

188

LLOREDA & CIA S. A.

ABOGADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-040024-00003-0000

Fecha: 2007-08-13 17:12:36 Dep. 2020 NUECREACION
Tra. 11 PATENTEYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

BOGOTÁ - COLOMBIA
CIudad FUNDADA EN 1941
AEROPUERTO AEREO 12304
57-1-3264270 57-1-6069700
57-1-3264271 57-1-6069701

ABOGADOS: LLOREDA

CALLE 72 No. 5-83 5º. PISO

www.lloredacamacho.com

jllcco@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-GLAXO GROUP LIMITED.-Solicitud de Patente de Invención
en Fase Nacional PCT para "DERIVADOS DE
FENETANOLAMINA PARA EL TRATAMIENTO DE
ENFERMEDADES RESPIRATORIAS".-Clase C07C 317/22.-
Expediente número 05-040.024.-

1. Me refiero a mi memorial de 29 de Junio de 2005.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **573** de 28 de Febrero de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo II.
4. Anexo me permito acompañar recibo número 07-62.669, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,


ALICIA LLOREDA RICAURTE

T.P. 53.215

1809

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-040024- -00003-0000

Fecha: 2007-08-13 17:12:36 Dep. 2020 NUECREACION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 62,669
FECHA : AGOSTO 3 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	47999435	03/08/2007	3,232,000.00

***** CONCEPTO *****

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

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-40024

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **573** DE

FECHA **28 DE FEBRERO DE 2007** EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL **30 DE MAYO DEL 2007**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ___X___

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number
WO 02/066422 A1(51) International Patent Classification⁷: **C07C 311/29**,
C07D 295/26, C07C 311/27, 311/58, C07D 295/12, A61K
31/18, A61P 11/06

(21) International Application Number: PCT/EP02/01387

(22) International Filing Date: 11 February 2002 (11.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0103630.0 14 February 2001 (14.02.2001) GB
0126998.4 9 November 2001 (09.11.2001) GB(71) Applicant (for all designated States except US): **GLAXO
GROUP LIMITED** [GB/GB]; Glaxo Wellcome House,
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BIGGADIKE,
Keith** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road,
Stevenage, Hertfordshire SG1 2NY (GB). **COE, Di-
ane, Mary** [GB/GB]; GlaxoSmithKline, Gunnels Wood
Road, Stevenage SG1 2NY (GB). **EDNEY, Dean, David**
[GB/GB]; GlaxoSmithKline, Temple Hill, Dartford, Kent
DA1 5AH (GB). **HALTON, Abigail** [GB/GB]; Glaxo-
SmithKline, Temple Hill, Dartford, Kent DA1 5AH (GB).
LOOKER, Brian, Edgar [GB/GB]; GlaxoSmithKline,
Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY
(GB). **MONTEITH, Michael, John** [GB/GB]; Glaxo-
SmithKline, Temple Hill, Dartford, Kent DA1 5AH (GB).**MOORE, Rebecca, Jane** [GB/GB]; GlaxoSmithKline,
Temple Hill, Dartford, Kent DA1 5AH (GB). **PATEL,
Rajnikant** [GB/GB]; GlaxoSmithKline, Temple Hill,
Dartford, Kent DA1 5AH (GB). **PROCOPIOU, Panayi-
otis, Alexandrou** [GB/GB]; GlaxoSmithKline, Gunnels
Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).(74) Agent: **FLORENCE, Julia, Anne**; Corporate Intel-
lectual Property, GlaxoSmithKline, 980 Great West Road
(CN925.1), Brentford, Middlesex TW8 9GS (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),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

— with international search 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.

WO 02/066422 A1

(54) Title: PHENETHANOLAMINE DERIVATIVES FOR TREATMENT OF RESPIRATORY DISEASES

(57) Abstract: The present invention relates to novel compounds of Formula (I), to a process for their manufacture, to pharmaceu-
tical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory
diseases.

WO 02/066422

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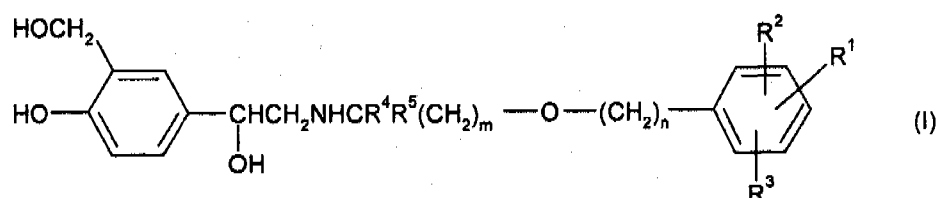
PHENETHANOLAMINE DERIVATIVES FOR TREATMENT OF RESPIRATORY DISEASES

5 The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

10 Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

15 Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

20 According to the present invention, there is provided a compound of formula (I)



25 or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11, preferably from 3 to 7;

with the proviso that m + n is 5 to 19, preferably 5 to 12;

30 R^1 is $-\text{XSO}_2\text{NR}^6\text{R}^7$

wherein X is $-(\text{CH}_2)_p$ - or C_{2-6} alkenylene;

R^6 and R^7 are independently selected from hydrogen, C_{1-6} alkyl,

C_{3-7} cycloalkyl, $\text{C}(\text{O})\text{NR}^8\text{R}^9$, phenyl, and phenyl (C_{1-4} alkyl)-,

35 or R^6 and R^7 , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring,

and R^6 and R^7 are each optionally substituted by one or two groups selected from halo,

C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy-substituted C_{1-6} alkoxy, $-\text{CO}_2\text{R}^8$, $-\text{SO}_2\text{NR}^8\text{R}^9$,

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-CONR⁸R⁹, -NR⁸C(O)R⁹, or a 5-, 6- or 7-membered heterocyclic ring;
R⁸ and R⁹ are independently selected from hydrogen, C₁₋₆alkyl,
C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-; and
p is an integer of from 0 to 6, preferably from 0 to 4;

5

R² and R³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl, and
C₁₋₆haloalkyl; and

10

R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total
number of carbon atoms in R⁴ and R⁵ is not more than 4.

In the compounds of formula (I) the group R¹ is preferably attached to the meta-position relative
to the -O-(CH₂)_n- link.

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R¹ preferably represents -SO₂NR⁶R⁷ wherein R⁶ and R⁷ are independently selected from
hydrogen and C₁₋₆alkyl, more preferably R¹ is -SO₂NH₂.

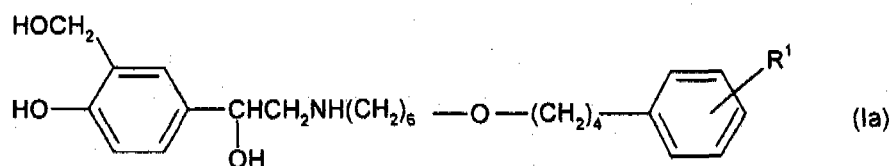
R⁴ and R⁵ are preferably independently selected from hydrogen and methyl, more preferably R⁴
and R⁵ are both hydrogen.

20

m is suitably 4, 5, or 6, and n is suitably 3, 4, 5 or 6. Preferably m is 5 or 6 and n is 3 or 4, such
that m + n is 8, 9 or 10, preferably 9.

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According to a preferred aspect of the invention, there is provided a compound of formula (Ia)

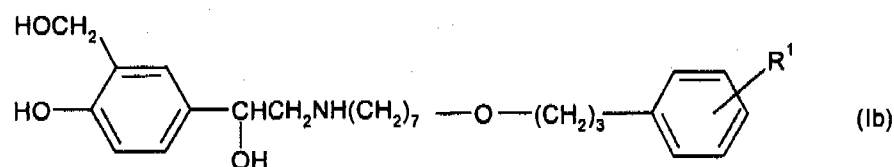


or a salt, solvate, or physiologically functional derivative thereof, wherein

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R¹ is as defined above for formula (I).

According to a further preferred aspect of the invention, there is provided a compound of
formula (Ib)



35



US005091422A

United States Patent [19]

Skidmore et al.

[11] Patent Number: 5,091,422

[45] Date of Patent: Feb. 25, 1992

[54] PHENETHANOLAMINE DERIVATIVES

[75] Inventors: Ian F. Skidmore, Welwyn; Lawrence H. C. Lunts, Broxbourne; Harry Finch, Hitchin; Alan Naylor, Royston, all of England

[73] Assignee: Glaxo Group Limited, London, England

[21] Appl. No.: 541,631

[22] Filed: Jun. 21, 1990

Related U.S. Application Data

[60] Division of Ser. No. 397,664, Aug. 23, 1989, Pat. No. 4,992,474, which is a continuation of Ser. No. 932,359, Nov. 19, 1986, abandoned, which is a continuation of Ser. No. 601,444, Apr. 18, 1984, abandoned.

[30] Foreign Application Priority Data

Apr. 18, 1983 [GB]	United Kingdom	8310477
Jun. 23, 1983 [GB]	United Kingdom	8317087
Nov. 4, 1983 [GB]	United Kingdom	8329568
Jan. 25, 1984 [GB]	United Kingdom	8401889

[51] Int. Cl.³ A01N 33/02

[52] U.S. Cl. 514/653; 514/863; 514/926; 514/927; 514/928

[58] Field of Search 514/653, 551, 653, 211, 514/212

[56] References Cited

U.S. PATENT DOCUMENTS

4,160,036	2/1979	Bradshaw et al.	424/330
4,288,456	9/1981	Sundeen et al.	424/330
4,985,459	1/1991	Sunshine et al.	514/561
4,990,505	2/1991	Skidmore et al.	514/211

OTHER PUBLICATIONS

Champion, BMJ, 4 pp. 730-732 (1973).
Kennes et al., Clin. Allergy, 7, pp. 35-39 (1977).
Das et al., Br. J. Dermatol., 99 pp. 197-200 (1978).

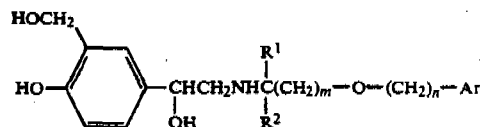
Primary Examiner—Frederick E. Waddell

Assistant Examiner—T. J. Criares

Attorney, Agent, or Firm—Morgan & Finnegan

[57] ABSTRACT

Phenethanolamine derivatives are disclosed of formula



wherein

m is 2 to 8;

n is 1 to 7 provided that m+n is 4 to 12;

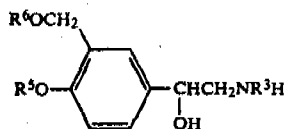
Ar is phenyl or phenyl substituted by one or two halogen atoms, alkyl or alkoxy groups or by an alkylene-dioxy group;

R¹ and R² are hydrogen or alkyl provided that the sum total of carbon atoms in R¹ and R² is not more than 4;

and the physiologically acceptable salts and solvates thereof.

The compounds have a selective stimulant action at B₂-adrenoreceptors and may be used inter alia in the treatment of diseases associated with reversible airways obstructions such as asthma and chronic bronchitis. The compounds may be formulated in conventional manner as pharmaceutical compositions with physiologically acceptable carriers or excipients.

The compounds may be prepared, for example by alkylation of an amine:



where R³, R⁵ and R⁶ is hydrogen or a protecting group, followed by removal of any protecting group.

12 Claims, No Drawings

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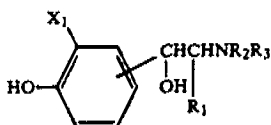
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PHENETHANOLAMINE DERIVATIVES

This is a divisional of co-pending application Ser. No. 07/397,664 filed Aug. 23, 1989 now U.S. Pat. No. 4,992,474, which is a continuation of 06/932,359 filed Nov. 19, 1986 now abandoned which is a continuation of Ser. No. 06/601,444 filed on Apr. 18, 1984 now abandoned.

This invention relates to phenethanolamine compounds having a stimulant action at β_2 -adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Certain phenethanolamine compounds are known to possess either stimulant or blocking actions at β -adrenoreceptors. For example, British Patent Specification No. 1200886 describes a group of such phenethanolamines of general structure:

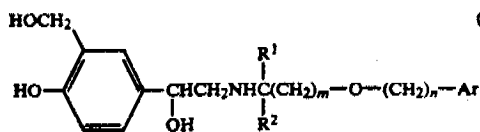


where, inter alia, X_1 is hydroxyalkyl, R_1 and R_2 is each a hydrogen atom, and R_3 is straight or branched C_{1-6} alkyl, aralkyl or aryloxyalkyl. One compound from within this particular group has been developed for clinical use. This is salbutamol [(α^1 -tert-butylaminomethyl)-4-hydroxy-m-xylene- α^1, α^3 -diol; $X_1 = CH_2OH$, $R_1 = -H$; $R_2 = -H$; $R_3 = t$ -butyl, above] which at the present time is widely prescribed for the treatment of conditions such as bronchial asthma and chronic bronchitis. The success of salbutamol devolves from its profile of action, in particular its potency, coupled with a selective stimulant action at β_2 -adrenoreceptors.

All β_2 -stimulants currently used in clinical practice suffer from the disadvantage that they have a relatively short duration of action when administered by inhalation. A β_2 -stimulant with a relatively long duration of action would therefore offer a significant advance in the treatment of bronchial asthma and related disorders.

In a search for new β -stimulants with advantageous properties, we have now found a novel group of phenethanolamine derivatives, which differ structurally from the group of compounds described in British Patent Specification No. 1200886, and which in our tests have shown a potent selective stimulant action at β_2 -adrenoreceptors, and, in addition, have an advantageous profile of action.

Thus, the present invention provides compounds of the general formula (I)



wherein

m is an integer from 2 to 8 and
 n is an integer from 1 to 7 with the proviso that the sum total of $m+n$ is 4 to 12;

Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, C_{1-3} alkyl or C_{1-3} alkoxy groups, or by an

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alkylenedioxy group of formula $-O(CH_2)_pO-$ where p is 1 or 2; and

R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It will be appreciated that the compounds of general formula (I) possess one or two asymmetric carbon atoms, namely the carbon atom of the



group and, when R^1 and R^2 are different groups, the carbon atom to which these group are attached.

The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the



group is in the R configuration are preferred.

In the general formula (I), the chain $-(CH_2)_m-$ may be, for example, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$ or $-(CH_2)_7-$, and the chain $-(CH_2)_n-$ may be, for example, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$ or $(CH_2)_6-$.

Preferably the sum total of the number of carbon atoms in the chains $-(CH_2)_m-$ and $-(CH_2)_n$ is 6 to 12 inclusive and may be, for example, 7, 8, 9 or 10. Compounds wherein the sum total of $m+n$ is 7, 8 or 9 are particularly preferred.

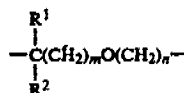
Preferred compounds of general formula (I) are those wherein m is 3 and n is 6, or m is 4 and n is 3, 4 or 5, or m is 5 and n is 2, 3, 4 or 5, or m is 6 and n is 2 or 3.

R^1 and R^2 , for example, may each be methyl, ethyl, propyl, or isopropyl groups except that if one of R^1 and R^2 is a propyl or isopropyl group, the other is a hydrogen atom or a methyl group. Thus, for example, R^1 may be a hydrogen atom or a methyl, ethyl or propyl group. R^2 , for example, may be a hydrogen atom or a methyl group.

R^1 and R^2 are each preferably a hydrogen atom or a methyl group.

A preferred group of compounds is that wherein R^1 and R^2 are both hydrogen atoms. In another preferred group of compounds R^1 is a hydrogen atom and R^2 is a C_{1-3} alkyl group, particularly a methyl group. In yet another preferred group of compounds R^1 and R^2 are both methyl groups.

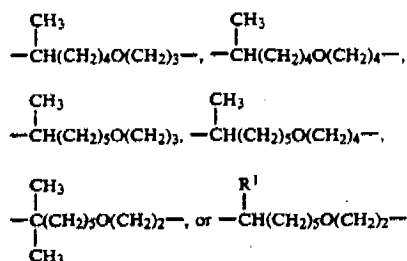
The chain



in general formula (I) may be, for example $-(CH_2)_4O(CH_2)_4-$, $(CH_2)_5O(CH_2)_2-$, $-(CH_2)_5O(CH_2)_3-$, $-(CH_2)_5O(CH_2)_4-$,

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methyl, ethyl or propyl.

Examples of the optional substituents which may be present on the phenyl group represented by Ar include bromine, iodine or, in particular, chlorine or fluorine atoms, or methyl, ethyl, methoxy or ethoxy groups. In general, Ar is preferably an unsubstituted phenyl group. According to another preference, Ar is a phenyl group substituted by one substituent, particularly a fluorine or chlorine atom or a methoxy or methyl group.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxybenzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, p-toluenesulphonates, methanesulphonates, ascorbates, salicylates, acetates, fumarates, succinates, lactates, glutarates, gluconates, tricarballates, hydroxynaphthalenecarboxylates e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenecarboxylates, or oleates. The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium and magnesium) salts.

The compounds according to the invention have a selective stimulant action at β_2 -adrenoreceptors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the guinea-pig, where compounds were shown to cause relaxation of PGF $_{2\alpha}$ -contracted isolated trachea. In another test, compounds of the invention were shown to afford protection against histamine-induced broncho-constriction when administered by inhalation or by an oral route in conscious guinea-pigs. In both tests, compounds according to the invention have shown a particularly long duration of action. The selective action of compounds of the invention was demonstrated in the rat or guinea pig. Where compounds were shown to have little or no effect on isolated rat or guinea pig left atria (β_1 -adrenoreceptor tissues) at concentrations where they cause relaxation of PGF $_{2\alpha}$ -contracted isolated trachea. Compounds according to the invention have also been shown to inhibit the anaphylactic release of spasmogens and inflammagens from sensitised human tissues e.g. lung fragments.

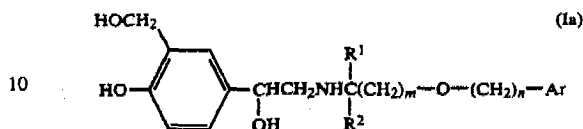
The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

The compounds according to the invention may also be used for the treatment of premature labour, depression and congestive heart failure, and are also indicated as useful for the treatment of inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma, and in the treatment of conditions in which there

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is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

A particularly important group of compounds by virtue of the advantageously long duration of action they have shown in our tests, has the formula (Ia):



in which

R^1 and R^2 are as defined for general formula (I);

m is an integer from 3 to 6,

n is an integer from 2 to 6,

and Ar is phenyl or phenyl substituted by a methoxy or methyl group, or more preferably a fluorine or chlorine atom, and the physiologically acceptable salts and solvates thereof, in each instance the sum total of carbon atoms in the chains $-(\text{CH}_2)_m-$ and $-(\text{CH}_2)_n-$ being an integer from 7 to 10 inclusive, in particular 7, 8 or 9.

A preferred group of compounds of formula (Ia) is that wherein R^1 and R^2 is each a hydrogen atom.

In another preferred group of compounds of formula (Ia) R^1 is a hydrogen atom or a methyl group and R^2 is a methyl group.

In a further group of compounds of formula (Ia) R^1 and R^2 each is a hydrogen atom and Ar is phenyl or phenyl substituted by a methoxy group, or more preferably a fluorine or chlorine atom.

A particularly preferred group of compounds has the formula (Ia) in which R^1 and R^2 each is a hydrogen atom or a methyl group, m is 4 or 5, n is 2, 3 or 4, and Ar is phenyl or phenyl substituted by a chlorine or fluorine atom or a methoxy or methyl group and the physiologically acceptable salts and solvates thereof.

Particularly important compounds are:

4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[6-(3-phenylpropoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[5-(4-phenylbutoxy)pentyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[1-methyl-6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[1-methyl-5-(3-phenylpropoxy)pentyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[1-methyl-5-(4-phenylbutoxy)pentyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

4-hydroxy- α^1 -[[[1-ethyl-6-(2-phenylethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

α^1 -[[[1,1-dimethyl-6-(2-phenylethoxy)hexyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol; and the physiologically acceptable salts thereof;

197

(12) **UK Patent Application** (19) **GB** (11) **2 140 800 A**

(43) Application published 5 Dec 1984

(21) Application No **8410124**

(22) Date of filing **18 Apr 1984**

(30) Priority data

(31) 8310477	(32) 18 Apr 1983	(33) GB
8317087	23 Jun 1983	
8329568	4 Nov 1983	
8401889	25 Jan 1984	

(51) INT CL³

C07C 93/00 A61K 31/135 // C07C
33/20 43/02 47/277 49/255 59/58
97/10 103/30 C07D 319/20

(52) Domestic classification

C2C 1494 1691 200 202 213 220 226 227 22Y 236
246 247 248 253 259 25Y 282 294 29X 29Y 304
30Y 311 313 314 315 31Y 321 322 323 32Y 335
338 339 342 348 34Y 350 351 355 35Y 360 361
362 364 365 366 367 368 36Y 388 401 409 40Y
43X 449 456 45X 45Y 46Y 496 500 509 50Y 593
620 623 624 625 628 62X 633 634 643 650 652
655 658 659 65X 662 665 668 675 682 697 699
69Y 770 779 802 80Y AA BX KQ LF LJ LM LS TB UQ
WD WP WS
U1S 1318 C2C

(71) Applicant

Glaxo Group Limited (United Kingdom),
Clarges House, 6-21 Clarges Street, London
W1Y 8DH

(72) Inventors

Ian Frederick Skidmore
Lawrence Henry Charles Lunts
Harry Finch
Alan Naylor

(56) Documents cited

GB 1529972 **GB 1200886**

(58) Field of search

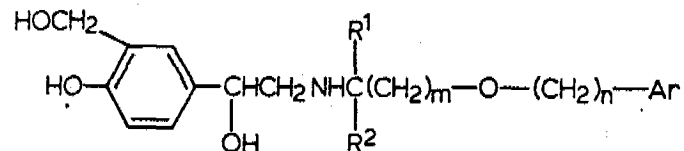
C2C

(74) Agent and/or Address for Service

Elkington and Fife,
High Holborn House, 52/54 High Holborn, London
WC1V 6SH

(54) **Phenethanolamine derivatives**

(57) Phenethanolamine derivatives are disclosed of formula



wherein m is 2 to 8; n is 1 to provided that m + n is 4 to 12;

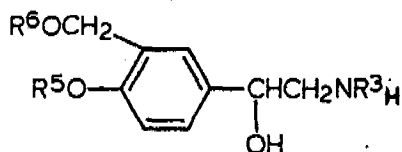
Ar is phenyl or phenyl substituted by one or two halogen atoms, alkyl or alkoxy groups or by an alkylendioxy group;

R¹ and R² are hydrogen or alkyl provided that the sum total of carbon atoms in R¹ and R² is not more than 4;

and the physiologically acceptable salts and solvates thereof.

The compounds have a selective stimulant action at β_2 -adrenoreceptors and may be used inter alia in the treatment of diseases associated with reversible airways obstructions such as asthma and chronic bronchitis. The compounds may be formulated in conventional manner as pharmaceutical compositions with physiologically acceptable carriers or excipients.

The compounds may be prepared, for example by alkylation of an amine:



where R³, R⁵ and R⁶ is hydrogen or a protecting group, followed by removal of any protecting group.

GB 2 140 800 A

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

2020
Bogotá, D.C.,

Abogada
ALICIA LLOREDA RICAURTE
(Apoderado)

ASUNTO	Radicación	05040024
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	Nº 5951
	Folios	014

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/EP2003/012035
Fecha de Presentación Internacional 24-10-2003

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: 37 a 155) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 21 (Folios: 156 a 168) como se radicó inicialmente.

1.3. Prioridad: 28/10/2002 y 28/10/2002, GB 0225022.3 y GB 0225028.0.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

La presente solicitud se titula: "Derivados de fenetanolamina para el tratamiento de enfermedades respiratorias".

El objeto de la presente solicitud se refiere a derivados de fenetanolamina, procesos para su preparación, composiciones que los contienen y su uso en medicina,

particularmente en la profilaxis y tratamiento de enfermedades respiratorias.

De acuerdo con la descripción, en la técnica son conocidos ciertos compuestos de fenetanolamina como que tienen una acción estimulante selectiva en los adreno-receptores- β_2 y por lo tanto, tienen utilidad en el tratamiento del asma bronquial, y las enfermedades relacionadas. Por lo tanto, la patente GB 2140800 describe compuestos de fenetanolamina que incluyen xinafoato del salmeterol, el cual es utilizado clínicamente en la actualidad en el tratamiento de dichos padecimientos médicos.

Aunque el salmeterol y otros agonistas de β_2 -adreno-receptor disponibles comercialmente son broncodilatadores efectivos, la duración de la acción es de aproximadamente 12 horas, de ahí que con frecuencia se requiere una dosificación de dos veces por día.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 14, 16 (folios: 156 a 163): Un compuesto de la fórmula (I), o una sal, solvato o un derivado fisiológicamente funcional del mismo.

Reivindicación 15 (folios: 162 y 163): Un método para la profilaxis o tratamiento de un padecimiento clínico en un mamífero, tal como un humano, para el cual está indicado un agonista selectivo del β_2 -adreno-receptor.

Reivindicación 17 (folio: 163): Una formulación farmacéutica que comprende un compuesto de la fórmula (I) o (Ia) y un vehículo o excipiente farmacéuticamente aceptable y opcionalmente uno o más de otros ingredientes terapéuticos.

Reivindicación 18 (folio: 163): Una combinación que comprende un compuesto de la fórmula (I) o (Ia) y uno o más de otros agentes terapéuticos.

Reivindicación 19 (folio: 164): El uso de un compuesto de la fórmula (I) o (Ia),... en la fabricación de un medicamento para la profilaxis o tratamiento de un padecimiento clínico para el cual está indicado un agonista selector del β_2 -adreno-receptor.

Reivindicación 20 (folios: 164 a 168): Un proceso para la preparación de un compuesto de la fórmula (I) o (Ia) o una sal, solvato, o un derivado fisiológicamente funcional del mismo.

Reivindicación 21 (folio: 168): Un intermediario seleccionado de un compuesto de la fórmula (II) (III) (IV) (X) y (XIX).

El problema planteado en esta solicitud es la necesidad clínica de compuestos que tengan una acción estimulante potente y selectiva en los β_2 -adreno-receptores, y que tenga un perfil de acción provechoso.

La solución propuesta por la presente solicitud consiste en compuestos de fenetanolamina de fórmula I.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/145; C07C 317/22; A61P 11/00.

4. De la solicitud de Patente

4.1. Descripción (artículo 28 D. 486)

De acuerdo con lo revelado en la descripción, el título de la solicitud se debe hacer más específico al tipo de compuestos que se reclaman y no hacer alusión a su uso terapéutico.

4.2. Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio, hay términos que no son claros ni concisos como por ejemplo: "derivado fisiológicamente funcional del mismo" (no se comprende cuál derivado, qué fórmula química tiene, etc.), "anillo heterocíclico" (no se dice cuál o cuáles heteroátomos tiene y en qué posiciones y sitio de unión al núcleo principal), "combinación farmacéutica" (no se encuentra la forma farmacéutica en que se puede encontrar, o si se trata de dos formas farmacéuticas en que en una está un principio activo y en la otra, otro fármaco), "uno o más agentes terapéuticos" (no se dice cuál o cuáles y cuántos exactamente).

La reivindicación 21 (folio: 168) debería hacerse dependiente de una reivindicación de compuesto para que no se vea desligada del objeto que se reclama.

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

De acuerdo con lo anterior, la(s) reivindicación(es): 15 (folios: 162 y 163), que se refiere(n) a un método para la profilaxis o tratamiento de un padecimiento clínico en un mamífero, tal como un humano, para el cual está indicado un agonista selectivo del β 2-adreno-receptor, no es (son) patentable(s) porque es un método de tratamiento.

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

La(s) reivindicación (es) 19 (folio: 164), que se refiere(n) a uso de un compuesto de la fórmula (I) o (Ia),... en la fabricación de un medicamento para la profilaxis o tratamiento de un padecimiento clínico para el cual está indicado un agonista selector del β 2-adreno-receptor, 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 28-10-2002.

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

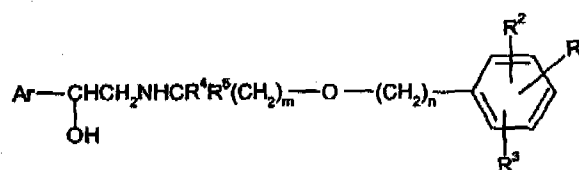
Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO 02/066422	Phenethanolamine derivatives for treatment of respiratory diseases	29 de agosto de 2002
D2	US 5091422	Phenethanolamine derivatives	25 de febrero de 1992
D3	GB 2140800	Phenethanolamine derivatives	5 de diciembre de 1984

9. Análisis de patentabilidad (artículo 14 D486)

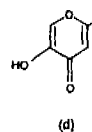
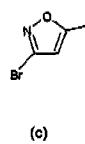
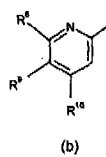
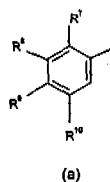
9.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Derivado de fenetanolamina de fórmula I, o una sal, solvato o un derivado fisiológicamente funcional del mismo.

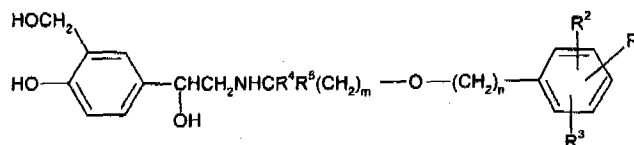


Donde

- R^1 es SR^6 , SOR^6 , SO_2R^6 ; donde R^6 es un grupo cicloalquilo C_{3-7} o cicloalquenoilo C_{3-7} .
- R^2 y R^3 son seleccionados independientemente de hidrógeno, alquilo C_{1-6} , alcoxi C_{1-6} , halo, fenilo y haloalquilo C_{1-6} .
- R^4 y R^5 son seleccionados independientemente de hidrógeno y alquilo C_{1-4} con la condición de que el número total de átomos de carbono en R^4 y R^5 no sea mayor de 4.
- Ar es un grupo seleccionado de:



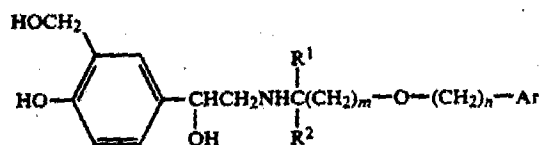
La anterioridad WO 02/066422 (folios: 191 a 193) se relaciona con derivados de fenetanolamina para el tratamiento de enfermedades respiratorias y que tienen la fórmula:



Donde:

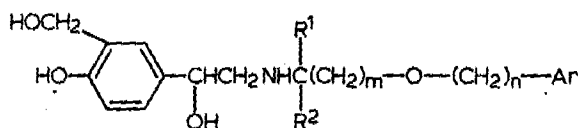
- R^1 puede ser $SO_2NR^6R^7$
- R^2 y R^3 son independientemente seleccionados de alquilo C_{1-6} , alcoxi C_{1-6} , halo, fenil y haloalquil C_{1-6} .
- R^4 y R^5 son independientemente seleccionados de hidrógeno y alquil C_{1-4} .

El documento US 5091422 (folios: 194 a 196) se refiere a derivados de fenetanolamina para el tratamiento de enfermedades asociadas con obstrucciones de vías aéreas como el asma y bronquitis crónica.



Donde: Ar es fenil o fenil sustituido por uno o dos halógenos, alquil o alcoxi o por alquilendioxi.

El documento GB 2140800 (folios: 197 y 198) menciona derivados de fenetanolamina que tienen actividad para el tratamiento de enfermedades tipo asma y bronquitis y tienen la fórmula:



Donde Ar es fenil o fenil sustituido por un metoxi o grupo metil, fluor o cloro.

Estos documentos revelan compuestos químicos muy semejantes a los compuestos de la presente solicitud; solo hay diferencia en la sustitución del grupo fenilo de la presente solicitud, que tiene los grupos R1, R2 y R3. No obstante, la actividad farmacológica sigue siendo la misma por lo cual no se observa un salto tecnológico importante gracias a estos sustituyentes, en especial, de R1. Además, ya estaba sugerido por el estado de la técnica que este grupo R1 es un sustituyente que tiene azufre y ni se observa a lo largo de la presente solicitud datos comparativos que demuestren que hay un cambio significativo en la actividad farmacológica de este tipo de compuestos, frente a lo que se encuentra en el estado del arte.

El problema técnico planteado en esta solicitud: a necesidad clínica de compuestos que tengan una acción estimulante potente y selectiva en los β_2 -adreno-receptores, y que tenga un perfil de acción provechoso, se había resuelto previamente mediante derivados de fenetanolamina ya conocidos(as). Por esta razón se considera que las sustituciones de las fenetanolaminas reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

La reivindicación 1 de esta solicitud no menciona una característica que conceda un efecto inesperado o especial a los compuestos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1, D2, D3 divulgaban previamente derivados de fenetanolamina (folios: 191 a 198), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud derivados de fenetanolamina; de manera que para una persona medianamente versada en la materia sería obvio utilizar 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 02/066422	1 a 14, 16, 17, 18, 20	Nivel Inventivo
D2	US 5091422	1 a 14, 16, 17, 18, 20	Nivel Inventivo
D3	GB 2140800	1 a 14, 16, 17, 18, 20	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 CÉSPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 22 MAYO 2009

CONCEPTO TÉCNICO No. 1534	EXAMINADOR TÉCNICO Código No. 202005
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