

CAVELIER

ABOGADOS

www.cavelier.com
cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTÁ 8, COLOMBIA

Teléfono: (57-1) 347 3611
Telefax: (57-1) 211 8650
(57-1) 700 4814
Fax in U.S.A.: (1-305) 675 7743

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-122625- -00008-0000

Fecha: 2011-10-13 16:58:10 Dep. 2020 DIR.NUEVASC
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 16

Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 329

Referencia : Expediente No. 07122625
Asunto : Solicitud de patente para: **DERIVADOS FLUORADOS DE 4-(AMINO-1-HIDROXIETIL)-FENOL COMO AGONISTAS DEL RECEPTOR β 2-ADRENÉRGICO**
Solicitante : ALMIRALL, S.A.
Fecha solicitud : 20 de noviembre de 2007

1. Yo, Oscar CORREA, en mi condición de apoderado de la sociedad solicitante de la patente de la referencia, me refiero a la respuesta presentada al oficio No. **8767** y radicada el día 29 de julio de 2011.

2. En este sentido, deseamos complementar la información y los argumentos presentados en el memorial radicado el 29 de julio de 2011, por cuanto resulta relevante para este caso la concesión de la patente equivalente en Europa y para la cual el Examinador Europeo emitió la misma objeción sobre el nivel inventivo. La objeción mencionada fue superada empleando los mismos argumentos presentados en respuesta al oficio No. **8767**.

Junto con el presente memorial presentamos copia de la primera hoja y de las reivindicaciones en inglés de la patente europea para mejor referencia. Adicionalmente, se adjunta copia de la respuesta presentada ante la Oficina Europea de Patentes, junto con el anexo de datos experimentales, en donde se pueden observar los argumentos que permitieron superar la objeción arriba mencionada.

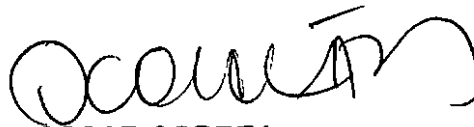
Finalmente, se adjunta una carta de solicitud de corrección de la publicación de concesión ya que la Oficina Europea de patente erróneamente no incluyó toda la lista de los ejemplos en la versión inglesa de la reivindicación 14, aunque se ve claramente la lista de todos los ejemplos de la reivindicación 14 en la versión francesa y alemana, y también en la descripción.

La anterior información constituye un indicio adicional del nivel inventivo para la presente solicitud y el cual atentamente solicitamos tener en cuenta al momento de realizar un nuevo análisis de patentabilidad.

3. Anexos

- Anexo 1: Copia de la primera hoja y reivindicaciones en inglés de la patente europea equivalente
- Anexo 2: Respuesta presentada ante la Oficina Europea de Patentes, junto con los argumentos que permitieron superar la objeción de nivel inventivo y los datos experimentales
- Anexo 3: Carta solicitando corrección de la publicación de la patente

Señor Director,



OSCAR CORREA

C.C. 79.524.634 de Bogotá

T.P.A. No. 71.027

COLO-17153-845-001-5
COLO-06734-841-004-3
JMS\JMS\ID-202767\WPC17153
No. M-2011-202767\JMS

(19)



(11)

EP 1 885 684 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
13.07.2011 Bulletin 2011/28

(21) Application number: 06742964.7

(22) Date of filing: 17.05.2006

(51) Int Cl.:

C07C 217/10^(2006.01) C07C 217/26^(2006.01)
C07C 233/43^(2006.01) C07C 275/32^(2006.01)
C07D 215/26^(2006.01) C07D 233/74^(2006.01)
A61K 31/135^(2006.01) A61K 31/415^(2006.01)
A61K 31/47^(2006.01) A61P 11/00^(2006.01)

(86) International application number:
PCT/EP2006/004680

(87) International publication number:
WO 2006/122788 (23.11.2006 Gazette 2006/47)

(54) DERIVATIVES OF 4-(2-AMINO-1-HYDROXYETHYL)PHENOL AS AGONISTS OF THE BETA-2
ADRENERGIC RECEPTOR

DERIVATE VON 4-(2-AMINO-1-HYDROXYETHYL)PHENOL ALS AGONISTEN DES BETA-2-
ADRENERGEN REZEPTORS

DERIVES DE 4-(2-AMINO-1-HYDROXYETHYL)PHENOL AGONISTES DU RECEPTEUR
ADRENERGIQUE BETA-2

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR
Designated Extension States:
AL BA HR MK YU

(30) Priority: 20.05.2005 ES 200501229

(43) Date of publication of application:
13.02.2008 Bulletin 2008/07

(60) Divisional application:
10010410.8 / 2 263 998

(73) Proprietor: Almirall, S.A.
08022 Barcelona (ES)

(72) Inventors:
• PUIG DURAN, Carlos
E-08024 Barcelona (ES)
• CRESPO CRESPO, Maria, Isabel
E-08036 Barcelona (ES)
• CASTRO PALOMINO LARIA, Julio, Cesar
E-08330 Premià de Mar (ES)
• GUAL ROIG, Silvia
E-08349 Cabrera de Mar (ES)

• NAVARRO ROMERO, Eloisa
E-08011 Barcelona (ES)

(74) Representative: Srinivasan, Ravi Chandran
J.A. Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

(56) References cited:
GB-A- 2 140 800 GB-A- 2 160 863

- ISMAIL F M D: "Important fluorinated drugs in experimental and clinical use" JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER SEQUIA, LAUSANNE, CH, vol. 118, no. 1-2, 1 December 2002 (2002-12-01), pages 27-33, XP004393604 ISSN: 0022-1139
- SMART B E: "Fluorine substituent effects (on bioactivity)" JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER SEQUIA, LAUSANNE, CH, vol. 109, no. 1, June 2001 (2001-06), pages 3-11, XP004246489 ISSN: 0022-1139

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

with an esophageal cannula (Venocath-14, Venisystems) connected to Celesco transducer. Once the cannulations were completed a Mumed pulmonary measurement computer program enabled the collection of pulmonary values. The baseline values were within the range of 0.3-0.9 mL/cm H₂O for compliance and within the range of 0.1-0.199 cm H₂O/mL per second for lung resistance (R_L).

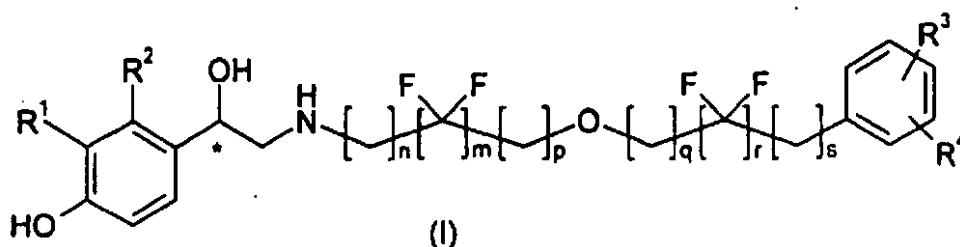
[0360] The bronchoprotective effect of inhaled compounds was determined with the concentration of the test compound causing a 50 % of inhibition of bronchoconstriction (EC₅₀) induced by acetylcholine at 30 µg/kg iv

Determination of duration of action

[0361] Exemplified compounds of this invention show long duration of action.

Claims

1. A compound of formula (I):



wherein:

- R¹ is a group selected from -CH₂OH, -NHC(O)H and
- R² is a hydrogen atom; or
- R¹ together with R² form the group -NH-C(O)-CH=CH- wherein the nitrogen atom is bound to the carbon atom in the phenyl ring holding R¹ and the carbon atom is bound to the carbon atom in the phenyl ring holding R²
- R³ is selected from hydrogen and halogen atoms or groups selected from -SO-R⁵, -SO₂-R⁵, -NH-CO-NH₂, -CO-NH₂, hydantoino, C₁₋₄alkyl, C₁₋₄alkoxy and -SO₂NR⁵R⁶,
- R⁴ is selected from hydrogen atoms, halogen atoms and C₁₋₄alkyl groups
- R⁵ is a C₁₋₄alkyl group or C₃₋₈ cycloalkyl
- R⁶ is independently selected from hydrogen atoms and C₁₋₄alkyl groups
- n, p and q are independently 0, 1, 2, 3 or 4
- m and s are independently 0, 1, 2 or 3
- r is 0, 1 or 2

with the provisos that:

- at least one of m and r is not 0
- the sum n+m+p+q+r+s is 7, 8, 9, 10, 11, 12 or 13
- the sum q+r+s is 2, 3, 4, 5 or 6

or a pharmaceutically-acceptable salt, solvate or stereoisomer thereof.

2. A compound according to claim 1 wherein at least one of m and r is 1.
3. A compound according to claim 2 wherein the sum m+r is 1.
4. A compound according to any preceding claim wherein the sum n+m+p+q+r+s is 8, 9 or 10.
5. A compound according to any preceding claim wherein the sum q+r+s is 2, 3 or 4.
6. A compound according to any preceding claim wherein s is an integer selected from 0 and 1.

EP 1 885 684 B1

7. A compound according to any preceding claim wherein the sum $n+p$ is 4, 5 or 6.
8. A compound according to any preceding claim wherein the sum $q+s$ is 1, 2, 3 or 4.
- 5 9. A compound according to any preceding claim wherein R^3 is a hydrogen atom, a halogen atom or a methyl group.
10. A compound according to claim 9 wherein R^3 is a chlorine or fluorine atom.
11. A compound according to claim 9 wherein R^3 is a methyl group.
- 10 12. A compound according to any preceding claim wherein R^4 is a hydrogen atom.
13. A compound according to anyone of claims 1 to 11 wherein R^4 is a chlorine atom.
- 15 14. A compound according to claim 1 selected from the group consisting of:

 (R, S)-4-(2-([6-(2,2-Difluoro-4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
 (R,S)-4-(2-([6-(2,2-Difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
- 20 15. A compound according to any one of claims 1 to 14 for use in the treatment of the human or animal body.
16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to anyone of claims 1 to 14 and a pharmaceutically acceptable carrier.
- 25 17. The pharmaceutical composition of claim 16, wherein the composition further comprises a therapeutically effective amount of one or more other therapeutic agents.
18. The pharmaceutical composition of claim 17 wherein the other therapeutic agent is a corticosteroid, an anticholinergic agent, or a PDE4 inhibitor
- 30 19. The pharmaceutical composition according to anyone of claims 16 to 18, wherein the composition is formulated for administration by inhalation.
20. A combination comprising a compound according to anyone of claims 1 to 14 and one or more other therapeutic agents.
- 35 21. The combination of claim 20 wherein the other therapeutic agent is a corticosteroid, an anticholinergic agent, or a PDE4 inhibitor.
- 40 22. A compound as defined in any one of claims 1 to 14 for use in treating a disease or condition associated with β_2 adrenergic receptor activity in a mammal.
23. A compound according to claim 22 wherein the disease or condition is selected from the group consisting of pulmonary disease, pre-term labor, glaucoma, neurological disorders, cardiac disorders, and inflammation.
- 45 24. A compound according to claim 23 wherein the pulmonary disease is asthma or chronic obstructive pulmonary disease.
25. Use of a compound according to any one of claims 1 to 14 in the manufacture of a medicament for treating a disease or condition as defined in any one of claims 22 to 24.
- 50

Patentansprüche

- 55 1. Verbindung der Formel (I):

J.A.KEMP & CO.

BY FAX & DHL COURIER

EPO - Munich
2314 SOUTH SQUARE, GRAY'S INN
LONDON WC1R 5JJThe European Patent Office
Erhardtstrasse 27
D-80469 Munich
Germany

10. Nov. 2008

TELEPHONE: + 44 20 7405 3292
FACSIMILE: + 44 20 7242 8932
E-MAIL: mail@jakemp.com
WEBSITE: www.jakemp.com

7 November 2008

Dear Sirs

European Patent Application No. 06742964.7-1211
LABORATORIOS ALMIRALL, S.A.
Our Ref: N.98195A - RCS/AJN/ejb

I reply to the Communication dated 30 June 2008. Please replace page 1 and 96 currently on file with new retyped pages 1, 1a and 96 enclosed herewith. To assist the Examiner, I also enclose a copy of original pages 1 and 96 showing the changes made in manuscript.

Amendments

A passage has been added at page 1 to acknowledge D1 and D2.

Claim 15 has been amended to be formally dependent on claim 1.

Section 1 of the Communication: Inventive Step

As the Examiner points out, the compounds described in D1 and D2 differ from the compounds of the present invention in that the compounds of the present invention are fluorinated, whereas the D1 and D2 compounds are not. Specifically, $-CH_2-$ groups in the compounds disclosed in D1 and D2 are replaced by $-CF_2-$ groups in the compounds of the present invention.

Before considering in detail the technical effect of this structural variation between the compounds of the present invention and those disclosed in the prior art, it may be helpful to review briefly the

OXFORD OFFICE · MAGDALEN CENTRE · THE OXFORD SCIENCE PARK · OXFORD OX4 4GA
TELEPHONE: + 44 1865 784760 · FACSIMILE: + 44 1865 784775MUNICH OFFICE · BAYER KARREE · BAYERSTRASSE 83 · D-80335 MÜNCHEN · GERMANY
TELEPHONE: + 49 89 24 22 97 340 · FACSIMILE: + 49 89 24 22 97 350M L S AYERS, BSC, EPA, CPA.
G C WOODS, MA, EPA, CPA.
T A CRESSWELL, BSC, EPA, CPA.
M A MARSHALL, BSC, EPA, CPA.*^Δ
A J WEBB, MA, EPA, CPA.^Δ
M J NICHOLLS, MA, EPA, CPA.^Δ
N J K PRICE, BSC, EPA, CPA.^Δ
C M KEEN, MA, EPA, CPA.
J G LEEMING, MA, EPA, CPA.
S L SMITH, MA, EPA, CPA.
J E BENSON, BSC, EPA, CPA.
DR. T J DUCKWORTH, EPA, CPA.S M WRIGHT, BSC, EPA, CPA.^Δ
P J H CAMPBELL, MA, EPA, CPA.
C H MERRYWEATHER, BA, EPA, CPA.
S E ROQUES, MA, EPA, CPA.^Δ
A BENTHAM, MA, EPA, CPA.
R C SRINIVASAN, MA, EPA, CPA.
J A FISH, LLB, LL.M. *^{ΔΔ}
J H SEXTON, BSC, EPA, CPA.*^Δ
G W MCCLUSKIE, BSC, EPA, CPA.^Δ
DR. R E TYSON, EPA, CPA.
DR. S ALI, EPA, CPA.
M P ROBERTS, MENG, EPA, CPA.A L SIMONS, MChem, EPA, CPA.
DR. P M TUXWORTH, EPA, CPA.
DR. M P JACKSON, EPA, CPA.
ASSOCIATES :-
DR. D POWER, EPA, CPA.
T J B HOPKIN, MA, MENG, EPA, CPA.
DR. H FORD, EPA, CPA.
S A CURRAN, MA, EPA, CPA.
DR. S A RAYNOR, EPA, CPA.
S P A STANES, LLB.*^Δ
L J GARLICK, MA, MSCI, EPA, CPA.
DR. L P CHAPMAN, EPA, CPA.
C V BACKUS, MSCI, EPA, CPA.DR. P J SILCOCK, EPA, CPA.
DR. J A TURNER, EPA, CPA.
K J GREHAN, MChem, EPA, CPA.
DR. D FORSYTHE, EPA, CPA.
DR. J F PERKINS, LLB, EPA, CPA.
C STIRLING, MA.*^ΔK M FITCHETT, LLB.^ΔCONSULTANT :-
A M SENIOR, MA, EPA, CPA.a Solicitor *MITMA
Δ European Trade Mark Representative

relevant technical Board of Appeal caselaw regarding this issue of inventive step over structurally similar compounds. The leading Decision in this regard is T852/91. A copy of that Decision is enclosed.

In T852/91, the Board of Appeal explains, at reason 8.2, that:

“... to deny inventive step for novel chemical compounds because of their “structural similarity” to known chemical compounds amounts to an allegation that a skilled person would have reasonably expected the same or similar usefulness of both the known and the novel compounds as the means of solving the technical problem underlying the application in question. Such an expectation would be justified, if the skilled person knew, be it from common general knowledge or from some specific disclosure, that the existing structural differences of the chemical compounds concerned were so small that they would have no essential bearing on these properties...” (emphasis added).

In the present case, the structural difference at issue is the replacement of -CH₂- groups in the prior art with -CF₂- groups. A medicinal chemist would expect such a change to have a profound effect on the biological properties of a molecule. This issue is discussed further below.

A skilled medicinal chemist would expect the replacement of -CH₂- groups with -CF₂- groups to affect the biological properties of a molecule

It simply cannot be said that the differences between a -CF₂- group and a -CH₂- group are “so small that they would have no essential bearing” on the biological properties of compounds containing such moieties.

Firstly, as the Examiner will be aware, fluorine is much more electronegative than hydrogen. Thus, the CF bond will be more polar than the CH bond. It will therefore be much more likely to interact non-covalently in a dipolar bonding interaction. Clearly, any such interaction would be likely to affect significantly the interaction of the molecule with the β-agonist receptor.

Secondly, the fluorine atom has quite different steric properties to a hydrogen atom. Fluorine has an extra shell of electrons compared with hydrogen, which means that fluorine has a larger atomic radius than hydrogen. A -CF₂- group will therefore be much more sterically demanding than a -CH₂- group. The steric bulk of the -CF₂- group will in turn affect the three dimensional conformation of the molecule, and restrict rotation about single bonds in the molecule.

A skilled medicinal chemist would therefore be well aware that replacing a -CH₂- moiety with a -CF₂- moiety would have a profound effect on both the electronic and steric properties of the molecule at issue. It is not therefore credible to suggest that a skilled medicinal chemist would have expected to be able to replace the -CH₂- groups in the D1/D2 compounds with -CF₂- groups without affecting the biological properties at the β-adrenergic receptor.

A skilled medicinal chemist would not have combined the teachings of either D1 or D2 with D3

Section C-IV-11.8 of the Guidelines for Examination in the European Patent Office states:

"In determining whether it would be obvious to combine two or more distinct disclosures, the examiner should also have regard in particular to the following:

(i) whether the content of the disclosures (e.g. documents) is such as to make it likely or unlikely that the person skilled in the art, when faced with the problem solved by the invention, would combine them..." (emphasis added)

Documents D1 and D2 are both concerned with β -agonists. It therefore seems reasonable that the skilled person would look to combine these documents with other documents that also discuss β agonists. D3, however, is wholly silent on the subject of β -agonists. D3 does discuss phosphodiesterase inhibitors, statins, cholesterol absorption inhibitors, microsomal triglyceride transfer protein inhibitors, selective serotonin reuptake inhibitors, quinone and artemisinin derivatives, ornithine decarboxylase inhibitors, plant microtubule inhibitors, kinases and antibacterials. However, β -agonists are not mentioned at all.

Furthermore, none of the fluorinated compounds exemplified in D3 have a $-\text{CF}_2-$ group in an alkylene chain. In fact, the majority of the compounds described in D3 are either monofluoro-substituted cyclic groups (see for example, compounds (1), (2), (4) to (7), (10) to (12), (20), and (26) to (29)) or trifluoro-substituted cyclic groups (see for example, compounds (8) and (9), compounds (13) to (19), (21), (22), (24), (30) and (34)). A skilled person would not, therefore, have looked to D3 for teaching as regards replacement of $-\text{CH}_2-$ groups with $-\text{CF}_2-$ groups.

It is therefore highly unlikely that the skilled person starting from D1 or D2 would ever have sought to combine either of their teachings with D3. Rather, the combination of D1/D2 with D3 is an example of the *ex post facto* reasoning specifically prohibited at section C-IV-11.9.2 of the Examination Guidelines.

The combination of D1 or D2 with D3 does not result in the present invention

Notwithstanding the above discussion, even if a skilled person had combined D1 or D2 with D3 (which they would not have done) they would not have arrived at the present invention. That is because D3 would have simply confirmed to a skilled medicinal chemist that the incorporation of fluorine into a molecule would have an unpredictable effect on its biological properties.

Thus, the overall teaching of D3 is simply that incorporation of fluorine into a drug allows modulation of electronic, lipophilic and steric parameters. Whilst D3 does show that fluorine has been incorporated into some drugs with clinical success, in others a loss of potency or undesired side-effects are observed.

For example, page 28 describes how Cerivastatin (5), which is a monofluoro-substituted compound, was withdrawn from the market due to its adverse effect on muscle tissue. Page 29 describes the decrease in biological activity of a bis-quinoline antimalarial compound substituted with a trifluoromethyl group (compound (16)). Page 29 further explains that Mefloquine (compound (17)), which contains two trifluoromethyl groups on the quinoline moiety, produces neuropsychiatric symptoms. Also described at page 29 is Halofantrine (compound (18)), another example of a compound containing a trifluoromethyl group. This compound has been found to be cardiotoxic, leading in some cases to sudden and unexpected mortality. At page 30, the bioisosteric replacement of a chlorine atom with a fluorine atom in topoisomerase II inhibitors leads to a dramatic and

unexpected loss of potency of 4-anilino-2-fluoro-4'-demethylpodophyllotoxin analogues, probably due to an unfavourable DNA-Fluorine interaction.

Clearly, therefore, D3 would not have suggested to a skilled medicinal chemist that the replacement of a -CH₂- group in the D1/D2 compounds with a -CF₂- group could be done without affecting significantly the biological properties of those compounds. Rather, insofar as D3 is relevant at all to the teaching in D1 and D2, it clearly warns that such a modification might lead to a loss of potency or undesired side-effects.

The subject matter claimed in the present application does therefore involve an inventive step over any combination of D1/D2 with D3.

Superior activity associated with the compounds of the present invention

Finally, in case the Examiner should have any remaining doubts on this issue of inventive step, his attention is drawn to the data in the attached Annex A. The Applicant has carried out several further experiments, which compare the selectivity of ethanolamine compounds embraced by the general formulae of D1 and D2 and their fluorinated analogues, which are exemplified in the present application. Thus, Examples 1, 3 and 4 of the present application are compared with Example 2 of D1 (salmeterol) and Example 14 of the present application is compared with its equivalent non-fluorinated compound, which is covered by the Markush formula disclosed in D2.

Functional activities in vitro were measured in the heart and in the trachea. The cardiac effect of the compounds was assessed in rat left atria. The activity was expressed as the concentration required to yield 20% cardiac contraction (EC20). The higher the EC20 value, the lower the probability of unwanted cardiac side-effects.

The bronchodilatory effect of the compounds was studied in guinea-pig trachea. The activity was expressed as the concentration required to yield 50% of relaxation (EC50). The lower the EC50 value, the higher the potency of the compound in inducing bronchodilatation, e.g. in the treatment of respiratory diseases.

The Therapeutic Index of the compounds is then defined as the ratio between the EC20 value in rat left atria and the EC50 value in guinea-pig trachea. The Therapeutic Index indicates the selectivity of the drug. The higher the value of this ratio, the more selective is the compound and the higher its safety margin.

The results of these experiments clearly show that the fluorinated compounds claimed in the present application are much more selective for β_2 receptors than their non-fluorinated equivalents. As can be seen from the table in Annex A, The EC20 values in rat left atria and the Therapeutic Index of the compounds of the present invention are higher than those of the corresponding non-fluorinated compounds described in D1 or D2. Moreover, these results demonstrate that the compounds of the present invention are potent and selective long-acting β_2 -adrenergic receptor agonists independent of the position of the fluorine atoms in the methylene chain, with an improved safety margin profile in comparison with the compounds disclosed in the prior art.

There is nothing in D1, D2 or D3 which suggests in any way that superior selectivity at the β_2 receptor could be obtained by replacing $-\text{CH}_2-$ groups with $-\text{CF}_2-$ groups as in the present application. This increase in selectivity accordingly constitutes an unexpected technical superiority, which provides further evidence for an inventive step.

Other matters

The objections raised in points 2 and 3 of the Official Action have been dealt with as mentioned above in the amendments section.

It is believed that the present application is in order for grant and I look forward to receiving notice to that effect in due course. If there is any outstanding difficulty or the Examiner wishes to propose any amendments, please telephone the writer. Merely as a precaution I request oral proceedings in the event that the refusal of the application is contemplated.

Please acknowledge safe receipt of this letter by stamping and returning the attached acknowledgement copy.

Yours faithfully

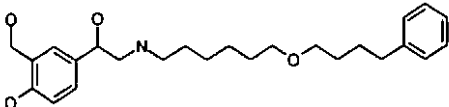
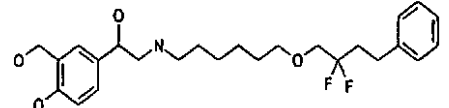
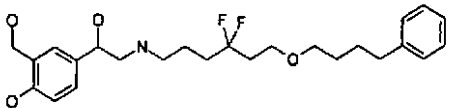
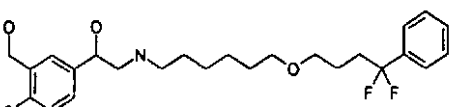
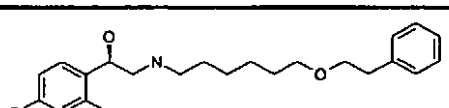
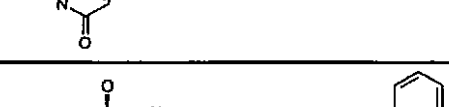


E.C. SRINIVASAN

AUTHORISED REPRESENTATIVE

ANNEX A

Examples 1, 3 and 4 of the present invention have been tested and compared with an equivalent non-fluorinated equivalent Example 2 of D1. Example 2 of D1 is Salmeterol, a commercially available, long-acting β_2 -adrenergic receptor agonist. Example 14 of the present invention has also been tested and compared with an equivalent non-fluorinated equivalent that is covered by the Markush formula in D2 but not exemplified therein. The test results are summarised in the following table:

EXAMPLES	STRUCTURE	Rat Left atria EC ₂₀ , (nM)	Guinea-pig trachea EC ₅₀ ,(nM)	Therapeutic Index [Left Atria EC ₂₀ / Trachea EC ₅₀]
Example 2 of D1 (Salmeterol)		4400	2.9	1517
Example 1 of the present application		43000	9	4778
Example 3 of the present application		51000	5	10200
Example 4 of the present application		30000	5	6000
Example within D2 Markush formula but not exemplified		57	0.04	1425
Example 14 of the present application		96	0.03	3200

J.A.KEMP & CO.

BY ONLINE FILING

14 SOUTH SQUARE, GRAY'S INN
LONDON WC1R 5JJThe European Patent Office
Bayerstrasse 34
(entrance via Zollstrasse 3)
80335 Munich
GermanyTELEPHONE: + 44 20 3077 8600
FACSIMILE: + 44 20 7242 8932
E-MAIL: mail@jakemp.com
WEBSITE: www.jakemp.com

1 August 2011

Dear Sirs

European Patent No. 1885684
European Patent Application No. 06742964.7-1211
ALMIRALL, S.A.
Our Ref: N.98195A RCS/TGL/jab

I request correction of the patent specification for this European patent which was published on 13 July 2011 under Article 98 EPC as EP-B-1885684.

In this regard, please correct claim 14 of the English version of the claims by inserting the text from page 97 of the Druckexemplar after the two specific compounds recited in the English version of the claim as published. Please also correct the German version of claim 14 by introducing line breaks in lines 18 and 21 of page 58 so that each compound name starts on a new line. I attach marked up versions of pages 56 and 58 of EP-B-1885684 indicating the corrections requested.

The errors mentioned above are clearly errors of transcription which were not intended by the Examining Division when making the decision to grant. That is evident because the Decision to Grant dated 17 June 2011 explicitly indicates that the amendments received at the EPO on 5 January 2011 have been taken into account. These amendments involved the replacement of pages 96 and 98 of the Druckexemplar by new pages 96 and 98 enclosed with the request. Replacement of page 97 of the Druckexemplar was not requested. Indeed, text present on page 97 of the Druckexemplar appears in the French and German translations of the claims which are reproduced in EP-B-1885684 (albeit with the further error of transcription present in the German version of that claim).

Under the circumstances, the published patent specification does not conform to the Decision to Grant and is clearly erroneous. It is therefore appropriate that it be correct pursuant to Rule 140 EPC

OXFORD OFFICE · NORTHBROOK HOUSE · THE OXFORD SCIENCE PARK · OXFORD OX4 4GA
TELEPHONE: + 44 1865 406150 · FACSIMILE: + 44 1865 406101MUNICH OFFICE · BAYER KARREE · HAYENSTRASSE 85 · D-80335 MÜNCHEN · GERMANY
TELEPHONE: + 49 89 24 22 97 340 · FACSIMILE: + 49 89 24 22 97 350M L S AYERS, BSC, EPA, CPA.
G C WOODS, MA, EPA, CPA.
A J WEBB, MA, EPA, CPA.[□]
M J NICHOLS, MA, EPA, CPA.[△]
N J K PRICE, BSC, EPA, CPA.[△]
C M KEEN, MA, EPA, CPA.
J G LEBMING, MA, EPA, CPA.
S I SMITH, MA, EPA, CPA.
J E BENSON, BSC, EPA, CPA.
DR. T J DUCKWORTH, EPA, CPA.
S M WRIGHT, BSC, EPA, CPA.[△]
P J H CAMPBELL, MA, EPA, CPA.
C H MERRYWEATHER, BA, EPA, CPA.
S E ROQUES, MA, EPA, CPA.[△]
A BENTHAM, MA, EPA, CPA.R C SRINIVASAN, MA, EPA, CPA.
J A PISH, LLB, LL.M.^{△△}
M P ROBERTS, MEng, EPA, CPA.
DR. P M TUXWORTH, EPA, CPA.
DR. M P JACKSON, EPA, CPA.
J H SEXTON, BSC, EPA, CPA.[△]
G W MCCLUSKIE, BSC, EPA, CPA.[△]
DR. R E TYSON, EPA, CPA.
A L SIMONS, MChem, EPA, CPA.
DR. D POWER, EPA, CPA.
T J B HOPKIN, MA, MEng, EPA, CPA.
DR. H FORD, EPA, CPA.
DR. S A RAYNOR, EPA, CPA.
DR. L P CHAPMAN, EPA, CPA.ASSOCIATES:-
DR. P J SLOOCK, EPA, CPA.
DR. J A CHEWTER, EPA, CPA.
K J GEEHAN, MChem, EPA, CPA.
DR. D FORSYTHE, EPA, CPA.
DR. J F PERKINS, LLB, EPA, CPA.
C STIRLING, MA.^{△△}
R S MILLER, LLB.^{△△}
DR. S TURBerville, EPA.
T P ALBERTINI, BA.^{△△}
DR. J N ROBERTS, EPA, CPA.
S GURNEY, BSC, EPA, CPA.
C J MILTON, MA, MSci, EPA, CPA.

K M FITCHETT, LLB.[□]DR. G M LEWIS, EPA.
DR. H J WEST, EPA, CPA.
DR. J R HIGGINS, EPA.
DR. A P CLARK, EPA.
A J M NEWMAN, MA, MSci, EPA.
DR. D T COONEY, EPA.CONSULTANT:-
A M SENIOR, MA, EPA, CPA.
-----[△] ATTORNS
[△] European Trade Mark Representatives
[□] Solicitor

Regulated by IPREG

(see for example, G8/95, reason 3.2). I therefore request that the above correction be made to the specification of the granted patent pursuant to Rule 140 EPC.

Please confirm as soon as possible that this request for correction is allowable and publish a corrected version of the patent specification in due course.

Yours faithfully

A handwritten signature in black ink, appearing to be 'R C Srinivasan', written in a cursive style.

R C SRINIVASAN

EP 1 885 684 B1

7. A compound according to any preceding claim wherein the sum $n+p$ is 4, 5 or 6.
8. A compound according to any preceding claim wherein the sum $q+s$ is 1, 2, 3 or 4.
- 5 9. A compound according to any preceding claim wherein R^3 is a hydrogen atom, a halogen atom or a methyl group.
10. A compound according to claim 9 wherein R^3 is a chlorine or fluorine atom.
11. A compound according to claim 9 wherein R^3 is a methyl group.
- 10 12. A compound according to any preceding claim wherein R^4 is a hydrogen atom.
13. A compound according to anyone of claims 1 to 11 wherein R^4 is a chlorine atom.
- 15 14. A compound according to claim 1 selected from the group consisting of:
- (R, S)-4-(2-[[6-(2,2-Difluoro-4-phenylbutoxy)hexyl]amino]-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol*
(R, S)-4-(2-[[6-(2,2-Difluoro-2-phenylethoxy)hexyl]amino]-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
<from pg 97 of Druckexemplar>
- 20 15. A compound according to any one of claims 1 to 14 for use in the treatment of the human or animal body.
16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to anyone of claims 1 to 14 and a pharmaceutically acceptable carrier.
- 25 17. The pharmaceutical composition of claim 16, wherein the composition further comprises a therapeutically effective amount of one or more other therapeutic agents.
18. The pharmaceutical composition of claim 17 wherein the other therapeutic agent is a corticosteroid, an anticholinergic agent, or a PDE4 inhibitor.
- 30 19. The pharmaceutical composition according to anyone of claims 16 to 18, wherein the composition is formulated for administration by inhalation.
20. A combination comprising a compound according to anyone of claims 1 to 14 and one or more other therapeutic agents.
- 35 21. The combination of claim 20 wherein the other therapeutic agent is a corticosteroid, an anticholinergic agent, or a PDE4 inhibitor.
- 40 22. A compound as defined in any one of claims 1 to 14 for use in treating a disease or condition associated with β_2 adrenergic receptor activity in a mammal.
23. A compound according to claim 22 wherein the disease or condition is selected from the group consisting of pulmonary disease, pre-term labor, glaucoma, neurological disorders, cardiac disorders, and inflammation.
- 45 24. A compound according to claim 23 wherein the pulmonary disease is asthma or chronic obstructive pulmonary disease.
25. Use of a compound according to any one of claims 1 to 14 in the manufacture of a medicament for treating a disease or condition as defined in any one of claims 22 to 24.
- 50

Patentansprüche

- 55 1. Verbindung der Formel (I):

- < (R,S)-4-(2-([4,4-Difluoro-6-(4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
- (R,S)-4-(2-([6-(4,4-Difluoro-4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
- 5 (R,S)-5-(2-([6-(2,2-Difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one
- (R,S)-4-[2-([6-(2,2-Difluoro-2-(3-methylphenyl)ethoxy)hexyl]amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol
- 10 4-((1R)-2-([6-(2,2-Difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
- (R,S)-2-(Hydroxymethyl)-4-(1-hydroxy-2-([4,4,5,5-tetrafluoro-6-(3-phenylpropoxy)hexyl]amino)ethyl)phenol
- (R,S)-[5-(2-([6-(2,2-Difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-2-hydroxyphenyl]formamide
- 15 (R,S)-4-[2-([6-(2-(3-Bromophenyl)-2,2-difluoroethoxy)hexyl]amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol
- (R,S)-N-[3-(1,1-Difluoro-2-([6-(2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy)ethyl)phenyl]urea
- 20 3-[3-(1,1-difluoro-2-([6-(2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy)ethyl)phenyl]imidazolidine-2,4-dione
- (R,S)-4-[2-([6-(2,2-difluoro-2-(3-methoxyphenyl)ethoxy)hexyl]amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol
- 5-((1R)-2-([6-(2,2-difluoro-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one
- 25 4-((1R)-2-([4,4-Difluoro-6-(4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
- (R,S)-4-(2-([6-(3,3-Difluoro-3-phenylpropoxy)hexyl]amino)-1-hydroxy ethyl)-2-(hydroxymethyl)phenol
- (R)-4-(2-([6-(2,2-Difluoro-2-phenylethoxy)-4,4-difluorohexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
- 30 (R,S)-4-(2-([6-(2,2-difluoro-3-phenylpropoxy)hexyl]amino)-1-hydroxy ethyl)-2-(hydroxymethyl)phenol, hydrochloride

and pharmaceutically-acceptable salts and solvates thereof. >

14. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe, bestehend aus:

(R,S)-4-(2-([6-(2,2-Difluor-4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
 (R,S)-4-(2-([6-(2,2-Difluor-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
 (R,S)-4-(2-([4,4-Difluor-6-(4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
 (R,S)-4-(2-([6-(4,4-Difluor-4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
 (R,S)-5-(2-([6-(2,2-Difluor-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-8-hydroxychinolin-2(1H)-on
 (R,S)-4-(2-([6-(2,2-Difluor-2-(3-methylphenyl)ethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
 4-((1R)-2-([6-(2,2-Difluor-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
 (R,S)-2-(Hydroxymethyl)-4-(1-hydroxy-2-([4,4,5,5-tetrafluor-6-(3-phenylpropoxy)hexyl]amino)ethyl)phenol
 (R,S)-5-(2-([6-(2,2-Difluor-2-phenylethoxy)hexyl]amino)-1-hydroxy-ethyl)-2-hydroxyphenylformamid
 (R,S)-4-(2-([6-(2-(3-Bromphenyl)-2,2-difluorethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
 (R,S)-N-[3-(1,1-Difluor-2-([6-(2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethyl)phenyl]-harnstoff,
 3-[3-(1,1-Difluor-2-([6-(2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethyl)phenyl]-imidazolidin-2,4-dion
 (R,S)-4-(2-([6-(2,2-Difluor-2-(3-methoxyphenyl)ethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
 5-((1R)-2-([6-(2,2-difluor-2-phenylethoxy)hexyl]amino)-1-hydroxyethyl)-8-hydroxychinolin-2(1H)-on
 4-((1R)-2-([4,4-Difluor-6-(4-phenylbutoxy)hexyl]amino)-1-hydroxy-ethyl)-2-(hydroxymethyl)phenol
 (R,S)-4-(2-([6-(3,3-Difluor-3-phenylpropoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
 (R)-4-(2-([6-(2,2-Difluor-2-phenylethoxy)-4,4-difluorhexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol
 (R,S)-4-(2-([6-(2,2-Difluor-3-phenylpropoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol-Hydrochlorid,

und pharmazeutisch verträgliche Salze und Solvate davon.

15. Verbindung nach einem der Ansprüche 1 bis 14 zur Verwendung bei der Behandlung des Menschen- oder Tierkörpers.

16. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 14 und einen pharmazeutisch verträglichen Träger.

17. Pharmazeutische Zusammensetzung nach Anspruch 16, wobei die Zusammensetzung außerdem eine therapeutisch wirksame Menge eines anderen therapeutischen Mittels oder mehrerer anderer therapeutischer Mittel umfasst.

18. Pharmazeutische Zusammensetzung nach Anspruch 17, wobei das andere therapeutische Mittel ein Corticosteroid, ein anticholinerges Mittel oder ein PDE4-Inhibitor ist.

19. Pharmazeutische Zusammensetzung nach einem der Ansprüche 16 bis 18, wobei die Zusammensetzung zur Verabreichung durch Inhalation formuliert ist.

20. Kombination, umfassend eine Verbindung nach einem der Ansprüche 1 bis 14 und ein anderes therapeutisches Mittel oder mehrere andere therapeutische Mittel.

21. Kombination nach Anspruch 20, wobei das andere therapeutische Mittel ein Corticosteroid, ein anticholinerges Mittel oder ein PDE4-Inhibitor ist.

22. Verbindung, wie sie in einem der Ansprüche 1 bis 14 definiert ist, zur Verwendung bei der Behandlung einer Erkrankung oder eines Zustandes, die/der mit β_2 -adrenerger Rezeptor-Aktivität assoziiert ist, bei einem Säuger.

23. Verbindung nach Anspruch 22, wobei die Erkrankung oder der Zustand ausgewählt ist aus der Gruppe, bestehend aus Lungenerkrankung, Frühgeburt, Glaukom, neurologischen Störungen, Herzkrankheiten und Entzündung.

24. Verbindung nach Anspruch 23, wobei die Lungenerkrankung Asthma oder chronisch-obstruktive Lungenerkrankung ist.

25. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 14 bei der Herstellung eines Medikaments zur Behandlung einer Erkrankung oder eines Zustandes, wie sie/er in einem der Ansprüche 22 bis 23 definiert ist.