



No. 11-098671- -00007-0000

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Act. 523 RESPUESTA Folios: 29

Clarke, Modet & C^o

COLOMBIA

P-3022

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. **11.098.671** ✓Solicitud de patente a nombre de **CHIESI FARMACEUTICI S.P.A.**

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **CHIESI FARMACEUTICI S.P.A.**, domiciliada Parma, Italia, solicitante de la patente de la referencia, en respuesta al oficio 367 notificado por fijación en lista el 22 de enero de 2013, nos permitimos manifestar lo siguiente:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo capítulo reivindicatorio donde se cancelaron las antiguas reivindicaciones 14, 17 y 18 que hacían mención a materia no patentable de acuerdo con la legislación andina.

Estas modificaciones se realizan con el fin de superar las objeciones de claridad planteadas por el señor examinador en su concepto técnico. En este sentido, nos permitimos decir que no se presenta tasa por reivindicaciones adicionales, toda vez que como el señor examinador puede corroborar, el nuevo capítulo reivindicatorio ahora contiene 15 cláusulas que corresponden prácticamente a aquellas originalmente presentadas y en donde se han eliminado reivindicaciones de uso.

2. Claridad

Sobre esta particular, nos permitimos manifestar que con las modificaciones realizadas en las reivindicaciones quedan cabalmente atendidas y superadas las objeciones presentadas por el señor examinador.

En cuanto a la reivindicación 10, atentamente nos permitimos decir que no nos encontramos de acuerdo con la objeción planteada dado que es clara la combinación de un compuesto de la fórmula (I) de acuerdo con la invención, específicamente con la reivindicación 1 a 7 con un componente farmacéuticamente activo seleccionado de agonistas beta2, antagonistas M3 y corticosteroides.

De hecho, una persona versada en la materia técnica entenderá que dichos ingredientes activos son aquellos relacionados con enfermedades respiratorias obstructoras tal como el asma, la bronquitis crónica y la enfermedad pulmonar obstructora crónica COPD. Además, considera el solicitante que resulta ser una restricción drástica remitirse a tan solo las composiciones que se encuentran ejemplificadas en la descripción.

3. REQUISITOS DE PATENTABILIDAD

3.1 Novedad

El señor examinador indicó en el acápite 7 de su concepto técnico que las características técnicas del compuesto de la reivindicación 1 ya habían sido reportadas en el documento D1 (CO-106261) y que *“La existencia del (-) enantiómero del compuesto corresponde a una característica implícita del compuesto lo cual no puede ser considerado como una característica novedosa.”*

En este orden de ideas, respetuosamente nos permitimos reiterar que el artículo 16 de la Decisión 486 establece que: **“Una invención se considera nueva cuando no está comprendida en el estado de la técnica.”**

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida....” (El resaltado es nuestro) y de acuerdo con el espíritu de la norma legal indicada, la invención no se considera como nueva si está **“comprendida”** en el estado de la técnica, dicha norma se está refiriendo, naturalmente, a la **totalidad del invento** y no a alguno o a algunos de los componentes que hacen parte de la nueva solicitud.

En efecto, para que la invención pierda su calidad de novedosa, es claro que ella, TODA ELLA, ha de estar contenida en el *“conjunto de conocimientos existentes que son aplicables al proceso industrial”* como define el estado de la técnica el Tribunal de justicia del Acuerdo de Cartagena (Proceso No. 6-IP-89, sentencia de 31 de octubre de 1989, publicada en Jurisprudencia del Tribunal de Justicia del Acuerdo de Cartagena, Tomo 11, BID-INTAL, Buenos Aires, 1994, página 60).

Esto se conoce como **NOVEDAD ABSOLUTA**, de conformidad con lo cual para desvirtuar el requisito de novedad de una invención será necesario que lo reivindicado por la invención bajo estudio corresponda de **forma total** con lo revelado en un documento o anterioridad señalada, conclusión a la que se llega después de un análisis exhaustivo mediante una comparación entre el capítulo reivindicatorio de la invención en estudio y la divulgación citada por ese despacho como anterioridad.

Ahora bien, si un determinado elemento, condición o circunstancia de la nueva creación ya hace parte del estado de la técnica no quiere ello decir, desde luego, que la invención deba ser rechazada por carecer del requisito de novedad. No sin razón ha dicho el mencionado Tribunal: *“hay que advertir que toda creación es en cierta forma, producto del estado de la técnica existente, en el sentido de que el inventor ha de tener en cuenta un conjunto de conocimientos técnicos que le permitan crear nuevos procedimientos aplicables a la industria”* (Ibidem, páginas 53 y 54) (El subrayado es nuestro).

Por lo tanto y teniendo en cuenta lo anteriormente expuesto, como mínimo la novedad debe contemplar los siguientes aspectos:

-Que la invención en estudio esté contenida de forma **TOTAL** y **ABSOLUTA** en cada uno de los documentos que se mencionan como anterioridades; y

-Que la invención en cuestión puede partir de conocimientos conocidos, caso en el cual habrá que hacer la comparación no de lo conocido sino de lo inédito y novedoso, teniendo que analizarse el **valor agregado** que aporta la invención con sus nuevas características al campo técnico al cual pertenece la solicitud en estudio.

Aplicando lo anterior al caso concreto, para que las razones que aduce ese despacho para desvirtuar la novedad fuesen ciertas, sería forzoso que se demostrara que la invención de mi mandante está comprendida en el estado de la técnica de forma **TOTAL**, lo cual no sucede toda vez que en el campo de la química, debe entenderse que un enantiómero es nuevo sobre la mezcla racémica.

En este sentido, es deseo del solicitante poner en consideración del señor examinador el IPER de la Oficina Europea de Patentes (Anexo 1) donde el documento que cita el señor examinador colombiano corresponde con la anterioridad D1 en la búsqueda internacional y aún así, la EPO reconoció la novedad de la solicitud la cual luego fue concedida. Por lo tanto, amablemente solicitamos retirar la objeción planteada en este sentido.

3.2 Nivel inventivo

El señor examinador indica que “La diferencia entre la invención, definida en la reivindicación 2 y el compuesto del documento D2 consiste en que el compuesto de la solicitud presenta a un grupo etilo enlazando los anillos de fenilo y piridina en lugar del grupo vinilo del compuesto divulgado en D2 y en que este documento no divulga específicamente que el sustituyente R1 puede corresponder a difluorometilo.”

En relación con estos argumentos, atentamente nos permitimos dirigir la atención del señor examinador desde el folio 59 línea 25 hasta el folio 60 línea 24 donde se indica que;

“ACTIVIDAD FARMACOLÓGICA DE LOS COMPUESTOS DE LA INVENCION

EJEMPLO 19

Determinación in vitro de la actividad inhibitoria de PDE4 en el ensayo de células mononucleares de sangre periférica (PBMCs)

El ensayo, que se basa en la actividad inhibitoria conocida ejercida por los inhibidores de PDE4 en el factor alfa de necrosis tumoral inducido por lipopolisacaridos (LPS) (liberación de TNF- α en las células mononucleares de sangre periférica (PBMCs), se realiza de acuerdo con un método descrito previamente (Hatzelmann A et al J. Pharmacol. Exp. Ther. 2001 ; 297:267-279; Draheim R et al J. Pharmacol. Exp. Ther. 2004; 308:555-563.

PBMCs humanas criopreservadas, (100 μ l/pozo) se incuban en placas de 96 pozos (10^5 células/pozo), por 30 minutos, en la presencia o ausencia (microl 50) de los compuestos de prueba cuyas concentraciones se encuentran en el intervalo de 10^{-12} M hasta 10^{-6} M. Posteriormente, se agregan LPS (3 ng/ml).

Después de la incubación de 18 horas a 37°C en una incubadora humedecida bajo una atmósfera de 95% de aire y 5% de CO₂, se recoge el medio de cultivo y TNF- α es medido por ELISA.

Los resultados con respecto a los compuestos C1 a C6, expresados promedio de $\pm$ 95% de límites de confianza de la concentración molar del compuesto de prueba que produce 50% de inhibición de liberación de TNF- α inducido por LPS (IC₅₀), son comprendidos entre 0.06 y 4.4 nM. Los efectos de los compuestos probados son calculados como porcentaje de inhibición de la liberación de TNF- α , si se asume que la producción de TNF- α inducida por LPS en ausencia del compuesto de inhibidor como 100% y la producción de TNF- α basal de PBMCs en la ausencia de LPS como 0%.

En este sentido, el solicitante desea manifestar que bajo las mismas condiciones en que se llevó la experimentación del ejemplo 19, compuestos de WO2008/006509 (D2) presentaron valores comprendidos entre 0.0009 y 0.026 **micromolar** (μ M), lo cual indica que la presente invención efectivamente está proporcionando inhibidores de PDE4 mucho más potentes que los reportados en el arte previo.

Así las cosas, es necesario señalar que una persona medianamente versada en la materia técnica no habría encontrado motivación alguna a partir de lo mostrado en D2 para llegar de manera evidente a los compuestos de la presente solicitud.

Habiendo atendido cabalmente las objeciones presentadas por el oponente, atentamente solicitamos se conceda el privilegio de patente de invención a la solicitud en estudio o si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *“habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares”* y *“(.) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso”*, respectivamente (El subrayado es nuestro).

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional

Señor Superintendente,



DILIA MARIA RODRIGUEZ D'ALEMAN
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ANEXO 1

COPIA INFORMAL DEL INFORME PRELIMINAR
INTERNACIONAL DE BÚSQUEDA (IPER)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SCB 1259-1 P	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2010/000676	International filing date (day/month/year) 04/02/2010	(Earliest) Priority Date (day/month/year) 06/02/2009
Applicant CHIESI FARMACEUTICI S.P.A.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6b/s(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

BENZOIC ACID (1-PHENYL-2-PYRIDIN-4-YL) ETHYL ESTERS AS PHOSPHODIESTERASE INHIBITORS

5. With regard to the **abstract**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☒ none of the figures is to be published with the abstract

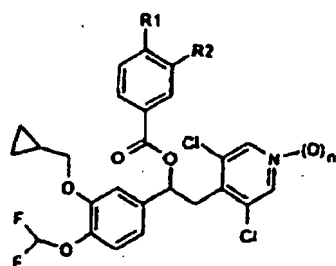
INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2010/000676

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to inhibitors of the phosphodiesterase 4 (PDE4) enzyme. More particularly, the invention relates to compounds that are derivatives of -phenyl-2-pyridinyl alkyl alcohols, methods of preparing such compounds, compositions comprising them, combinations and therapeutic uses thereof.



(I)

wherein

n is 0 or 1;

R1 and R2 may be the same or different, and are selected from the group consisting of:

- linear or branched C₁-C₆ alkyl;
- OR3 wherein R3 is C₁-C₆ alkyl optionally substituted by one or more C₃-C₇ cycloalkyl groups; and
- HNSO₂R4 wherein R4 is C₁-C₄ alkyl optionally substituted with one or more halogen atoms or with a C₁-C₄ group.

wherein at least one of R1 and R2 is HNSO₂R4.

The other variables are as defined in the claims.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/000676

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/61 C07D213/89 A61K31/44 A61P11/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/018909 A (CHIESI FARMA SPA [IT]; DELCANALE MAURIZIO [IT]; AMARI GABRIELE [IT]; A) 12 February 2009 (2009-02-12) 3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester as unspecified stereoisomer: ; pages 14,36; example 11 3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester as unspecified stereoisomer: ; pages 15,38; example 14 3-cyclopropylmethoxy-4-methanesulfonylaminobenzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-/--	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

1 June 2010

Date of mailing of the international search report

10/06/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Tel. (+31-70) 340-2040,
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Authorized officer

Lange, Tim

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/000676

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	)ethyl ester as unspecified stereoisomer;; page 19; example 69 1-(3-cyclopropylmethoxy-4-difluoromethoxy) -phenyl-2-(3,5-dichloro-pyridin-4-yl)ethan ol as intermediate;; page 32; example 2b; table 2 1-(3-cyclopropylmethoxy-4-difluoromethoxy) -phenyl-2-(3,5-dichloro-1-oxy-pyridin-4-yl))ethanol; page 48; example 18; table 7 disclosure of combination with additional drugs:claim 16 disclosure of pharmaceutical compositions:claims 14-16 the compounds as medicaments:claim 18 Use of compounds in treatment of asthma and COPD:claims 20-21 use in kits as e.g. nebulizers;; page 27, line 24 - line 28 use against dermatitis and rhinitis;; page 28, line 23 ----- A WO 2008/006509 A (CHIESI FARMA SPA [IT]; AMARI GABRIELE [IT]; ARMANI ELISABETTA [IT]; GH) 17 January 2008 (2008-01-17) Disclosure of 3,4-Dimethoxy-benzoic acid (Z)-2-(3,5-dichloropyridin-4-yl)-1-(3,4-di methoxy-phenyl)-vinyl ester and 3.cyclopropylmethoxy-4-difluoromethoxy-ben zoic acid (Z)-2-(3,5-dichloropyridin-4-yl)-1-(3,4-di methoxy-phenyl)-vinyl ester: ; page 16; claims 18-20; compounds CHF5472, CHF5514 Use as PDE4 inhibitor:claim 18 Use in therapy of asthma and COPDclaim 20 ----- A WO 95/01338 A (BYK GULDEN LOMBERG CHEM FAB [DE]; AMSCHLER HERMANN [DE]) 12 January 1995 (1995-01-12) Disclosure of Roflumilast (i.e. N-(3,5-dichloropyridin-4-yl)-3-cyclopropyl methoxy-4-difluoromethoxy-benzamide;; page 15; claim 24; example 5 Use as PDE4-inhibitor;; page 22, line 12 ----- A ODINGO J O: "Inhibitors of PDE4: A review of recent patent literature" EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 15, no. 7, 1 January 2005 (2005-01-01), pages 773-787, XP002413778 ISSN: 1354-3776 the whole document -----	1-18 1-18 1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/000676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009018909 A	12-02-2009	AR 068057 A1	04-11-2009
		AU 2008286027 A1	12-02-2009
		CA 2695580 A1	12-02-2009
		EP 2022783 A1	11-02-2009
		EP 2185515 A2	19-05-2010
		PE 06982009 A1	06-07-2009
		US 2009048220 A1	19-02-2009
WO 2008006509 A	17-01-2008	AR 062074 A1	15-10-2008
		CN 101490004 A	22-07-2009
		EP 2044023 A1	08-04-2009
		US 2008015226 A1	17-01-2008
WO 9501338 A	12-01-1995	AT 217612 T	15-06-2002
		AU 687087 B2	19-02-1998
		CA 2165192 A1	12-01-1995
		CN 1126468 A	10-07-1996
		CY 2389 B1	10-09-2004
		CZ 9600001 A3	12-06-1996
		DE 59410119 D1	20-06-2002
		DK 0706513 T3	09-09-2002
		EP 0706513 A1	17-04-1996
		ES 2176252 T3	01-12-2002
		FI 956333 A	29-12-1995
		HK 1011690 A1	11-10-2002
		HU 73232 A2	29-07-1996
		JP 3093271 B2	03-10-2000
		JP 8512041 T	17-12-1996
		LV 13074 B	20-03-2004
		NO 955211 A	21-12-1995
		NZ 271316 A	24-11-1997
		PL 311820 A1	18-03-1996
		PT 706513 E	31-10-2002
		RU 2137754 C1	20-09-1999
		SG 143011 A1	27-06-2008
		SI 706513 T1	31-10-2002
		SK 161795 A3	03-07-1996
		US 5712298 A	27-01-1998

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2010/000676

International filing date (day/month/year)
04.02.2010

Priority date (day/month/year)
06.02.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C07D213/61 C07D213/89 A61K31/44 A61P11/00

Applicant
CHIESI FARMACEUTICI S.P.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Lange, Tim

Telephone No. +31 70 340-2475



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2010/000676

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2010/000676

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-18</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2010/000676

1 **Reference** is made to the following documents:

- D1 WO 2009/018909 A (CHIESI FARMA SPA [IT]; DELCANALE MAURIZIO [IT]; AMARI GABRIELE [IT]; A) 12 February 2009 (2009-02-12)
- D2 WO 2008/006509 A (CHIESI FARMA SPA [IT]; AMARI GABRIELE [IT]; ARMANI ELISABETTA [IT]; GH) 17 January 2008 (2008-01-17)
- D3 WO 95/01338 A (BYK GULDEN LOMBERG CHEM FAB [DE]; AMSCHLER HERMANN [DE]) 12 January 1995 (1995-01-12)
- D4 ODINGO J O: "Inhibitors of PDE4: A review of recent patent literature" EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 15, no. 7, 1 January 2005 (2005-01-01) , pages 773-787, XP002413778 ISSN: 1354-3776

Re Item II.

Priority

2 This International Searching Authority found the claimed priority (06.02.2009) not to be valid for the following reason:

2.1 The European patent application EP09001660, from which the present application claims priority is compounds alike those of the present application. These compounds possess a stereocenter, marked in formula (I) of the present application with an asterisk. The present application specifically claims the (-) enantiomer, whereas the priority document essentially claims the same subject matter, yet as unspecified stereoisomer.

- 2.1.1 Applying the principle that a drug in chiral form is considered novel over a drug in racemic form, the present application directed towards the (-) enantiomer is new subject matter over the priority document directed towards the racemic form.
- 2.1.2 Consequently, the present application is NOT enjoying the priority of the European application, which has considerable consequences for the assessment of novelty and inventive step.

Re Item V

Reasoned statement with regard to novelty and inventive step

Novelty

Claims 17-18 (Method of treatment...) relate to subject-matter considered by this authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions, for use in a first or further medical treatment.

- 3 The subject-matter of claims 1-18 **is new** in the sense of Article 33(2) PCT.
- 3.1 Document D1 is considered the closest prior art. This document is in the formal sense an intermediate document, filed before both the present application as well as the European application, from which the present application claims the priority, but published in between the claimed priority and filing date of the present application.

3.2 Since, according to point 2.1 the claimed priority of the present application was found not to be valid, D1 is *de facto* not an intermediate document, but an ordinary prior art document and hence can be used for novelty- and inventive step assessment.

3.3 D1 discloses:

a) (3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester as unspecified stereoisomer, see pages 14,36; example 11;

b) 3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester as unspecified stereoisomer, see pages 15,38; example 14;

c) 3-cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy)-phenyl-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester as unspecified stereoisomer, see page 19; example 69;

d) 1-(3-cyclopropylmethoxy-4-difluoromethoxy)-phenyl-2-(3,5-dichloro-pyridin-4-yl)**ethanol** as intermediate; page 32; example 2b; table 2;

e) 1-(3-cyclopropylmethoxy-4-difluoromethoxy)-phenyl-2-(3,5-dichloro-1-oxy-pyridin-4-yl)**ethanol**, see page 48; example 18; table 7;

f) The combination of above compounds with additional drugs, see claim 16;

g) Pharmaceutical compositions with above compounds, see claims 14-16;

h) Above compounds as medicaments, see claim 18;

i) The use of above compounds in treatment of asthma and COPD, see claims 20-21;

j) The use in kits as e.g. nebulizers, page 27, line 24 - line 28;

k) The use against dermatitis and rhinitis, page 28, line 23.

3.4 The difference between the present application, claims 1-3, 8-18 and the prior art D1 is that this application claims the (-) enantiomer, whereas D1 only discloses the same subject matter in stereo-unspecific manner.

3.5 Due to this difference, claims 1-3, 8-18 are novel over D1.

3.6 The subject matter of claims 4 relates to a narrowly defined Markush-formula, and the prior art does not disclose such a specific selection from the general Markush formula (I) given in claim 1 of D1. Therefore the specific selection is novel over the generic disclosure in D1.

3.7 The subject matter of claims 5-7 is directed to discrete molecules, which are neither disclosed in D1 nor in any other prior art document; Hence this subject matter is novel.

3.8 For completeness sake the other prior art documents D2-D4 are mentioned. These documents disclose PDE-IV inhibitors, which is also the mode of action of the presently claimed compounds. However, the structures of D2-D4 are remote from the presently claimed subject matter, hence claims 1-18 are also novel over these documents.

3.9 In summary, **claims 1-18 are novel.**

4 Inventive step

4.1 The present application **does not meet** the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 **does not involve an inventive step** in the sense of Article 33(3) PCT.

4.2 Due to the non-validity of the claimed priority, document D1 - though formally an intermediate document - can be used for inventive step assessment.

4.3 For the subject matter of claims 1-3, 9-18 document D1 was identified as being the closest prior art. D1 discloses:

- a) 3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)ethyl ester as unspecified stereoisomer, see D1, pages 14,36; example 11;
- b) 3-Cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester as unspecified stereoisomer, see pages 15,38; example 14;
- c) 3-cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy)-phenyl-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester as unspecified stereoisomer, see page 19; example 69;
- d) 1-(3-cyclopropylmethoxy-4-difluoromethoxy)-phenyl-2-(3,5-dichloro-pyridin-4-yl)**ethanol** as intermediate;; page 32; example 2b; table 2;
- e) 1-(3-cyclopropylmethoxy-4-difluoromethoxy)-phenyl-2-(3,5-dichloro-1-oxy-pyridin-4-yl)**ethanol**, see page 48; example 18; table 7;
- f) The combination of above compounds with additional drugs, see claim 16;
- g) Pharmaceutical compositions with above compounds, see claims 14-16;
- h) Above compounds as medicaments, see claim 18;
- i) The use of above compounds in treatment of asthma and COPD, see claims 20-21;
- j) The use in kits as e.g. nebulizers, see page 27, line 24 - line 28;
- k) The use against dermatitis and rhinitis, see page 28, line 23.

4.4 The difference between the present application, claims 1-3, 8-18 and the prior art D1 is that this application claims the (-) enantiomer, whereas D1 only discloses the same subject matter in stereo-unspecific manner.

- 4.5 The technical effect of this difference is that the (-) enantiomer is more potent in inhibiting the target enzyme (PDE-IV) than the (+) isomer or the racemate.
- 4.6 The objective technical problem to be solved by the present application, when departing from D1 can thus be formulated as "provision of more potent stereoisomers of 3,4-substituted-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl esters as inhibitors of PDE-IV or for therapy of diseases such as asthma and COPD".
- 4.7 The solution as presented by the application is obvious and requires no inventive step. As skilled person knows that in a chiral world such as the human body usually one enantiomer usually is more potent. The skilled person would have to select from a limited list, namely the (R) and the (S) enantiomer of examples 11, 14 and 69 disclosed in D1 in order to solve the objective technical problem. The skilled person can do this without any inventive skills.
- 4.8 Consequently, **claims 1-3, 9-18 are not inventive.**
- 4.9 With respect to the **subject matter of claim 8** document D1 too is the closest prior art. D1 discloses: A process to 3,4-substituted-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl esters starting from benzaldehyde derivatives and 4-methylpyridine derivatives followed by acylation (see D1, scheme on page 23). The difference to the presently claimed subject process and that of D1 are additional steps for acylation, separation of diastereomers and hydrolysis with chiral agents such as maleic acid and naproxene derivatives. The technical effect of this difference is that the present process is leading to pure enantiomeric compounds, whereas the process of D1 is racemic. The objective technical problem is thus formulated as provision of a process to 3,4-substituted-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl esters leading to pure enantiomeric products. A skilled person knowledgeable about chiral synthesis can solve this objective technical problem without inventive skills.
- 4.10 Hence **claim 8 is not inventive either.**

- 4.11 With respect to the **subject matter of claims 4-7** document D1 too is the closest prior art. D1 discloses a general formula (I) in claim 1 describing compounds, for which inhibitory activity on PDE-IV or therapeutic activity against asthma or COPD can be expected. The difference between the subject matter of claims 4-7 and document D1 is, that claims 4-7 are describing discrete molecules (claims 5-7) or small subset selections (claim 4) falling into the scope of claim 1 of D1. There is no technical effect reported for this selection made. The objective technical problem to be solved, when departing from D1 can thus be formulated as: Provision of alternative benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)ethyl ester derivatives for use in therapy of asthma or COPD.
- 4.12 The solution as presented by the applicant is not involving an inventive step. For said selection from within the teaching of formula (I) of D1 to be acknowledged an inventive step it would require an unexpected technical effect to be present, which is associated to the selection made. Since no such technical effect is reported, **claims 4-7 are not inventive**.
- 4.13 In summary, the subject matter of the **claims 1-18 is not inventive**.

Re Item VIII.

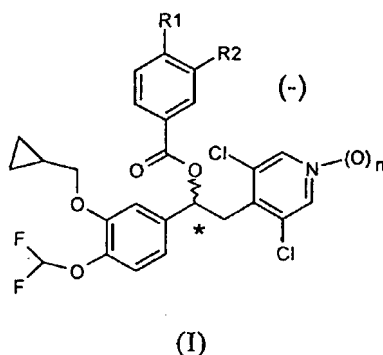
Certain observations on the international application

- 5 The application does not meet the requirements of Article 6 PCT, because claims 1-18 are not clear:
- 5.1 Claims 1 is not clear, as it defines the scope being formula (I) compounds and "addition complexes". It is not clear for a person skilled in the art, what qualifies as "addition complexes".
- 5.2 Claim 8 is not clear for several reason:

- 5.2.1 This process claim is directed towards providing levorotatory compounds of formula (I) in pure enantiomeric form. It is not clear, if intermediate "14" on page 42 is to be understood as being racemic or a pure enantiomeric form. On the other hand "14" later has the optical rotation sign "(+)" on page 43/first line and on page 16/line 23 of the description.
- 5.2.2 In claim 8 it is furthermore not clear, why (+)-14 and (+)-7 reacted with benzoic acid derivatives lead to (-)- formula (I) compounds. Since the benzoic acid derivatives are achiral, optical superposition according to van't Hoff rule can be disregarded. Hence the only applicable law is that of Freudenberg's optical displacement rule (sometimes translated as shift rule), which states that (+) compounds, when derivatized also give (+) derivatives (see K. Freudenberg et al, Ber. Dtsch. Chem. Ges 1923, 56, 193). Thus, the subject matter of claim 8 is contradicting that of the previous claims and hence there is a lack of clarity.
- 5.3 Claims 11-12 are not clear as both refers to "a combination according to claims 9". The subject-matter of claim 9 though is not directed towards a combination, but a substance claim (formula II).
- 5.4 Claims 15-16 are not clear as they are referring to "a composition according to claim 11". The subject-matter of claim 11 though is not directed towards a composition, but to a drug-combination.

REIVINDICACIONES

1. Un compuesto de la fórmula general (I) como (-) enantiómero



caracterizado porque:

10 n es 0 o 1;

R1 y R2 pueden ser iguales o diferentes, y son seleccionados del grupo que consiste de:

- alquilo C_1-C_6 lineal o ramificado, substituido opcionalmente por uno o más átomos de halógeno;

15 - OR3 en donde R3 es un alquilo C_1-C_6 lineal o ramificado opcionalmente substituido con uno o más átomos de halógeno o grupos cicloalquilo C_3-C_7 ; y

- $HNSO_2R_4$ en donde R4 es un alquilo C_1-C_4 lineal o ramificado opcionalmente substituido con uno o más átomos de halógeno,

en donde por lo menos uno de R1 y R2 es $HNSO_2R_4$, las sales inorgánicas u orgánicas,

20 hidratos y solvatos farmacéuticamente aceptables.

2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R1 es $HNSO_2R_4$, en donde R4 es metilo, R2 es OR3, en donde R3 es ciclopropilmetilo y n es 0.

3. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R1 es HNSO_2R_4 , en donde R4 es metilo, R2 es OR_3 , en donde R3 es ciclopropilmetilo y n es 1.

5 4. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R1 es OR_3 , R2 es HNSO_2R_4 en donde R4 es metilo y n es 1.

5. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R1 es metilo, R2 es HNSO_2R_4 , en donde R4 es metilo y n es 1.

10

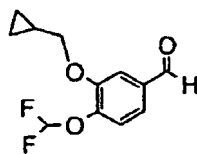
6. Un compuesto de conformidad con la reivindicación 1, caracterizado porque ambos R1 y R2 son HNSO_2R_4 en donde R4 es metilo y n es 0.

7. Un compuesto de conformidad con la reivindicación 1, caracterizado porque ambos R1 y R2 son HNSO_2R_4 , en donde R4 es metilo y n es 0.

15

8. Un proceso para la preparación de los compuestos de conformidad con las reivindicaciones 1 a 7, caracterizado porque comprende el paso de reaccionar el aldehído (1)

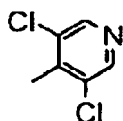
20



(1)

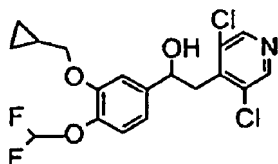
con metildicloropiridina (2)

25



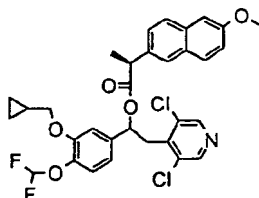
(2)

5 para obtener el alcohol racémico (3) que es opcionalmente oxidado al derivado de N-óxido correspondiente (4)



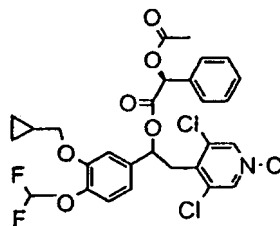
(3)

10 mediante la condensación de (3) ó (4) con un ácido quiral tal como (S)-naproxeno o ácido (S)-acetilmandélico para obtener respectivamente, una mezcla diastereomérica (10)



(10)

o (5)

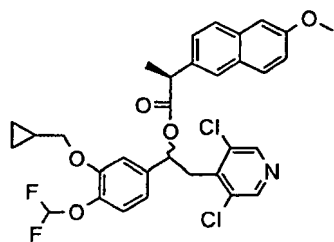


(5)

25 mediante la separación de la mezcla diastereomérica (10) o (5) en dos

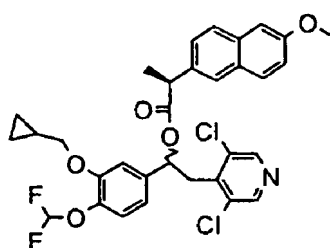
P-3022
Rvs modificadas
13-04-13

diastereoisómeros solos respectivamente (11)



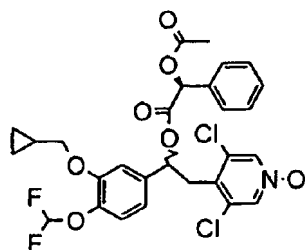
(11)

y (13)



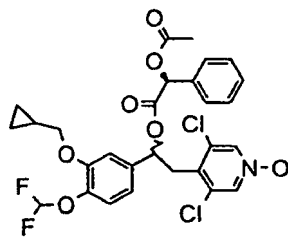
(13)

o (6)



(6)

y (8)

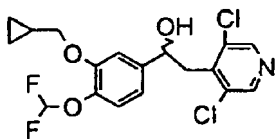


(8)

por cromatografía, o cristalización, después de la división se obtiene, el alcohol

P-3022
Rvs modificadas
13-04-13

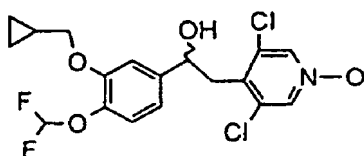
(+) (14)



(14)

5

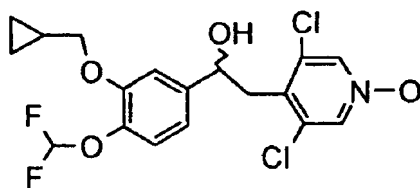
o (+)(7)



(7)

10

y (-)(9)

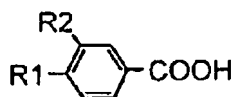


(9)

15

y después reaccionar el compuesto (+)(14) o (+)(7) con el ácido benzoico apropiado (15)

20

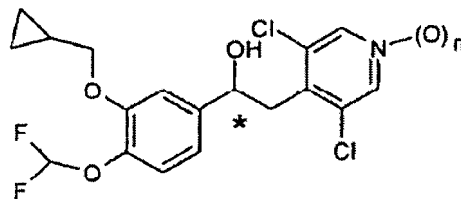


(15)

25 para dar los compuestos de la fórmula general (I), en donde R1 y R2 son de

conformidad con la reivindicación 1.

9. Un compuesto de la fórmula (II)



(II)

caracterizado porque n es de conformidad con la reivindicación 1 y el átomo de carbono representado con un asterisco abajo muestra una configuración (S).

10. Una combinación de un compuesto de la fórmula (I) de conformidad con cualquiera con las reivindicaciones 1 a 7, caracterizada porque tiene un segundo componente farmacéutico activo seleccionado de las clases de agonistas β_2 , antagonistas M3 y corticoesteroides.

11. Una combinación de conformidad con la reivindicación 10, caracterizada porque el segundo componente activo es formoterol o carmoterol.

12. Una composición farmacéutica caracterizada porque comprende un compuesto de la fórmula (I) de conformidad con cualquiera con las reivindicaciones 1 a 7, o una combinación de conformidad con cualquiera con las reivindicaciones 10 u 11, y uno o más portadores y/o excipientes farmacéuticamente aceptables.

13. Un compuesto de la fórmula (I) de conformidad con cualquiera con las reivindicaciones 1 a 7, caracterizado porque es un medicamento.

14. Un dispositivo caracterizado porque comprende una composición farmacéutica de conformidad con la reivindicación 12.

15. Un kit caracterizado porque comprende las composiciones farmacéuticas de conformidad con la reivindicación 12 y un dispositivo que puede ser un inhalador de polvo seco de una sola dosis o múltiples dosis.