

CAVELIER

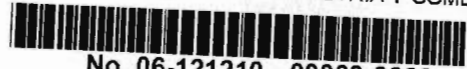
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-121210- -00003-0000

Fecha: 2008-06-11 16:43:07 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

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

Trámite : 011 Evento : 378 Actuación : 538

Referencia : Expediente No. 06121210
Asunto : Solicitud de patente para COMBINACIONES QUE
COMPRENDEN AGENTES ANTIMUSCARINICOS Y
AGONISTAS BETA-ADRENERGICOS
Solicitante : LABORATORIOS ALMIRALL, S.A.
Publicada en : La Gaceta No. 583 del 18 de diciembre de 2007

SOLICITUD EXAMEN DE PATENTABILIDAD

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado de la sociedad LABORATORIOS ALMIRALL, S.A., atentamente solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con las reglas del Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina.

Para tal efecto presento junto con este escrito el recibo No. 08-46,039 por valor de \$420.000.00 que corresponde a la tasa legal fijada para el efecto.

2. Por lo anterior, comedidamente solicito se prosiga con el trámite de este asunto.

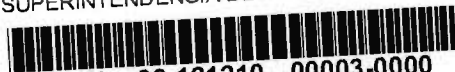
Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO-06734-845-004-9
COLO-11197-841-015-9
SCT\SCT\ID-127989\WPCL6734
No. M-2008-127989\SCT

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 46,039
FECHA : JUNIO 9 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678328	09/06/2008	89,445,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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. _____

060 06734-845-004-9

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-121210

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO 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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04118 A2(51) International Patent Classification⁷: C07D 453/02(74) Agent: GOLDIN, Douglas, Michael; J.A. Kemp & Co.,
14 South Square, Gray's Inn, London WC1R 5EU (GB).

(21) International Application Number: PCT/EP00/06469

(22) International Filing Date: 7 July 2000 (07.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P 9901580 14 July 1999 (14.07.1999) ES(71) Applicant (for all designated States except US): ALMI-
RALL PRODESFARMA S.A. [ES/ES]; General Mitre,
151, E-08022 Barcelona (ES).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, 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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, 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, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

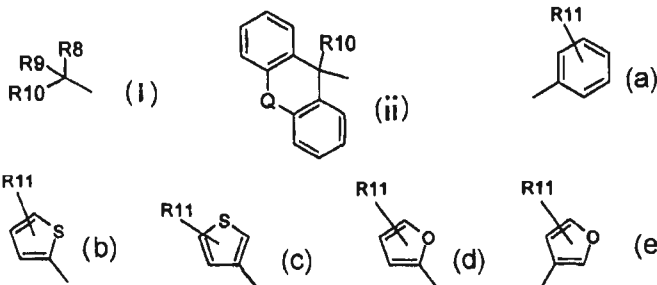
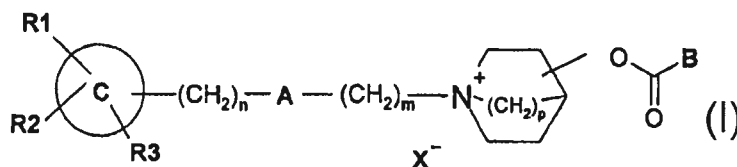
(72) Inventors; and

(75) Inventors/Applicants (for US only): FERNANDEZ
FORNER, Dolores [ES/ES]; Roget de Flor, 221, 5^a-4^a,
E-08025 Barcelona (ES). PRAT QUIÑONES, Maria
[ES/ES]; Andrea Doria, 2, 1^a-1^a, E-08003 Barcelona (ES).
BUIL ALBERO, Maria Antonia [ES/ES]; Calle Paris,
50, 1^a-4^a, E-08029 Barcelona (ES).

Published:

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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: NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS CONTAINING THE SAME

(57) Abstract: A compound according to
formula (I) wherein zC is a phenyl ring, a C₄
to C₉ heteroaromatic compound containing
one or more heteroatoms, or a naphthalenyl,
5,6,7,8-tetrahydronaphthalenyl or biphenyl
group; R¹, R² and R³ each independently
represent a hydrogen or halogen atom, or
a hydroxy group, or a phenyl, -OR⁴, -SR⁴,
-NR⁴R⁵, -NHCOR⁴, -CONR⁴R⁵, -CN, -NO₂,
-COOR⁴ or -CF₃ group, or a straight or
branched lower alkyl group which may
optionally be substituted, for example, with
a hydroxy or alkoxy group, wherein R⁴ and
R⁵ each independently represent a hydrogen
atom, straight or branched lower alkyl group,
or together form an alicyclic ring; or R¹ and
R² together form an aromatic, alicyclic or
heterocyclic ring; n is an integer from 0 to4; A represents a -CH₂-, -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ or NR⁶- group, wherein R⁶ and R⁷ each
independently represent a hydrogen atom, straight or branched lower alkyl group, or R⁶ and R⁷ together form an alicyclic ring;
m is an integer from 0 to 8; provided that when m = 0, A is not -CH₂-; p is an integer from 1 to 2 and the substitution in the
azoniabicyclic ring may be in the 2,3 or 4 position including all possible configurations of the asymmetric carbons; B represents a
group of formula (i) or (ii), wherein R¹⁰ represents a hydrogen atom, a hydroxy or methyl group; and R⁸ and R⁹ each independently
represents formulae (a), (b), (c), (d) and wherein R¹¹ represents a hydrogen or halogen atom, or a straight or branched lower alkyl
group and Q represents a single bond, -CH₂-, -CH₂-CH₂-, -O-, -O-CH₂-, -S-, -S-CH₂- or -CH=CH-, and when (i) or (ii) contain a
chiral centre they may represent either configuration; X represents a pharmaceutically acceptable anion of a mono or polyvalent
acid, which shows high affinity for muscarinic M₃ receptors (Hm3).

NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS
CONTAINING THE SAME

This invention relates to new therapeutically useful quinuclidine derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

The novel structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity for muscarinic M_3 receptors ($Hm3$).

In accordance with their nature as M_3 antagonists, the new compounds are suitable for treating the following diseases: respiratory disorders such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, bronchial hyperreactivity, asthma and rhinitis; urological disorders such as urinary incontinence, pollakiuria in neuripenia pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; and gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration.

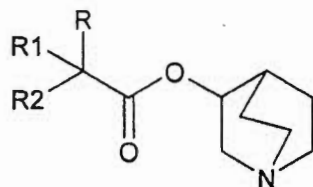
The compounds claimed are also useful for the treatment of the respiratory diseases detailed above in association with β_2 agonists, steroids, antiallergic drugs or phosphodiesterase IV inhibitors.

Compounds of the present invention may also be expected to have anti-tussive properties.

Depending on their nature the new compounds may be suitable for treating vagally induced sinus bradycardia.

Compounds with related structures have been described as anti-spasmodics and anti-cholinergic agents in several patents.

For example, in patent FR 2012964 are described quinuclidinol derivatives of the formula



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International Bureau



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PCT

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A61K 31/439, A61P 43/00

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(30) Priority Data:
P0003130 28 December 2000 (28.12.2000) ES

(71) Applicant (for all designated States except US): **ALMIRALL PRODESFARMA AG** [CH/CH]; Lindenhof, Dorfstrasse 38, CH-6341 Baar (CH).

(72) Inventors; and

(75) **Inventors/Applicants (for US only):** PRAT QUINONES,

Maria [ES/ES]; Calle Andrea Doria, 2, 1° 1a, E-08003 Barcelona (ES). **FERNANDEZ FORNER, Maria, Dolors** [ES/ES]; Roger de Flor 221, 5°, 4a, E-08025 Barcelona (ES). **BUIL ALBERO, Maria, Antonia** [ES/ES]; Paris, 50, 1° 4a, E-08029 Barcelona (ES).

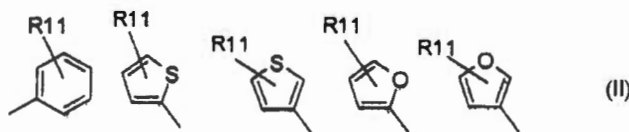
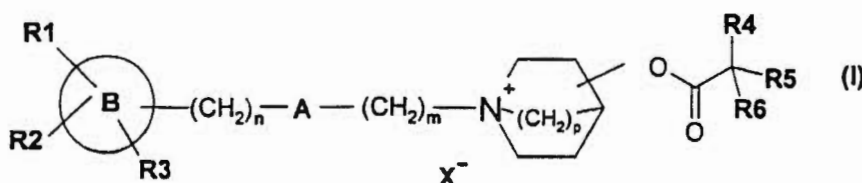
(74) **Agents:** SRINIVASAN, Ravi, Chandran et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

(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),

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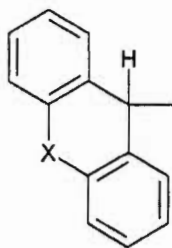
(54) Title: NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS CONTAINING THE SAME



(57) Abstract: A compound of formula (I), wherein B is a phenyl ring, a 5 to 10 membered heteroaromatic group containing one or more heteroatoms, or a naphthalenyl, 5, 6, 7, 8- tetrahydronaphthalenyl, benzo[1,3]dioxolyl, or biphenyl group; R₁, R₂ and R₃ each independently represent a hydrogen or halogen atom, or a hydroxy group, a phenyl group, -OR⁷, -SR⁷, -NR⁷R⁸, -NHCOR⁷, -CONR⁷R⁸, -CN, -NO₂, -COOR⁷ or CF₃ group, or a strait or branched, substituted or unsubstituted lower alkyl group, wherein R⁷ and R⁸ each independently represent a hydrogen atom, a strait or branched lower alkyl group, or together form an

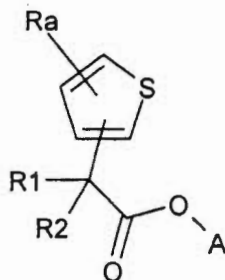
alicyclic ring; or R¹ and R² together form an aromatic or alicyclic ring or a heterocyclic group. n is an integer from 0 to 4; A represents a group selected from -CH₂-, -CH=CR⁹-, -CR⁹=CH-, -CR⁹R¹⁰-, -CO-, -O-, -S-, -S(O)-, -S(O)₂- and NR⁹, wherein R⁹ and R¹⁰ each independently represent a hydrogen atom, a straight or branched lower alkyl group, or together form an alicyclic ring; m is an integer from 0 to 8, provided that when m=0, A is not -CH₂-; p is an integer from 1 to 2 and the substitution in the azonia bicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons; R₄ represents a group of structure: (Formulae II) wherein R¹¹ represents a hydrogen or halogen atom, a hydroxy group, an alkoxy group, a nitro group, a cyano group, -CO₂R¹² or -NR¹²R¹³, wherein R¹² and R¹³ are identical or different and are selected from hydrogen and straight or branched lower alkyl groups, or a straight or branched, substituted or unsubstituted lower alkyl group; R⁵ represents an alkyl group of 1 to 7 carbon atoms, an alkenyl group containing 2 to 7 carbon atoms, or a group of formula (III) wherein q=1 or 2 and R¹¹ is as defined above; R⁶ represents a hydrogen atom, a hydroxy group, a methyl group or a -CH₂OH group; and X⁻ represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

in which R is H, OH or an alkyl group having 1 to 4 carbon atoms; R_1 is a phenyl or thienyl group; and R_2 is a cyclohexyl, cyclopentyl or thienyl group, or, when R is H, R_1 and R_2 together with the carbon atom to which they are attached, form a tricyclic group of the formula:

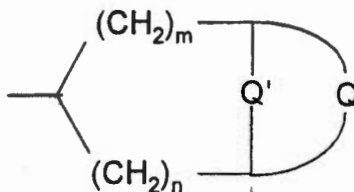


- 5 in which X is -O-, -S- or -CH₂-, or an acid addition or quaternary ammonium salt thereof.

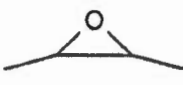
EP- 418716 describes thienyl carboxylate esters of formula



wherein A is a group

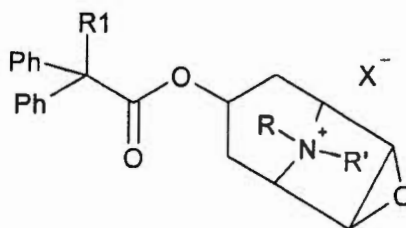


m and n = 1 or 2

- 10 Q is a -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH=CH-,  group

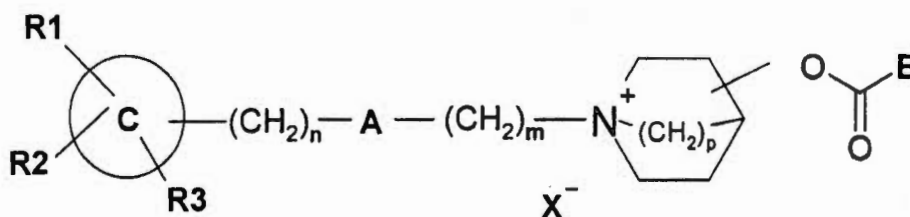
Q' is a =NR or NRR' group; R_1 is a thienyl, phenyl, furyl, cyclopentyl or cyclohexyl group, optionally substituted; R_2 is H, OH, C₁-C₄ alkoxy or C₁-C₄ alkyl and R_a is H, F, Cl, CH₃- or -NR.

- 15 US 5,654,314 describes compounds of formula:



wherein R is an optionally halo- or hydroxy-substituted C₁₋₄ alkyl group; R is a C₁₋₄ alkyl group; or R and R' together form a C₄₋₆ alkylene group; X⁻ is an anion; and R₁ is H, OH, -CH₂OH, C₁₋₄ alkyl or C₁₋₄ alkoxy.

The present invention provides new quinuclidine derivatives with potent antagonist activity at muscarinic M₃ receptors which have the chemical structure described in formula (I):



(I)

wherein:

© is a phenyl ring, a C₄ to C₉ heteroaromatic group containing one or more heteroatoms (preferably selected from nitrogen, oxygen and sulphur atoms), or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;

R¹, R² and R³ each independently represent a hydrogen or halogen atom,

130
129**Example 44**

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane; bromide

The title compound was synthesised according to methods c and a. The yield of final step was 490 mg, 90%. ¹H-NMR (DMSO-d₆): δ 1.7 (m, 2H), 1.95 (m, 2H), 2.1 (m, 2H), 2.3 (m, 1H), 3.2 (m, 1H), 3.45 (m, 6H), 4.0 (m, 3H), 5.15 (m, 1H), 6.9 (m, 3H), 7.0 (m, 2H), 7.2 (m, 2H), 7.3 (t, 2H), 7.5 (m, 3H); MS [M-Br]⁺: 484; mp 227°C.

Example 45

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-o-tolyloxypropyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 18%. ¹H-NMR (DMSO-d₆): δ 1.7- 2.0 (m, 4H), 2.1 - 2.2 (m, 5H), 2.3 (m, 1H), 3.15 - 3.5 (m, 7H), 3.9 - 4.05 (m, 3H), 5.05 (m, 1H), 6.85 (t, 1H), 6.9 (d, 1H), 7.0 (m, 2H), 7.15 (m, 4H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 498.

Example 46

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(2,4,6-trimethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 20%. ¹H-NMR (DMSO-d₆): δ 1.7 (m, 2H), 1.95 (m, 2H), 2.1 (m, 2H), 2.2 (s, 9H), 2.35 (m, 1H), 3.2 - 3.5 (m, 7H), 3.7 (t, 2H), 3.95 (m, 1H), 5.25 (m, 1H), 6.8 (s, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 526.

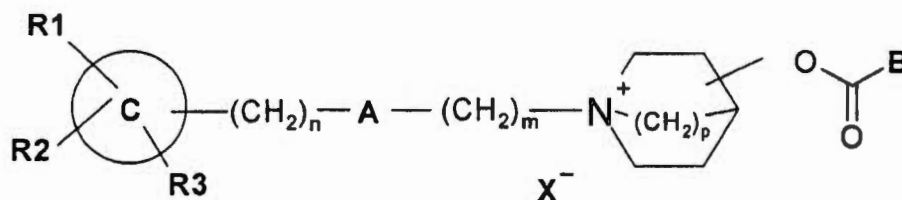
Example 47

1-[3-(2-tert-Butyl-6-methylphenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ¹H-NMR (DMSO-d₆): δ 1.3 (s, 9H), 2.7 (m, 2H), 2.9 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.3 (m, 1H), 3.2 - 3.5 (m, 7H), 3.8 (t, 2H), 3.95 (m, 1H), 5.2 (m, 1H), 6.9 - 7.15 (m, 7H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 554.

CLAIMS

1. A compound according to formula (I)



5 wherein:

© is a phenyl ring, a C₄ to C₉ heteroaromatic compound containing one or more heteroatoms or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;

10 R¹, R² and R³ each independently represent a hydrogen atom or halogen atom, or a hydroxy group, or a phenyl, -OR⁴, -SR⁴, -NR⁴R⁵, -NHCOR⁴, -CONR⁴R⁵, -CN, -NO₂, -COOR⁴ or -CF₃ group, or a straight or branched lower alkyl group which may optionally be substituted, for example, with a hydroxy or alkoxy group, wherein R⁴ and R⁵ each independently represent a hydrogen atom, straight or branched lower alkyl group or together form an alicyclic ring; or R¹ and R² together form an aromatic, alicyclic or heterocyclic ring,

15 n is an integer from 0 to 4;

A represents a -CH₂-, -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ or -NR⁶- group, wherein R⁶ and R⁷ each independently represent a hydrogen atom, straight or branched lower alkyl group or R⁶ and R⁷ together form an alicyclic ring;

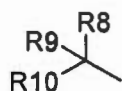
20 m is an integer from 0 to 8; provided that when m = 0, A is not -CH₂-;

p is an integer from 1 to 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;

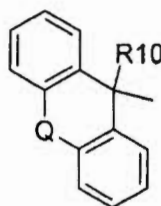
25 B represents a group of formula i) or ii):

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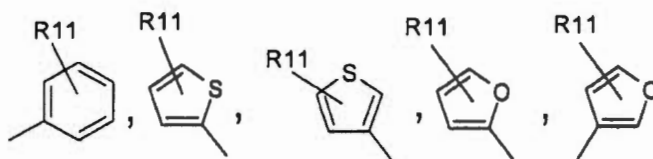
i)



ii)



wherein R¹⁰ represents a hydrogen atom, a hydroxy or methyl group; and R⁸ and R⁹ each independently represent



wherein R¹¹ represents a hydrogen or halogen atom or a straight or branched lower alkyl group and Q represents a single bond, -CH₂-, -CH₂-CH₂-, -O-, -O-CH₂-, -S-, -S-CH₂- or -CH=CH-; and X represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

2. A compound according to claim 1, wherein any alkyl group present as R¹ to R⁷ or R¹¹ contains from 1 to 4 carbon atoms.

3. A compound according to claim 1 or 2 wherein p=2.

4. A compound according to any one of the preceding claims wherein © represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group.

5. A compound according to claim 4, wherein © represents a phenyl, pyrrolyl or thienyl group.

6. A compound according to any one of the preceding claims wherein R¹, R² and R³ each independently represent a hydrogen or halogen atom or a hydroxy, methyl, tert-butyl, -CH₂OH, 3-hydroxypropyl, -OMe, -NMe₂, -NHCOMe, -CONH₂, -CN, -NO₂, -COOMe or -CF₃ group.

7. A compound according to claim 6 wherein R¹, R² and R³ each independently represent a hydrogen or halogen atom or a hydroxy group.

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NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS
CONTAINING THE SAME

This invention relates to new therapeutically useful quinuclidine derivatives, to
5 some processes for their preparation and to pharmaceutical compositions containing
them.

The novel structures according to the invention are antimuscarinic agents with a
potent and long lasting effect. In particular, these compounds show high affinity for
muscarinic M3 receptors. This subtype of muscarinic receptor is present in glands and
10 smooth muscle and mediates the excitatory effects of the parasympathetic system on
glandular secretion and on the contraction of visceral smooth muscle (Chapter 6,
Cholinergic Transmission, in H.P. Rang et al., *Pharmacology*, Churchill Livingstone,
New York, 1995).

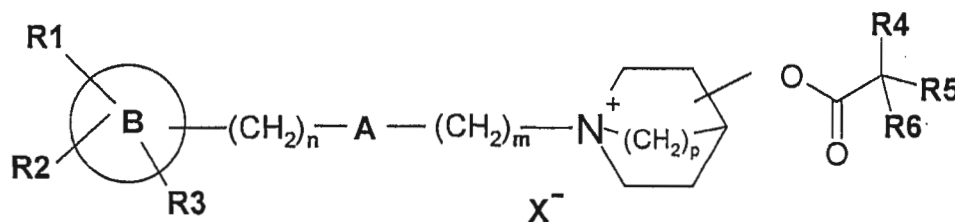
M3 antagonists are therefore known to be useful for treating diseases
15 characterised by an increased parasympathetic tone, by excessive glandular secretion
or by smooth muscle contraction (R.M. Eglen and S.S. Hegde, (1997), *Drug News*
Perspect., 10(8):462-469).

Examples of this kind of diseases are respiratory disorders such as chronic
obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma,
20 cough and rhinitis; urological disorders such as urinary incontinence, pollakiuria,
neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal
disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic
ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia
(Chapter 7, *Muscarinic Receptor Agonists and Antagonists*, in *Goodman and Gilman's*
25 *The Pharmacological Basis of Therapeutics*, 10th edition, McGraw Hill, New York,
2001).

The compounds of the invention can be used alone or in association with other
drugs commonly regarded as effective in the treatment of these diseases. For example,
they can be administered in combination with β_2 -agonists, steroids, antiallergic drugs,
30 phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) antagonists for
simultaneous, separate or sequential use in the treatment of a respiratory disease. The
claimed compounds are useful for the treatment of the respiratory diseases detailed
above in association with β_2 -agonists, steroids, antiallergic drugs or phosphodiesterase
IV inhibitors.

CLAIMS

1. A compound of formula (I):



(I)

wherein B is a phenyl ring, a 5 to 10 membered heteroaromatic group containing one or more heteroatoms, or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, or biphenyl group;

R¹, R² and R³ each independently represent a hydrogen or halogen atom, or a hydroxy group, a phenyl group, -OR⁷, -SR⁷, -NR⁷R⁸, -NHCOR⁷, -CONR⁷R⁸, -CN, -NO₂, -COOR⁷ or -CF₃ group, or a straight or branched, substituted or unsubstituted lower alkyl group, wherein R⁷ and R⁸ each independently represent a hydrogen atom, a straight or branched lower alkyl group, or together form an alicyclic ring; or R¹ and R² together form an aromatic or alicyclic ring or a heterocyclic group.

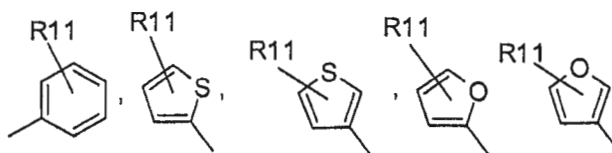
n is an integer from 0 to 4;

A represents a group selected from -CH₂-, -CH=CR⁹-, -CR⁹=CH-, -CR⁹R¹⁰-, -CO-, -O-, -S-, -S(O)-, -S(O)₂- and NR⁹, wherein R⁹ and R¹⁰ each independently represent a hydrogen atom, a straight or branched lower alkyl group, or together form an alicyclic ring;

m is an integer from 0 to 8, provided that when m=0, A is not -CH₂-;

p is an integer from 1 to 2 and the substitution in the azonia bicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;

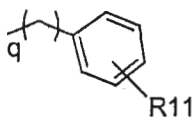
R⁴ represents a group of structure:



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wherein R^{11} represents a hydrogen or halogen atom, a hydroxy group, an alkoxy group, a nitro group, a cyano group, $-CO_2R^{12}$ or $-NR^{12}R^{13}$, wherein R^{12} and R^{13} are identical or different and are selected from hydrogen and straight or branched lower alkyl groups, or a straight or branched, substituted or unsubstituted lower alkyl group;

R^5 represents an alkyl group of 1 to 7 carbon atoms, an alkenyl group containing 2 to 7 carbon atoms, an alkynyl group containing 2 to 7 carbon atoms, a cycloalkyl group of 3 to 7 carbon atoms, or a group of formula



wherein $q = 1$ or 2 and R^{11} is as defined above;

R^6 represents a hydrogen atom, a hydroxy group, a methyl group or a $-CH_2OH$ group; and

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

2. A compound according to claim 1, wherein p is 2.
3. A compound according to claim 1 or claim 2, wherein R^4 represents an unsubstituted phenyl, 2-thienyl, 3-thienyl, 2-furyl or 3-furyl group.
4. A compound according to any one of the preceding claims, wherein R^5 represents a cyclopentyl, cyclohexyl, pentyl, allyl, vinyl, propynyl, benzyl or phenethyl group.
5. A compound according to any one of the preceding claims, wherein the group $-O-CO-C(R^4)(R^5)(R^6)$ represents a group selected from 2-cyclopentyl-2-hydroxy-2-thien-2-ylacetoxyl; 2,3-diphenylpropionyl; 2-hydroxymethyl-2,3-diphenylpropionyl; 2-hydroxy-2,3-diphenylpropionyl; 2-hydroxy-3-phenyl-2-thien-2-ylpropionyl; 2-hydroxy-2-thien-2-ylpent-4-enoyl; 2-hydroxy-2-thien-2-ylheptanoyl; 2-hydroxy-2-thien-2-ylpent-3-ynoyl; 2-hydroxy-2-thien-2-ylbut-3-enoyl; 2-cyclopentyl-2-fur-2-yl-2-hydroxyacetoxyl; 2-cyclohexyl-2-hydroxy-2-phenylacetoxyl; 2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxyl; 2-

(2S)-2-Cyclohexyl-2-fur-2-yl-2-hydroxyacetic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester;

(2R)-2-Cyclohexyl-2-hydroxy-2-phenylacetic acid 1-azabicyclo[2.2.2]oct-4-yl ester

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31. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20 in admixture with a pharmaceutically acceptable carrier or diluent.
- 10 32. A compound according to any one of claims 1 to 20, or a pharmaceutical composition according to claim 31, for therapeutic use in a method of treatment of the human or animal body by therapy.
- 15 33. Use of a compound according to any one of claims 1 to 20, or a pharmaceutical composition according to claim 31, in the manufacture of a medicament for the treatment of a respiratory, urological or gastrointestinal disease or disorder.
- 20 34. A method of treating a respiratory, urological or gastrointestinal disease or disorder, which method comprises administering to a human or animal patient in need of treatment an effective non-toxic amount of a compound according to any one of claims 1 to 20 or a pharmaceutical composition according to claim 31.
- 25 35. A combination product comprising
- (i) a compound according to any one of claims 1 to 20; and
 - (iii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder
- for simultaneous, separate or sequential use.
- 30 36. A combination product according to claim 35 comprising
- (i) a compound according to any one of claims 1 to 20; and
 - (iv) a β_2 agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonist
- for simultaneous, separate or sequential use in the treatment of a respiratory
- 35 disease.

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International Bureau



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23 October 2003 (23.10.2003)

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(10) International Publication Number
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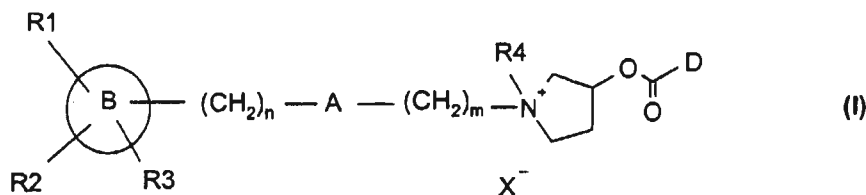
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Published:

— without international search report and to be republished upon receipt of that report

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: NEW PYRROLIDINIUM DERIVATIVES



(57) Abstract: New pyrrolidinium derivatives having the chemical structure of general formula (I) are disclosed; as well as processes for their preparation, pharmaceutical compositions comprising them and their use in therapy as antagonists of M3 muscarinic receptors.

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NEW PYRROLIDINIUM DERIVATIVES

This invention relates to new therapeutically useful pyrrolidinium derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

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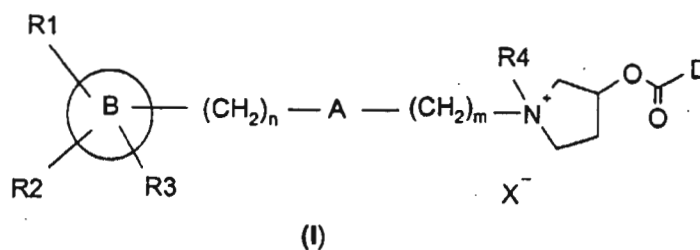
The novel structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity for M3 muscarinic receptors. This subtype of muscarinic receptor is present in glands and smooth muscle and mediates the excitatory effects of the parasympathetic system on glandular secretion and on the contraction of visceral smooth muscle (Chapter 6, Cholinergic Transmission, in H.P. Rang et al., Pharmacology, Churchill Livingstone, New York, 1995).

M3 antagonists are therefore known to be useful for treating diseases characterised by an increased parasympathetic tone, by excessive glandular secretion or by smooth muscle contraction (R.M. Eglen and S.S. Hegde, (1997), Drug News Perspect., 10(8):462-469).

Examples of this kind of diseases are respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urological disorders such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia (Chapter 7, Muscarinic Receptor Agonists and Antagonists, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw Hill, New York, 2001).

The compounds of the invention can be used alone or in association with other drugs commonly regarded as effective in the treatment of these diseases. For example, they can be administered in combination with β_2 -agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors an/or leukotriene D4 (LTD4) antagonists for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The new pyrrolidinium derivatives of the invention have the chemical structure of formula (I):



wherein

B is a phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl or biphenyl
5 group or a 5 to 10-membered heteroaromatic group containing one or more, for example
1, 2, 3 or 4, heteroatoms selected from N, O or S;

R¹, R² and R³ each independently represent a hydrogen or halogen atom, or a hydroxy,
phenyl, -OR⁵, -SR⁵, -NR⁵R⁶, -NHCOR⁵, -CONR⁵R⁶, -CN, -NO₂, -COOR⁵ or -CF₃ group, or
10 a straight or branched, optionally substituted lower alkyl group;

or R¹ and R² together form an aromatic or alicyclic ring or a heterocyclic group;

R⁵ and R⁶ each independently represent a hydrogen atom, a straight or branched,
15 optionally substituted lower alkyl group, or together form an alicyclic ring;

n is an integer from 0 to 4;

A represents a group selected from -CH₂-, -CH=CR⁷-, -CR⁷=CH-, -CR⁷R⁸-, -CO-, -O-, -S-,
20 -S(O)-, -S(O)₂- and -NR⁷-, wherein R⁷ and R⁸ each independently represent a hydrogen
atom, a straight or branched, optionally substituted lower alkyl group, or together form an
alicyclic ring;

m is an integer from 0 to 8;

25

R⁴ represents a lower alkyl group;

D represents a group of formula i) or ii)

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

2020
Bogotá, D.C.,

Abogado
EMILIO FERRERO
(Apoderado)

ASUNTO Radicación 06121210
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 04358
 Folios 021

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2005/005841
Fecha de Presentación Internacional 31-05-2005

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:

- 1.1. Descripción: (Folios: 55 a 94) como se radicó inicialmente.
- 1.2. Reivindicaciones: 1 a 18 (Folios: 95 a 98) como se radicó inicialmente.
- 1.3. Gráficas: Folios: 99 a 102.
- 1.4. Prioridad: 31/05/2004 ES P200401312.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

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3. Objeto de la invención:

La presente solicitud se titula: "Combinaciones que comprenden agentes antimuscarínicos y agonistas beta-adrenérgicos".

El objeto de la presente solicitud se refiere a combinaciones de ciertos agentes antimuscarínicos con agonistas β -adrenérgicos y a su uso en el tratamiento de trastornos respiratorios.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 3, 13 a 18 (folios: 95, 97 y 98): Combinación que comprende (a) un agonista β_2 y (b) un antagonista de los receptores muscarínicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano, en forma de una sal que tiene un anión X, que es un anión farmacéuticamente aceptable de un ácido mono o polivalente.

Reivindicaciones 4 y 12 (folios: 95 y 97): Producto que comprende (a) un agonista β_2 y (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2, en forma de una preparación combinada para uso simultáneo, concurrente, por separado o secuencial en el tratamiento de un paciente que sufre, o es susceptible de sufrir, una enfermedad respiratoria que responde a un efecto antagonista de M3.

Reivindicación 5 (folio: 95): Kit de partes que comprende (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2 junto con instrucciones para el uso simultáneo, concurrente, por separado o secuencial en combinación con (a) un agonista β_2 .

Reivindicación 6 (folio: 95): Envase que comprende (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2 y (a) un agonista β_2 para el uso simultáneo, concurrente, por separado o secuencial.

Reivindicaciones 7 a 9 (folio: 96): Uso de (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2 para la preparación de un medicamento para el uso simultáneo, concurrente, por separado o secuencial en combinación con (a) un agonista β_2 .

Reivindicaciones 10 y 11 (folio: 96): Método para tratar un paciente que sufre o es susceptible de sufrir una enfermedad o estado patológico que responde a un efecto antagonista de M3, comprendiendo el procedimiento la administración simultánea, concurrente, por separado o secuencial a dicho paciente de una cantidad eficaz de (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2 y (a) un agonista β_2 .

El problema planteado en esta solicitud es la necesidad de combinaciones de antagonistas de receptores muscarínicos M3 y agonistas β_2 -adrenérgicos con efectos secundarios cardíacos significativamente menores tales como taquicardia, y que tengan una fuerte actividad en el tracto respiratorio.

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La solución propuesta por la presente solicitud consiste en una combinación que comprende (a) un agonista $\beta 2$ y (b) un antagonista de los receptores muscarínicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/439, 31/167, 31/137; A61P 11/00, 11/06, 11/08.

4. Unidad de Invención (artículo 25 D 486)

Según lo anterior la (s) reivindicación (es) 5, 6, 14 a 18 (folios: 95, 97 y 98), que se refiere(n) a un kit y envase que comprende (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2 y (a) un agonista $\beta 2$, no guarda(n) unidad de invención con la reivindicación 1, que se relacionan con una combinación que comprende (a) un agonista $\beta 2$ y (b) un antagonista de los receptores muscarínicos M3, puesto que el kit o envase pertenecen a otro sector de la tecnología. Cabe recordar que éstos no se deben caracterizar por su contenido sino por sus propias características técnicas.

5. Excepciones de Patentabilidad (artículo 20 D486 literal a)-d))

De acuerdo con lo anterior, la(s) reivindicación(es): 10 y 11 (folio: 96), que se refiere(n) a un método para tratar un paciente, no es (son) patentable(s) porque se relacionan con un método de tratamiento de una enfermedad.

6. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

La(s) reivindicación (es) 7 a 9 (folio: 96), que se refiere(n) a un uso de (b) un antagonista de los receptores muscarínicos M3 como se ha definido en las reivindicaciones 1 ó 2 para la preparación de un medicamento para el uso simultáneo, concurrente, por separado o secuencial en combinación con (a) un agonista $\beta 2$ no se encuentra(n) dentro del campo de la patentabilidad (productos y procedimientos).

7. Análisis de la(s) Oposición(es): (artículo 43 D. 486)

No se presentaron oposiciones al objeto reivindicado.

8. 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 31-05-2004.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

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Nº	Documento	Título	Fecha de Publicación
D1	WO 01/04118	Novel quinuclidine derivatives and medicinal compositions containing the same	18 de enero de 2001
D2	WO 02/053564	Novel quinuclidine derivatives and medicinal compositions containing the same	11 de Julio de 2002
D3	WO 03/087094	New pyrrolidinium derivatives	23 de octubre de 2003

9. Análisis de patentabilidad (artículo 14 D486)

9.1. Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 06121210, se refiere a:

Combinación que comprende (a) un agonista β_2 y (b) un antagonista de los receptores muscarínicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano, en forma de una sal que tiene un anión X, que es un anión farmacéuticamente aceptable de un ácido mono o polivalente.

La anterioridad: WO 01/04118 (folios: 126 a 132), se relaciona con: derivados de quinuclidina y composiciones que los contienen; estos compuestos son antagonistas de los receptores muscarínicos M3 y sirven para el tratamiento de enfermedades respiratorias como por ejemplo la enfermedad obstructiva pulmonar (EPOC o COPD). Entre los derivados que se mencionan en este documento se encuentra el compuesto 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano y sus sales como las de bromuro. Este compuesto se puede emplear en combinación con agonistas β_2 , esteroides, antialérgicos o inhibidores de fosfodiesterasa IV.

La anterioridad: WO 02/053564 (folios: 133 a 137), trata sobre: derivados de quinuclidina y composiciones que los contienen. Son agentes antimuscarínicos con un efecto potente y de larga duración. Estos compuestos se pueden administrar solos o en combinación con otros fármacos para el tratamiento de enfermedades respiratorias, como por ejemplo agonistas β_2 , esteroides, fármacos antialérgicos, inhibidores de fosfodiesterasa IV y/o antagonistas de leucotrieno D4 para administrarse en forma simultánea, por separado o en forma secuencial para el tratamiento de enfermedades respiratorias.

El elemento característico de las combinaciones reivindicadas, ya era conocido en los documentos D1 y D2; por lo cual el objeto de las reivindicaciones 1 a 4, 12 a 18 (folios: 95, 97, 98) no pueden considerarse nuevos.

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9.2. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Combinación que comprende (a) un agonista β_2 y (b) un antagonista de los receptores muscarínicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano, en forma de una sal que tiene un anión X, que es un anión farmacéuticamente aceptable de un ácido mono o polivalente.

La anterioridad WO 01/04118 (folios: 126 a 132) menciona derivados de quinuclidina y composiciones que los contienen; estos compuestos son antagonistas de los receptores muscarínicos M3 y sirven para el tratamiento de enfermedades respiratorias como por ejemplo la enfermedad obstructiva pulmonar (EPOC o COPD). Entre los derivados que se mencionan en este documento se encuentra el compuesto 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano y sus sales como las de bromuro. Este compuesto se puede emplear en combinación con agonistas β_2 , esteroides, antialérgicos o inhibidores de fosfodiesterasa IV.

El documento WO 02/053564 (folios: 133 a 137) se refiere a derivados de quinuclidina y composiciones que los contienen. Son agentes antimuscarínicos con un efecto potente y de larga duración. Estos compuestos se pueden administrar solos o en combinación con otros fármacos para el tratamiento de enfermedades respiratorias, como por ejemplo agonistas β_2 , esteroides, fármacos antialérgicos, inhibidores de fosfodiesterasa IV y/o antagonistas de leucotrieno D4 para administrarse en forma simultánea, por separado o en forma secuencial para el tratamiento de enfermedades respiratorias.

La anterioridad WO 03/087094 (folios: 138 a 140) se relaciona con derivados de pirrolidina que son agentes antimuscarínicos M3. Estos compuestos se pueden administrar solos o en combinación con otros fármacos para el tratamiento de enfermedades de tipo respiratorio como EPOC. Entre los fármacos que se pueden administrar en el tratamiento están: agonistas β_2 , esteroides, antialérgicos, inhibidores de fosfodiesterasa IV, antagonistas de leucotrieno D4; se administran en forma simultánea, por separado o de manera secuencial.

El problema técnico planteado en esta solicitud: la necesidad de combinaciones de antagonistas de receptores muscarínicos M3 y agonistas β_2 -adrenérgicos con efectos secundarios cardíacos significativamente menores tales como taquicardia, y que tengan una fuerte actividad en el tracto respiratorio se había resuelto previamente mediante combinaciones de antagonistas M3 y agonistas β_2 -adrenérgicos ya conocidos(as). Por esta razón se considera que los componentes de las combinaciones reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

La(s) reivindicación(es) 1 a 4, 12 a 18 de esta solicitud no menciona(n) una característica que conceda un efecto inesperado o especial a las combinaciones, que pueda considerarse como un aporte a la técnica, así que son obvios(as) para una persona versada en la materia.

Además, puesto que D1-D3 y D2-D3 divulgaban previamente compuestos antagonistas M3 y sus combinaciones para administrarse en forma simultánea, por separado o en forma secuencial junto con agonistas β 2-adrenérgicos para el tratamiento de enfermedades respiratorias (folios: 126 a 140), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud combinaciones de un agonista β 2 y un antagonista de los receptores muscarínicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano; de manera que para una persona medianamente versada en la materia sería obvio emplear estos documentos. Por lo cual puede no haber Nivel Inventivo.

10. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO 01/04118	1 a 4, 12 a 18	Novedad y Nivel Inventivo
D2	WO 02/053564	1 a 4, 12 a 18	Novedad y Nivel Inventivo
D3	WO 03/087094	1 a 4, 12 a 18	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 la 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 Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 09 ABR, 2010

CONCEPTO TÉCNICO No. 1234	EXAMINADOR TÉCNICO Código No. 202005
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