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Seæora Jefe de la
DIVISION DE NUEVAS CREAC1ONES
Superintendencia de Industria y Comercio
E. S. D.

TrÆmite 011 Evento 378 Actuaci6n 538

Referencia Expediente No. 06121209
Asunto : Solicitud de patente para COMBINACIONES QUE
COMPRENDEN AGENTES ANTIMUSCARINICOS Y
CORTICOSTEROIDES
Solicitante LAEORATORIOS 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 LAEOR.ATORIOS ALMIRALL, S.A., atentamente solicito se efectcte el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con las reglas del Capitulo I del PCT y segün lo establecido en el articulo 44 de la Decision 486 de la Comisidn de la Comunidad.Andina.

Para tal efecto presento junto con eate escrito los recibos
Nos. 08-42,142 y 08-42,140 del 27 de mayo de 2008 por valor $420.000.00 que corresponde de la tasa legal fijada para el efecto.

2. Por lo anterior, comedidamente solicito sØ prosiga con el trÆmite de este asunto.

Seæora Jefe,

- 

EMILIO FERRERO
- T.P.A. No. 31.929

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____ BUlL ALBERO, Maria Antonia [ES/ES]; Calle Paris, ance Notes on Codes and4bbreviations"appearingat the begin-50, 1°4, E-08029 Barcelona (ES). ning ofeach regular issue ofthe PCT Gazette.

(54) Title: NOVEL 9UINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS CONTAINING THE SAME

RI (5 1)Abstract: A compound according to formula (I) wherein z' is a phenyl ring, a C4

(CH2)fl_A

(CH2),N

O..B to C9 heteroaromatic compound containing
OEM__ one or more heteroatoms, or a naphthalenyi,

R2 _ 0 (I) 5,6,7,8-tetrahydronaphthalenyl or biphenyl
R3 x group; R’, R2 and R3 each independently

represent a hydrogen or halogen atom, or

%kN

O

a hydroxy group, or a phenyl, -OR4, -SB4,

))(a)-NR4R5, -NHCOR4, -CONR4R5, -CN, -NO2.

RO -COOR4 or -CF3 group, or a straight or
RIO (I)branched lower alkyl group which may
(ii) optionally be substituted, for example, with
a hydroxy or alcoxy group, wherein R4 and

R11 R11 V each independently represent a hydrogen

atom, straight or branched lower alkyl group, Ru $ or together form an alicyclic ring; or R and
(b) "_ (C) (d) (e) B2 together form an aromatic. alicycic or
heterocyclic ring; n is an integer from I) to
TNO 4; A represents -CH2-, -CH=CR6, -CR6=CH-, -CR6R7-, -CO-, -0-, -S-, -S(0)-, SO2 or NB6- group, wherein R6 and B7 each
- independently represent a hydrogen atom, straight or branched lower alkyl group, or B6 and R7 together form an alicycic ring; in is an integer from 0 to 8; provided that when in = 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 R° represents a hydrogen atom, a hydroxy or methyl group; and B6 and R9 each independently represents formulae (a), (b), (c), (d) and wherein R’ represents a hydrogen or halogen atom, or a straight or branched lower alkyl group and Q represents a single bond, -CRr, -CHrCH2, -0-, -O-CH2-, -S., -S-CR2- or -CR=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).

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OVELQUXNUCLXDINE DERIVAXVES. AND MEDXCflThL COMOSXTIONS

COINXNG.TU. . .....

This invention relates to new therapeutically useful quinuclidine
5 derivatives, to some processes foz 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 H3
10 receptorsOm3).
In accordance. With their nature as H3 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
15 disorders. such as urinary incontinence, pollakinuria in neuripenia
pollakinuria, nØurogenic or unstable bladder, cystospasm and chronic cystitis; and gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, divertiôulitis and peptic ulceration.
The compounds claimed.are also useful for the treatment of the
20 respiratory diseases detailed: above: in association with 12 agonists,,
steroids, antiallergic drugs orphospliodiesterase IV inhibitors.

. ’.

Compounds of the present invention may also be expected to have anti-tussive properties..
Dependngon their. nature the new compounds maybe suitable for
25 treating iragally 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 derivàtives.of the formula
30 .

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40 t1
Example 44
3(R) - (2-Nydroxy-2, 2-dithien-2-ylacetoxy) -1- (3-phenoxypropyl) -1-azoniabicyclot2.2.21 octane; bromide
The title compound.was synthesised according to methods c and a. The
5:.. yield of final step was 490 mg, 90%.’H NMR (DMSO-d6): 5 1.7 (m, 211).,
1.95 (m, 211), 2.1 (m, 211), 2.3 (m, 111), 3.2 (in, 111), 3.45 (m, 611), 4.0
(in, 3ff), 5.15 (m, 111), 6.9 (in, 311), 7.0 (ni, 211), 7.2 (m,211), 7.3 Ct,
. 211), 7.5 (in, 311); MS (M-8rJ: 484; nip 227°C.

10. Example 45

3(R)-(2-Sydroxy-2,2-dithien-2-ylaOetOXY) -1- (3-o-tolyloxypropyl) -1-azoniabicyclo(2.2.23 octane; trifluoroacetate
The title compound was synthesisedaccordthg to methods c and b The yield of final step was 19 mg, M. 1B-NMR (DMSO-d6): 8 1.7- 2.0 (m,
15.. 411), 2.1 -2.2 (rn, 511), 23 (in,1H), 3.15- 3.5 (in, 711), 3.9- 4.05 (m,
311), 5.05 (m, 111), 6.85 (t, 111), 6.9 (d, 111), 7.0 (in, 211), 7.15 (m,
.. 411), 7.5 (in, 311); MS (M-CF3COOJt: 498.

Example 46

20 3(R) - (2-Uydxoxy-2,2-dithien2ylaCetOXY) -1- [3- (2,41 6-trimethyiphenex
.y)propyli-1-azOfliabiaYOlOC2.2. 2]octaxme; trifluoroacetate
The compound was synthesised according to methods c and b. The yield of final step was 22 mg, 20%. ’B- NMR C DMSO-d6): 6 1.7(m, 21!),
1.95 (in, 211), 2.1 (m, 2ff), 2.2 (s, 9ff) 2.35 (m,1}3), 3.2 - 3.5 (in,
25: 711), 3.7 (t,2F1), 3.95 (mu, 111), 5.25 (m,.111)., 6.8 (s, 2ff), 7.0 (in, 211),
7.2 (m, 2H), 7.5 (in, 3M); 5 (M-CF3COO] 526.

Example 47

... 1-[3- (2_tŁrt_Butyl6-mnethYlPheflQxY)Pr0PYl]-3 (R) - (2-hydroxy-2,2-
30 dithien-2-ylacetoxy) -1-azeniabicyclo [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%..}1- NMR (DMSO-d6): 8 1.3 (s, 911),
2.7 211), 2.9 211), 2.1 2ff), 2.2 311), 2.3 111), 3.2 35(m 711), 3.8 (t, 213), 3.95 (m, 111), 5.2 (m, 1ff), 6.9 -

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CLAIMS

A compound according to formula (I)

RI

- (CH2)N
R2&
R3 X

(I)

5 wherein:

PCT/EP00/06469

OyB

is a phenyl ring, a C4 to C. heteroaromatic compound containing one
or more heteroatoms or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl
or biphenyl group;
R’, R2 and R3 each independently represent a hydrogen atom or halogen
10 atom, or a hydroxy group, or a phenyl, -OR’, -5R4, -NR4R5, -NHCOR4, -
CONR4R5, -CN, -I401 -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 andR5 each independently represent
a hydrogen atom, straight or branched lower alkyl group or together
 15 form an alicyclic ring; or R1 and R2 together form an aromatic,
alicyclic or heterocyclic ring,
n is an integer from 0 to 4;
A represents a -CH2-1 -CHCR6--, -CR6CH-, -CR6R1-, -CO-, -0-1 -5--,
- 5(0)-, $02 or -NR6- group, wherein R6 and R’ each independently
20 represent a hydrogen atom, straight or branched lower alkyl group or
R6 and R7 together form an alicyclic ring;
in is an integer from 0 to 8; provided that when in = 0, A is not -C112--;
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
25 configurations of the asymmetric carbons;
B represents a group of formula I) or ii):

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%JR OR98
RI

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wherein R’° represents a hydrogen atom, a hydroxy or methyl group; and R8 and R9 each independently represent
R11 R11 R11 Ru

)LkRI

I

wherein R11 represents a hydrogen or halogen atom or a straight or
branched lower alkyl group and Q represents a single bond, -CR2-, -Cl!2-CR2-1 -0-, -0-CH2-, -5-1 -S-CR2- or -CR=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 RI to R’7 or R’1 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[l, 3]dioxolyl, imidazolyl or benzothiazolyl group.
5. A compound according to claim 4, wherein ' represents a
phenyl, pyrrolyl or thieny]. group.
6. A compound according to any one of the preceding claims
wherein R1, P.2 and RI each independently represent a hydrogen or halogen
atom or a hydroxy, methyl, tert-butyl, -CH20R, 3-hydroxypropyl, -OMe,
- N4e2, -NHCOMe, -CONH2, -CN, -NO2, -COOMe or -CF3 group.
7. A compound according to claim 6 wherein R1, P.2 and P.3 each
independently represent a hydrogen or halogen atom or a hydroxy group.

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3(R) -Diphenylacetoxy-1- (3-phenoxy-propyl) -1-azoniabicyclo(2 2.2) octane;

bromide

3 () * (2-Hydroxy2, 2-diphenyl-acetoxy) -1- (3-phenoxypropyl) -1-azoniabi cyclo(2.2..21oôtane; bromide
5 3(R) - (2, 2-Diphenyipropionyloxy) -1- (3-phenoxypropyl) -1-azoniabicyclo (2 *
2.21octane; bromide
3U (2-Hydroxy-2-phenyl-2-thien-2-yl-aCetOXY) -1- (3-phenoxypropyl) -1-azonia-bicyclót2.2.2] octane;.. bromide
3(R) -.(2-Furan-2-.yl-2-hydroXy-2-pheflylaCetOXy) -1- (3-phenylallyl) -].--azo
101 niabicycló(2.2.2)octane; bromide
3(R) - (2-Furan-2-yl-2-hydroxy-2-PhenYlaCetOXY) -1- (2-phenoxyethyl) -1-azo niabicyclo(2.2.2]octane; bromide
3(R) - (2-Furan-2-yl-2-hydroxy-2-pheflYlaCetOXY) -1- (3-phenoxypropyl) -1-azo niabicyclo (2.2.21 octane; bromide
. 15 3(R)-(2,2-Dithien-2-ylacetoxy)-i-(3-phenoXYPrOPYl)-1-aZOfliabiCYClO
(22.2]octane; bromide
3(R) - (2-Mydroxy-2, 2-di-thien-2-ylacetoxy) -1-phenethyl-3.-azoniabicy clo[2.2..2]octane; bromide
3(R) (2-Hydroxy-2, 2-di-thien-2-ylace.tOXy) -1--.(4-phenylbutyl) -1-dzonia
20 bicyclo(2.2.2]octane; bromide
.3(I.:). (2Rydroy-2, 2-dithien-2-ylaceoXy) -1- (3-phenoxypropyl) -1-azonia-
. . bjcyclot2.2.2]octane; bromide
l-[3- (4-i.uorophenoxy)prOpyl)-3(R) -(2-hydroxy--2,2-dithien-2-ylaceto
xy) --azóniabicyclo(2.2.2)oCtafle; chloride
25 3 (R)-(2-Nydroxy-2, 2-dithien-2-ylacetoxy) -1-(3- (2-hydroxyphenoxy) pro
pyl)-1-azoæiabicyclo (2.2.2) octane; trifluoroacetate 3(R)(2._Hydroxy_2,2-dithiefl-2-YlaCetOXY)-l(3PYrrO1l-YlPr0PYi)la :zoni*bicyClo [2.2. 2]octane; trifluoroÆcetate
3(i) - (2-Hydroxy-2, 2-dithien-2-ylacetoxy) -1- (2-thien-2-ylethyl) -1-azo
30 niabicyclo(2.2.2)octane; bromide
3(R)-(2-1lydroxy-2, 2-dithien-2-ylacetoxy) -1- (3-thien-2-ylpropyl) -1-a zoniabicyclo f 2 2.2] octane; bromide
1- (2-Senzyloxyethyl).-3 (R) - (2-2iydroxy-2, 2-dithien-2-ylacetoxy) -1-azon iabicyclo[2.2.2] octane; trifluoroacetate
3$ 3(R) -. (2-Nydroxy-2, 2-dithien-3--ylacetoxy) -1- (3-phenoxypropyl) -1-azoni

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28. A compound according to claim 27, wherein R0 is a 2-thienyl or
2-furyl group
29 A compound according to claim 27 which is
Oxothien-2-y1-acetic acid 1-azabicyclo[2 2 2]oct-4-yl ester,
5 0.xothien-2-yl-acetic.acid1-azabicyclo(2..2..2]Oct-3(R)--yl ester; or
Oxofuran-2-yl-acetic acid 1-azabicyclo2.2.2]oct-3(R)-yl ester.
30. Use of a compound according to any one of claims 24 to 29
process for producing a compound of formula (I) as defined in
any one.of claims:1.to 20. ...
10 31. A pharmaceutical composition comprising a comound.
according to any one of claims 1 to 21 in admixture with a pharmaceutically acceptable carrier or: diluent.
32. A compound according to any one of claims.1 to 21, or a
pharmaceutical oomposition. according to claim 31 for use in.a method
15 Of treatment of the human or animal body by therapy.
33. Use of a compound according to any one of claims 1-to 21,
or a pharmaceutical composition according to claim 31 for the
manufacture of a znedicament.for use in.the treatment of respiratory, urinary or gastrointestinal disease. .
20 34 Use of a compound according to any one of claims 1 to 21
or a pharmaceutical. composition according to claim 31 for the.. .
manufacture of a medicament for use in the treatment of COD,
chronic bronchitis, asthma and rhinitis.
35 A method for treating respiratory, urinary and/or
25 gastrointestinal disease which method comprises administering to a
human or animal patient:in need of such treatment an effective 1
mount of a compound according to any one of claims 1 to 21 or at a pharmaceutical compositionaccording to claim 31.

30 :i. :. ;

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(71) Applicant (for all designated States except US): ALMI- Si, SL. Ti, TM, TN, TR. T. ’12, UA. UG, US, UZ,
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strasse 38, CH-6341 Baar (CH).
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-_ (75) inventors/Applicants (for US only): PRAT QUINONES, Eurasian patent (AM, AZ. BY, KG, KZ, MD, RU, TJ, TM),
- [Continued on next page]

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

- RI R4 (57) Abstract: A compound of

formula (I), wherein B is a phenyl

R5 (I) ring, a to 10 membered heteroaro-

-

,(CH2)_A -(CH2)_._Ni

matic group containing one or more
beteroatorns, or a naphthalenyl,

5, 6, 7, 8- tetrahydronaphthalenyl. R3 X benzo[I,3ldioxolyl, or biphenyl

group; R1, R2 and R each
- independently represent a hydrogen
-_ RI I RI I RI i or halogen atom. or a hydroxy
RI I Ri 1 group, a phenyl group. -OR’, -SR’,
- NR7R5, -NHCOR’,
-CN, -NO2, -COOR’ or CF3 group,
or a strait or branched, substituted
or unsubstituted lower alkyl
group. wherein K7 and R5 each
independently represent a hydrogen
atom, a straight or branched lower
alkyl group, or together form an
i alicyclic ring; or R’ and R2 together form an aromatic or alicyclic ring or a heterocyclic group, n is an integer from 0 to 4; A ’Z represents a group selected from -CH2-, -CH--CR9-, -CR9=CH-, -CR9R’°-, -CO-, -0-, -S., -S(0)-, -5(0)2- and NR9, wherein R9 and Ita We each independently represent a hydrogen atom, a straight or branched lower alkyl group, or together form an alicyclic ring; in is an integer from 0 to 8, provided that when m--O, A is not -CH2-; p is an integer from I 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 U) wherein R" represents a hydrogen or halogen atom, a hydroxy group, an alkoxy group. a nitro group, a N cyano group, -CO21112 or -NR ’2W, 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 tower alkyl group; R5 represents an alkyl group of I to 7 carbon atoms, an alkenyl group containing 2 to 7 carbon atoms, or a group of formula (III) wherein q=l or 2 and R’ iss a defined above; R6 represents a hydrogen atom, a hydroxy group, a methyl group or a -CH20H group; and X represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

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WO 02/053564 PCTIEPOI/15168

NOVEL QIJINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS

CONTAINING THE SAME I ’

This invention relates to new therapeutically useful quinuctidine 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, Choilnergic 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. Egieri 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; urologlcal disorders such as urinary incontinence, poHakiuria,
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 ’a
25 The Pharmacological Basis of Therapeutics, lOthe edition, McGraw Hill, Ney 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 f32-agonists, steroids, antiallergic drugs,
30 phosphodiesterase IV inhibitors an/or leukotriene 04 (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 -agonists, steroids, antiallergic drugs or phosphodiesterase
IV Inhibitàrs.
35

WO 02/053564

CLAIMS

I. A compound of formula (I):
RI

R22fl -(CH2)rW

**’&

R3 X-

PCTIEP01/15168

R4

aI I
0

R6
0

5

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]dioxolyI, or biphenyl group;
R1, R2 and R3 each independently represent a hydrogen or halogen atom, or a
10 hydroxy group, a phenyl group, -OW, -SR7, -NR7R8, -NHCOR7, CONR7RB, -ON,
- NO2, -COOR1 or -CF3. group, or a straight or branched, substituted or
unsubstituted lower alkyl group, wherein R7 and R6 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 aHcyclic ring or a
15 heterocyclic group.
n Is an Integer from 0 to 4;
A represents a group selected from -CH2-, -CH=CR9-, -CR9CH-, -CR9R10-, -GO-, -0-, -S-, -8(0)-, -8(0)2- and NW, wherein R9 and R10 each independently represent a hydrogen atom, a straight or branched lower alkyl group, or together
20 form an allcydkc ring;
m is an integer from 0 to 8, provided that when m=0, A Is not -OH2-;
p Is an integer from I 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;
25 R4 represents a group of structure:

RI I Ru 1 Ru
RI I Rh

30

IN

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- ?4

31

wherein R11 represents a hydrogen or halogen atom, a hydroxy group, an alkoxy
group, a nitro group, a cyano group, -0O2R12 or NR12R13, wherein R12 and R13
are identical or different and are selected from hydrogen and straight or branched
5 lower alkyl groups, or a straight or branched, substituted or unsubstituted lower
alkyl group;
R5 represents an alkyl group of I 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

q’

. 10

15

wherein q = I or 2 and R11 is as defined above;
R6 represents a hydrogen atom, a hydroxy group, a methyl group or a -CH20H group; and
X represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

2. A compound according to claim I, wherein p is 2.

3. A compound according to claim I.or claim 2, wherein R4 represents an
unsubstituted phenyl, 2-thienyl, 3-thienyl, 2-furyl or 3-furyl group.

20

4. A compound according to any one of the preceding claims, wherein R5
represents a cyclopentyl, cyclohexyl, pentyl, allyl, vinyl, propynyl, benzyl or phenethyl group.

25 5. A compound according to any one of the preceding claims, wherein the group
-0-CO-C(R4)(R5)(R5) represents a group selected from 2-cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy; 2,3-dlphenyipropionyloxy; 2-hydroxymethyl-2,3-diphenyipropionyloxy; 2-hydroxy-2,3-diphenylproplonyloxy; 2-hydroxy-3-pheny!-2-thien-2-ylpropionyloxy; 2-hydroxy-2-thien-2-ylpent-4-enoyloxy; 2-hydroxy-2-thien-
30 2-ylheptanoyloxy; 2-hydroxy-2-thien-2-ylpent-3-ynoyloxy; 2-hydroxy-2-thlen-2-
ylbut-3-enoyioxy; 2-cyclopentyl-2-fur-2-yl-2-hydroxyacetoxy; 2-cyclohexyl-2-hydroxy-2-phenylaCetoxy; 2-cyclohexyl-2-fur-2-yl-2-hydroxyacetoxy; 2-

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(2S)-2-Cyclohexyl-2-fur-2-yI-2-hydroxyacetic acid (3R)-1 -azabicyciot2.2.2]oct-
.3-yl ester;
(2R)-2.Cyciohexyl-2-hydroxy-2-phenylacetic acid I-azabicyclo[2,2.2]oct-4-yl

aster
5

$1. A pharmaceutical composition comprising a compound according to any one of
claims I to 20 In admixture with a pharmaceutically acceptable carder or
dlluent.

10 32. A compound according to any of claims I to 20, a pharmaceutical
composition according to claim 31 for therapeutic tise in a method of treatment
of the human or animal body by therapy.

33. Use of a compound according to. any one of claims I to20, 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.

34. A method of treating a respIratory, urological or gastrointestinal disease or
disorder, which method comprises administering to a human or animal patient In
20.:. need of treatment an effective non-toxic amount of a compound according to
any one of claims I to 20 or a pharmaceutical composition according to claim
31.

35... A combination product comprising
25 (I) a compound according to any one of claims I to 20; and
(iii) another compound effective in the treament 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 I to 20; and.
(iv) a 02 agonist, steroid, antiallergic drug, phosphodlesterase IV inhibitor
and/or leukotriene 04 (LTD4) antagonist
for simultaneous, separate or sequential use In the treatment of a respiratory
35 disease.

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(71) Applicant (for all designated Stales except US): ALMI- European patent (AT, BE, BO, CU, CY, (2, DE, DK, BE,
EALL PRODESFARMA SA. [BS/ES]; Ronda del Gen- ES, Pt, FR, GB, OR, RU, TB, IT, LU, MC, NL, PT, RO,
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(72) Inventors; and

(75) Inventors/Applicants (for US only): PEAT QUINONES, Published: Maria [ESIESI; Calle Andrea Doria, 2, 1° la, E-08003 without international search report and to be republished Barcelona (ES). FERNANDEZ FORNER, Maria, Do- upon receipt ofthat report

MM loss [ES/ES]; Calle Roger de for 221, 50 E-08025

Barcelona (ES). Fortwo-letter codes and other abbreviations, refer to the "Quid-
(74) Agent: SRINJVASAN, Ravi, Chandran; J.A. Kemp ance Notes on Codes andAbbreviations" appearing at the begin-
CO, 14 South Square, Gray’sInn, London WC1R 5JJ (GB). ning ofeach regular issue ofthe PCT Gazette.

(54) Title: NEW PYRROLIDINIUM DERIVATIVES

1’ RI
R4 D

N (CH2), A (CH2)m NcJ" 0 (I)

R2 R3 x

0 (51) Abstract: New pyrrolidinium derivatives having the chemical structure of general formula (I) are disclosed; as well as pro-cesses for their preparation, pharmaceutical compositions comprising them and their use in therapy as antagonists ofM3 muscarinic
receptors.

10)ldr3
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NEW PYRROUDINIUM DERIVATIVES

This invention relates to new therapeutically useful pyrrolidlnlum 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
10 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
15 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 hyperreactMty, asthma, cough and
20 rhinitis; urologlcal disorders such as urinary incontinence, pollakiurla, neurogenic or
unstable bladder, cystospasm and chronic cytitis; gastrointestinal disorders such as
irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagauy induced sinus bradycardia (Chapter 7,
Muscarinic Receptor Agonists and Antagonists, In Goodman and GHman’s The
25 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 13z.agonists, steroids, antiallergic drugs,
30 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):

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CLAIMS

I A compound of formula

(CH A.-(CH2)rn4(J"

R2 R3
5
wherein

B: IS a phenyl, naphthalenyl:5,e,7,ehydmnaphthalenyI, benzo[1,3]dloxoiyl or biphenyl group or a 6t10-membered hSteroaromatic group containing one or more heteroatoms
10 selected from N, 0 or S;

R1, R2 and R3 each independently repreSent a hydrogen or halogen atom, or a hydroxy, phenyl, -OR -SW, -NR5R8, -NHCOR8, -CONR5R, -CN, -NO2, -COOR5 or -CF3 group, or
a straight or branched, optionally substituted lower alkyl group;
15 :
or R1 and 142 together form aromatic or alicydlic ring or a heterocyclic group;

R6 and R° each independently.represeri a hydrogen atom, a Straight or branched,
optionally substituted tower alkyl. group, or together form an ailcyctic ring;
20

.n Is an Integer from 0 to 4; ..

A represents a group selected from -CHr, CHCR7, *.CR’CH, CR’R,-CO., -0-, -S-, .-S(0)-, -S(0)r and -NRT-, wherein R’ and each Independently represent a hydrogen
25. atom, a. straight or branched, optionally substituted lower alkyl group, or together form an alicyclic ring’

rn Is an integer from 0 to 8;

30 R4 represents a lower alkyl group;

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_70 -

wherein R4 and D are as defined in claim 1.

26. A pharmaceutical composition comprising a compound according to any one of claims
5 1 to 20 In admixture with a pharmaceutically acceptable carrier or diluent.

10

27. A compound according to any one of claimsi to 20 for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscaiinic
receptors.

28. Use of a compound according to any one of claims I to 20 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

15 29. Use according to claim 28 wherein the pathological condition is a respiratory,
urological or gastrointestinal disease or disorder.

30. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors,. which comprises
20 administering to said subject an effective amount of a compound as defined in any one of
claims I to 20.

25

31. A method according to claim 30 wherein the pathological condition Is a respiratory, urological or gastrointestinal disease or disorder.

32. A combination product comprising
(i) a compound according to any one of claims ’I to 20; and
(ii) another compound effective In the treament of a respiratory, urological or gastrointestinal disease or disorder
30 for simultaneous, separate or sequential use.

33. A combination product according to claim 32 comprising
(I) a compound according to any one of claims I to 20; and
(ii) a 32 agonist, steroid, antiallergic drug, phosphodiesterase IV Inhibitor and/or
35 leukotriene 04 (LTD4) antagonist

I

SUPERINTENDENCIA DE INDUSTRIA V COMERCIO DIRECCION DE NUEVAS CREACIONES

2020
Bogota, D.C.,

Abogado
EMILIO FERRERO
(Apoderado)

ASUNTO RadicaciOn 06121209
TrÆmite 002
Evento 001
Actuaciôn 430

Oficio U 48
Folios 023

Patente de InvenciOn Eli

Via Nacional El

Patente de Modelo de Utilidad

Via PCT (fase nacional) Ffl Cap.I FRI Cap. H

No. Sol. Internacional PCT/EP2005/005840
Fecha de Presentación Internacional 31-05-2005

Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de Is DecisiOn 486 de Is ComisiOn de Is Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1.Descripci6n: (Folios: 50 a 97) como se radicO inicialmente.

1.2.Reivindicaciones: I a 17 (Folios: 98 a 101) como se radicó
inicialmente.

1.3.Gr6ficas: Folio: 103.

1.4. Prioridad: 31/05/2004 ES P200401312.

2 Anâlisls de la Prioridad:

La prioridad de Is presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

La presente solicitud se titula: "Combinaciones que comprenden agentes antimuscarinicos y corticosteroides".

El objeto de la presente solicitud se refiere a combinaciones de ciertos agentes antimuscarincos con corticosteroides y a su uso en el tratamiento de trastornos respiratorios.

En el capitulo reivindicatorio se reclama to siguiente:

Reivindicaciones I a 3, 12 a 17 (folios: 98, 100 y 101): Una combiriaciôn caracterizada porque comprende (a) un corticosteroide y (b) un antagonista de los receptores muscarinicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-itacetoxi)-1 -(3-fenoxipropil)-1-azoniabiciclo[2.2.2]octano, en forma de una sal que tiene Un anion X, que es un anion farmacØuticamente aceptable de un Æcidomono o polivalente.

Reivindicaciones 4 y 11 (folios: 98 y 100): Un producto caracterizado porque comprende (a) un corticosteroide y (b) un antagonista de los receptores muscarinicos M3 como se define de conformidad con la reivindicaciones I 2, como una preparaciOn combinada para el uso simultÆneo,concurrente, separado o secuencial en el tratamiento de un paciente que sufre de o es susceptible a una enfermedad respiratoria que resporide at antagonismo de M3.

ReivindicaciOn 5 (folios: 98 y 99): Un kit de partes, caracterizado porque comprende (b) un antagonista de receptores muscarinicos M3 como se define de conformidad con la reivindicaciOn I 2 junto con las instrucciones para et uso simultÆneo, concurrente, separado o secuencial en combinaciOn con (a) un corticosteroide.

ReivindicaciOn 6 (folio: 99): Un paquete, caracterizado porque comprende (b) un antagonista de los receptores muscarinicos M3 como se define de conformidad con la reivindicaciOn 16 2 y (a) un corticosteroide para el uso simultªneo, concurrente, separado o secuencial.

Reivindicaciones 7 a 9 (folio: 99): El uso de (b) un antagonista de los receptores muscarinicos M3 de conformidad con la reivindicaciôn 16 2 para la preparaciOn de un medicamento para el uso simultÆneo, concurrente, separado o secuencial en combinaciOn con (a) un corticosteroide.

Reivindicaciones 10 (folios: 100): Un mØtodo de tratamiento de un paciente humano o animal que sufre de o es susceptible a una enfermedad o condiciOn respiratoria que responde at antagonismo de M3, caracterizado el mØtodo porque comprende administrar simultÆnea,concurrente, separado o secuencialmente at paciente una cantidad eficaz de (b) un antagonista de los receptores muscarinicos M3 de conformidad con la reivindicaciOn 16 2y (a) un corticosteroide.

El problema planteado en esta solicitud es la necesidad cilnica para las terapias contra el asma y el COPD con acción potente y selectiva y que tengan un pertH de acciOn ventajoso.

La solución propuesta por la presente solicitud consiste en una combinaciOn que comprende (a) un corticosteroide y (b) un antagonista de los receptores muscarinicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-itacetoxi)-1 -(3-fenoxipropit)-l-azoniabiciclo[2.2.2]octano.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61 K 45/00, 31/439, 31/58, 31/573; A61P 11/00, 11/06, 11/08.

4. Unidad de Invenciôn (artfculo 250486)

Segün Jo anterior la (s) reivindicaciôn (es) 5, 6, 12 a 17 (folios: 98 a 101), que se refiere(n) a un kit de partes y un paquete caracterizado porque comprende (b) un antagonista de los receptores muscarinicos M3 como se define en la reivindicaciOn I
2 y (a) un corticosteroide, no guarda(n) unidad de invenciôn con la reivindicación
1, que se relacionan con una combinación que comprende (a) un corticosteroide y (b)
un antagonista de los receptores muscarinicos M3, puesto que el kit de partes y el
paquete pertenecen a otro sector de la tecnologia. Cabe recordar que Œstos nose
, deben caracterizar por su contenido sino por sus propias caracteristicas tØcnicas.

5. Excepciones de Patentabilidad (artIculo 200486 literal a)-d))

De acuerdo con to anterior, la(s) reivindicaciôn(es): 10 (folio: 100), que se refiere(n) a
mØtodo de tratamiento de un paciente, no es (son) patentable(s) porque los mØtodos
de tratamiento estÆnexceptuados de pateritabilidad.

6. Reivindicaciones retativas a un uso o a un uso distinto (articulos 14 y21 0
486)

La(s) reivindicación (es) 7 a 9 (folio: 99), que se refiere(n) at uso de (b) un antagonista de los receptores muscarinicos M3 como se ha definido en las reivindicaciones I 2 para la preparación de un medicamento para el uso simultÆneo, concurrente, por separado o secuencial en combinación con (a) un corticosteroide no se encuentra(n) dentro del campo de la patentabilidad (productos y procedimientos).

7. Anâtisis de la(s) Oposición(es): (ärticulo 430. 486

No se presentaron oposiciones at objeto reivindicado.

8. Detorminaciôn del Estado de la TØcnica:

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

Fechas de presentación de la solicitud prioritaria: 31-05-2004.

Teniendo en cuenta las fechas indicadas, se buscaron documentos del estado de la tØcnica relacionados, con fecha de publicaciôn anteriores a estas.

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

NO Documento Titulo Fecha de

Publicación

Novel quinuclidine derivatives and 18 de enero de Dl WO 01/04118 medicinal compositions containing 2001 the same
Novel quinuclidine derivatives and -11 de Julio de 02 WO 02/053564 medicinal compositions containing 2002 the same
03 WO 03/087094 New pyrrolidinium derivatives 23 de octubre de2003

9. AnÆlisisde patentabilidad (articulo 14 D486)

9.1. Novedad (articulo 16 D486)

S Comparando elemento por elemento el objeto de esta solicitud con Ia mencionado

en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 06121209, se refiere a:

Una combinaciôn caracterizada porque comprende (a) un corticosteroide y (b) un antagonista de los receptores muscarinicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabiciclo[2.2.2]octanO, en forma de una sal que
tiene un anion X, que es un anion farmacØuticamente aceptable de un Æcido monoo polivalente.

La anterioridad: WO 01/04118 (folios: 129 a 136), se relaciona con: derivados de quinuclidina y composiciones que los contienen; estos compuestos son antagonistas
de los receptores muscarinicos M3 y sirven para el tratamiento de enfermedades respiratorias como por ejemplo la enfermedad obstructiva pulmonar (EPOC a
COPD). Entre los derivados que se mencionan en este documento se encuentra el
compuesto 3(R)-.1 -fenetl-3-(9H-xanten-9-carboniloxi)-1 -azoniabiciclo[2.2.2]octano y
S sus sales como las de bromuro. Este compuesto se puede emplear en combinaciOn con agoriistas 132, esteroides, antialØrgicos o inhibidores de fosfodiesterasa IV.

La anterioridad: WO 02/053564 (folios: 137 a 141), trata sobre: derivados de quinuclidina y composiciones que los contienen. Son agentes antimuscarinicos con
un efecto potente y de larga duraciOn. Estos compuestos se pueden administrar
solos o en combinaciOn con otros fØrmacos para el tratamiento de enfermedades respiratorias, como par ejemplo agonistas 132, esteroides, fÆrmacos antialØrgicos, inhibidores de fosfodiesterasa IV y/o antagonistas de leucotrieno D4 para administrarse en forma simultÆnea, por separado o en forma secuencial para el tratamiento de enfermedades respiratorias.

El elemento caracteristico de las combinaciones reivindicadas, ya era conocido en los documentos Dl y D2; par 10 cual el objeto de las reivindicaciones 1 a 4, 11 a 17

(folios: 98, 100 y 101) no pueden considerarse nuevos.

9.2. Nivel inventivo art1cuI6 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Una combinaciOn caracterizada porque comprende (a) un corticosteroide y (b) un antagonista de los receptores muscarinicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-I -(3-fenoxipropil)-1-azoniabiciclo[2.2.2]octano, en forma de una sal que tiene un anion X, que es un aniOn farmacØuticamente aceptable de un Æcidomono o polivalente.

La anterioridad WO 01/04118 (folios: 129 a 136) menciona derivados de quinuclidina y composiciones que los contienen; estos compuestos son antagonistas de los receptores muscarinicos M3 y sirven para el tratamiento de enfermedades respiratorias como por ejemplo (a enfermedad obstructiva pulmonar (EPOC o COPD). Entre los derivados que se mencionan en este documento se encuentra el compuesto 3(R)-I-fenetl-3-(9H-xanten-9-carboniloxi)-I-azoniabiciclo[2.2.2]octano y sus sales como las de bromuro. Este compuesto se puede emplear en combinaciOn con agonistas 132, esteroides, antialØrgicos o inhibidores de fosfodiesterasa IV.

El documento WO 02/053564 (folios: 137 a 141) se refiere a derivados de quinuclidina y composiciones que los contienen. Son agentes antimuscarinicos con un efecto potente y de larga duración. Estos compuestos se pueden administrar solos o en combinaciOn con otros fÆrmacospara el tratamiento de enfermedades respiratorias, como por ejemplo agonistas 132, esteroides, fÆrrnacos antialØrgicos, inhibidores de fosfodiesterasa IV y/o antagonistas de leucotrieno D4 para administrarse en forma simultÆnea, por separado o en forma secuencial para el tratamiento de enfermedades respiratorias.

La anterioridad WO 03/087094 (folios: 142 a 145) se relaciona con derivados de pirrolidina que son agentes antimuscarinicos M3. Estos compuestos se pueden
administrar solos a en combinaciOn con otros fÆrmacos para el tratamiento de enfermedades de tipo respiratorio como EPOC. Entre los fârmacos que se pueden administrar en el tratamiento estÆn: agonistas 132, esteroides, antialØrgicos,
inhibidores de fosfodiesterasa IV, antagonistas de leucotrieno D4; se administran en
forma simultânea, por separado o de manera secuencial.

S El problems tØcnico planteado en esta solicitud: Is necesidad clinica para las terapias contra el asma y el COPO con acciOn potente y selectiva y que tengan un perfil de
acciOn ventajoso, se habia resuelto previamente mediante combinaciones de antagonistas M3 y corticosteroides ya conocidos(as). Por esta razOn 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) reivindicaciôn(es) I a 4, 11 a 17 de esta solicitud no menciona(n) una caracteristica que conceda un efecto inesperado o especial a las combinaciones, que pueda considerarse como un aporte a la tØcnica, asi que son obvios(as) para una persona versada en (a materia.

AdemØs, puesto que 01-03 y D2-D3 divulgaban previamente compuestos

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antagonistas M3 y sus combinaciones para administrarse en forma simultÆnea, por separado o en forma secuencial junto con corticosteroides para at tratamiento de enfermedades respiratorias (folios: 129 a 145), una persona conocedora de la materia motivada por tal sugerencia lograria el objeto de esta solicitud combinación qua comprende (a) un corticosteroide y (b) un antagonista de los receptores muscarinicos M3 que es 3-(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1 -(3-fenoxipropil)-1 - azoniabicicto[2.2.2]octano; de manera que para una persona medianamente versada en la materia serla obvio emplear estos documentos. Por Jo cual puede no haber Nivel Inventivo.

10. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados as!:

NO Documento NO ReivindicacionesT

afectadas Reqsfto w que afecta
Dl WO 01/04118 1 a4, 11 a 17 T Novedad Nivel Inventivo
02 WO 02/053564 1 a4, 11 a 17 Novedad Nivel Inventivo
D3 WO 03/087094 Ia 4,1 IaI7t Nivel Inventivo

En cumplimiento del articulo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dias contados a partir de la fecha de la notificaciôn de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesiOn, se denegarÆ lapatente.

Notiffquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capitulo quinto del titulo proerofio Circular Unica NO 10 de 2001.

ALIX CARMENZA%ESPEDES DE VERGEL
Directora de tvs Creaciones (c)

El anterior requerimiento fu-.e notificado por fijaciOn en lista, de fecha_______________________

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CONCEPTO TECNICO No. 1257 EXAMINADOR TECNICO - -

COdigo No. 202005