alcance definido y sustento al revisar la fórmula I con los sustituyentes dados y los compuestos ejemplificados con acción inhibitoria PDE10, en vista de las siguientes observaciones:

- Se reclaman hidratos de los compuestos de fórmula (I) y de sus sales, pero en la descripción no existe sustento de síntesis de alguno de estos hidratos.
- El término "sustituido predominantemente" presente en diversos radicales no tiene un significado claro ni conciso.
- Se establecen sustituyentes con términos generales y ambiguos como "arilo, ariloxi, arilalcoxi, arilalquilo, arilsulfonilo, los radicales R11 y R612 forman un anillo heterociclo saturado de 5-7 miembros con un N (Het1), R7 es Het2: un radical heteroarilo de 5-10 miembros monociclo o biciclo fusionado con 1-3 heteroatomos de N,O ó S, ó un radical de anillo heterocíclico de 9-10 miembros, biciclo fusionado, parcialmente saturado, que contiene una anillo de benceno y 1-2 heteroatomos de N,O ó S.

Es necesario que los arilos y dicho anillos sean definidos de manera específica y acorde con los ejemplos que presentan actividad farmacológica.

- En la reivindicación 15, no es adecuada la caracterización de un compuesto por usarse en terapia, ya que un compuesto sólo debe caracterizarse por su estructura o fórmula química.
- No existe sustento para la amplia materia solicitada, puesto que de los sustituyentes que representan cada radical, en los compuestos sintetizados y de los que se señalan con actividad sólo se ejemplifican los siguientes:

R^1 : H, Cl ó F

R^2 : alcoxi C_{1-2}

R^3 : metoxi

R^4 : H R^{41} : H

R^5 : H, alquilo C_{1-2} , -CN, metoxycarbonilo,
ó R^4 y R^5 son un alquilenoc $_4$ formando un anillo de fenantridina

R^6 : alquilo C_{1-2}

alquilo C_{1-2} sustituido por metoxycarbonilo ó metilmorfolinilo

R^7 : fenilo

7a3

sustituido por -OH, -F, -NO₂, metilo, -NH₂, -C(O)OH, metilsulfonilamino, morfolinsulfonilamino ó -C(O)NH₂.

quinolina o isoquinolina

indolilo

opcionalmente sustituido por metilfenil-4-sulfonilo, morfolinsulfonilo, dimetilaminosulfonilo

pirrolilo

sustituido por metilfenil-4-sulfonilo

N-oxi-piridilo

naftilo

R⁸: -CN, -C(O)-R⁹ con R⁹ etilo

En reivindicación 17, se solicita una composición farmacéutica que comprende por lo menos un compuesto de formula (I). Sin, embargo el termino por lo menos no es conciso porque significa uno o mas (de forma ilimitada) compuestos en la composición.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de tener claridad, concisión y sustento de acuerdo con las exigencias del artículo 30 de la Decisión 486.

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

De acuerdo con los artículos anteriores, la reivindicación 16, relacionada con el uso de un compuesto, no se considera objeto de protección puesto que el uso no es un producto o un procedimiento tecnológico. Por lo que se recomienda al solicitante eliminarla del alcance de la invención.

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

Las reivindicaciones 17-20, relacionadas con un método de tratamiento, están exceptuadas de patentabilidad de acuerdo con el artículo anterior. Por lo que es recomendable eliminarlas del alcance de la solicitud.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 30-06-2003, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

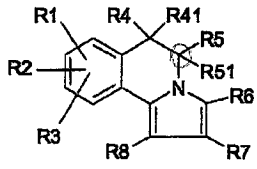
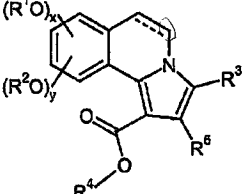
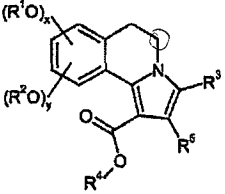
N°	Documento	Título	Fecha de publicación
D1	WO0314117	3-substituted pyrrolo[2.1-a]isoquinoline derivatives	20-02-2003
D2	WO0248144	pyrrolo (2.1-a) dihydroisoquinolines and their use as phosphodiesterase 10a inhibitors	20-06-2002

Anterioridad D1 en folios 275-282 y D2 en folios 283-290

7. Análisis de patentabilidad (artículo 14 D486)

7.1 Nivel inventivo (artículo 18 D486)

Se solicita en las reivindicaciones 1-15 un compuesto de fórmula I y sus sales, estereoisómeros, hidratos e hidratos de sus sales y en la reivindicación 17 una composición farmacéutica que comprende por lo menos uno de dichos compuestos en un vehículo farmacéuticamente.

SOLICITUD	D1	D2
Un compuesto de fórmula  (I) Con radicales R¹-R⁸, R⁴¹ y R⁵¹ según capítulo reivindicatorio.	Un compuesto de fórmula (I)  (I) ---: enlace simple o doble x: 1 y: 1 R¹: H, alquilo R²: H, alquilo ó R¹ y R²: alquilenoc₁₋₄ R³: formilo, amino R⁴: alquiloC₁₋₄ R⁵: ariloC₆₋₁₄ opcionalmente sustituido con halógeno, alquilo, -NH2, alcoxi, OH, -COOH, -COOalquilo, mono ó di alquilaminocarbonilo, -SO2alquilo, -SO2arilo, entre otros. Heteroaromático de C₂₋₉ y 1-4 heteroátomos de NO, O ó S opcionalmente sustituido por OH, alquilo, alcoxi, ariloC₆₋₁₀, carboxi, halógeno, CN, entre otros. (folios 276-282; pág. 16, 70-75)	Un compuesto de fórmula (I)  (I) x: 1 y: 1 R¹: H, alquilo R²: H, alquilo ó R¹ y R²: alquilenoc₁₋₄ R³: alquiloC₁₋₄ R⁴: alquiloC₁₋₄ R⁵: ariloC₆₋₁₄ opcionalmente sustituido con halógeno, alquilo, -NO2, -NH2, alcoxi, OH, aquilamino, dialquilamino, fenilo, feniloxi, entre otros. (folios 284-286 y 290; pág. 4-6 y 10)

Los documentos D1 (folios 276-282; pág. 16, 70-75) y D2 (folios 284-286 y 290, pág. 4-6 y 10) revelan compuestos derivados de pirrolo[2,1-b]isoquinolina de formulas (I) como inhibidores de PDE10, tal como se enseña arriba en el cuadro comparativo.

La solicitud se diferencia tanto de D1 como de D2 en que en la posición 5 tiene un metilo (acorde con los ejemplos que presentan actividad), mientras que en D1 y D2 existe un H en esa posición.

El Efecto Técnico que logra la diferencia es que los compuestos presentan actividad como inhibidores de PDE10, siendo útiles para el tratamiento de desordenes neurológicos y psiquiátricos.

El Problema Técnico Objetivo de esta solicitud esta relacionado con la necesidad de obtener otros compuestos derivados de pirrolo[2,1-b]isoquinolina como inhibidores de PDE10, útiles en el tratamiento de desordenes neurológicos y psiquiátricos.

No obstante, puesto que la introducción de un metilo en la posición 5 de la pirrolo[2,1-b]isoquinolina mantiene la actividad biológica de los compuestos análogos divulgados en D1 y D2, se considera que los compuestos de la solicitud y composiciones que los contienen no tienen nivel inventivo, siendo entonces una alternativa a los compuestos de D1 y D2.

8. Conclusión

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO0314117	1-15 y 17	Nivel inventivo
D2	WO0248144	1-15 y 17	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 sesenta 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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
19 JUN. 2009

CONCEPTO TECNICO No. 1667	EXAMINADOR TECNICO Código No. 202079
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