Castillo Grau & Asociados
ABOGADOS

71 77

Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00014625 00000004 Folios: 2
Fecha (AMD): 2002-09-03 14:05:36
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re.: Código 02-01-538
Expediente No. 00-14.625
Solicitud de Patente
SMITHKLINE BEECHAM CORPORATION

En relación con el Expediente de la referencia por medio del presente escrito muy respetuosamente me permito solicitarles se sirvan proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago por concepto de $ 318.000.oo, recibo No. 02 58216.

De Ustedes Atentamente,

GERMAN CASTILLO GRAU
T.P. # 2978 del C.S.J.

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78

Industria y Comercio

SUPERINTENDENCIA

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00014625 00000004 Folios: 2
Fecha (AMD): 2002-09-03 14:05:36
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 58,216
FECHA : SEPTIEMBRE 3 DE 2002

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	2982129	02/09/2002	714,000.00

***** C O N C E P T O *****

CANT.	ITISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
			TOTAL : $	318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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2005-01-13
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Germán Castillo Grau **Oficio Nº 11827**
Apoderado

REFERENCIA	**Radicación**	**00 14625**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**008**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 00 14625, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

. Descripción: folios 4-14
. Ejemplos: folios 14-23
. Capítulo reivindicatorio estudiado: folios 40-41
. Se perdió el derecho a prioridad, según lo establecido en folio 76

Objeto de la invención

Según las reivindicaciones 1 a 7 de la presente solicitud, se refiere a un método para el tratamiento de COPD que comprende administrar un inhibidor de PDE 4. Se reivindican además la fabricación de un medicamento que contenga dichos compuestos

Clasificación internacional de patentes A 61 K 31/40

Claridad de la solicitud

El artículo 30 de la decisión 486 establece que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

El contenido de las reivindicaciones 5-7 no describe ningún proceso de fabricación, puesto que pretende definir la fabricación de un medicamento mediante las características de inhibición del compuesto que lo contiene, además, dichas reivindicaciones no se encuentran sustentadas por la descripción, debido a que a lo largo de ésta no se describe ningún procedimiento de fabricación de medicamentos que contienen inhibidores de PDE 4. Cabe anotar que un procedimiento de fabricación se debe definir por sus pasos específicos que lo diferencien de los demás procedimientos de fabricación que se encuentran revelados en el estado de la técnica

Favor hacer las aclaraciones y correcciones del caso.

Excepciones a la patentabilidad

El artículo 20d de la decisión 486 establece que *"No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 1-4, que trata de "Un método para la profilaxis o tratamiento de CODP..." no es patentable

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 01.03.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	US 5552438	"Compuestos útiles para el tratamiento de enfermedades alérgicas e inflamatorias"	03.09.96

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel

inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 dispone *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La patente US 5552438 se relaciona con compuestos de fórmula (I) que son inhibidores de PDE 4 y composiciones farmacéuticas que los contienen. Finalmente, se describe que se demuestra una IC 50 con respecto a la actividad inhibitoria de PDE 4.

Comparando elemento por elemento, las composiciones de la anterioridad citada son iguales a las de las reivindicaciones 5-7 y pueden afectar la novedad de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 552438	5-7	Novedad

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 5 del título primero de la Circular Única Nº 10 de 2001

Doris Polo Córdoba
Jefe de la División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 13 ENE. 2005

CONCEPTO TÉCNICO Número 1672	**EXAMINADOR TÉCNICO** Código 202024

US005552438A

United States Patent [19]

Christensen, IV

[11] Patent Number: 5,552,438

[45] Date of Patent: Sep. 3, 1996

[54] **COMPOUNDS USEFUL FOR TREATING ALLERGIC AND INFLAMMATORY DISEASES**

[75] Inventor: **Siegfried B. Christensen, IV**, Philadelphia, Pa.

[73] Assignee: **SmithKline Beecham Corporation**, Philadelphia, Pa.

[21] Appl. No.: **313,094**

[22] PCT Filed: **Mar. 5, 1993**

[86] PCT No.: **PCT/US93/01991**

§ 371 Date: **Sep. 29, 1994**

§ 102(e) Date: **Sep. 29, 1994**

[87] PCT Pub. No.: **WO93/19749**

PCT Pub. Date: **Oct. 14, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 968,762, Oct. 30, 1992, abandoned, which is a continuation-in-part of Ser. No. 862,030, Apr. 2, 1992, abandoned.

[51] **Int. Cl.**[6] **A61K 31/275**; C07C 255/50

[52] **U.S. Cl.** **514/520**; 514/521; 514/362; 514/363; 514/364; 514/381; 548/127; 548/128; 548/131; 548/134; 548/136; 548/143; 548/252; 558/426; 558/431

[58] **Field of Search** 558/426; 548/127, 548/128, 131, 134, 136, 143, 252; 514/520, 521, 362, 363, 364, 381

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,862,239	1/1975	Karmas	562/469
3,979,444	9/1976	Lednicer	260/490
4,795,757	1/1989	Regan et al.	514/415

FOREIGN PATENT DOCUMENTS

WO-A-9307111	4/1993	WIPO .
WO-A-9319720	10/1993	WIPO .
WO-A-9319750	10/1993	WIPO .
WO-A-9319748	10/1993	WIPO .

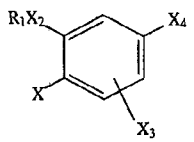
OTHER PUBLICATIONS

Chemical Abstracts, vol. 90, No. 11, Mar. 1979, abstract 86895p.

Primary Examiner—Jacqueline Haley
Attorney, Agent, or Firm—James M. Kanagy; Stuart R. Suter; Edward T. Lentz

[57] **ABSTRACT**

Novel compounds of Formula (I)



where X_4 is a substituted cyclohexane or cyclohexane group and the other radicals are defined herein. These compounds inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production. The compounds of the present invention are also useful in the mediation or inhibition of enzymatic or catalytic activity of phosphodiesterase IV and are therefore useful in the treatment of disease states in need of mediation or inhibition thereof.

9 Claims, No Drawings

COMPOUNDS USEFUL FOR TREATING ALLERGIC AND INFLAMMATORY DISEASES

This is a National Stage application of PCT/US93/01991 filed Mar. 5, 1993 and published as WO93/19749 on Oct. 14, 1993 which is a continuation-in-part of U.S. Ser. No. 07/968,762 filed Oct. 30, 1992, now abandoned which is a continuation-in-part of U.S. Ser. No. 07/862,030 filed Apr. 2, 1992, now abandoned.

FIELD OF INVENTION

The present invention relates to novel compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

BACKGROUND OF THE INVENTION

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17–29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts Mg^{+2}-ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit the production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli et at., Proc. Natl. Acad. Sci., 87:782–784, 1990], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

as levels of reverse transcriptase or vital proteins, and/or for progression of monokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is seen following the normal treatment regimen, then the amount of the monokine activity interfering agent administered is increased. e.g., by fifty percent per week.

The pharmaoeutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable career or diluent. The compounds of Formula (I) are administered in conventional dosage forms prepared by combining a compound of Formula (I) in an amount sufficient to produce TNF production inhibiting activity, respectively, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating, and compressing or dissolving the ingredients as appropriate to the desired preparation.

Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates, or oils and are incorporated in a soft gelatin capsule shell. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine, or water with a flavoring or coloring agent.

The daily dosage regimen for oral administration is suitably about 001 mg/kg to 100 mg/kg, preferably 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.

While it is possible for an active ingredient to be administered neat, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of formulation, although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of Formulation.

Formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) thereof and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of Formulation and not deleterious to the recipient thereof.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable career or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration, and other well-known variables.

No toxic effects are expected when these compounds are administered in accordance with the present invention.

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of the Formula (I) on in vitro TNF production by human monocytes.

The inhibitory effect of compounds of the Formula (I) on in vitro TNF production by human monocytes may be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, Feb. 6, 1991, and in Hanna, WO 90/15534, Dec. 27, 1990.

EXAMPLE B

Two models of endotoxic shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is described in Badger et al., EPO published Application 0 411 754 A2, Feb. 6, 1991, and in Hanna, WO 90/15534, Dec. 27, 1990.

The exemplified compounds herein demonstrated a positive in vivo response in reducing serum levels of TNF induced by the injection of endotoxin.

EXAMPLE C

Isolation of PDE Isozymes

The phosphodiesterase inhibitory activity and selectivity of the compounds of the Formula (I) can be determined using a battery of five distinct PDE isozymes. The tissues used as sources of the different isozymes are as follows: 1) PDE Ib, porcine aorta; 2) PDE Ic, guinea-pig heart; 3) PDE III, guinea-pig heart; 4) PDE IV, human monocyte; and 5) PDE V (also called "Ia"), canine tracheaolis. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torphy and Cieslinski, Mol. Pharmacol., 37:206–214, 1990]. PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography [Torphy et al., J. Biol. Chem., 267:1798–1804, 1992].

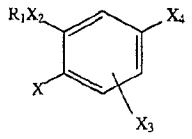
Phosphodiesterase activity is assayed as described in the protocol of Torphy and Cieslinski, Mol. Pharmacol., 37:206–214, 1990. Positive $IC_{50's}$ in the nanomolar to μM range for compounds of the workings examples described herein for Formula (I) have been demonstrated.

EXAMPLE D

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01–1000 μM) of PDE inhibitors for one minute and 1 μM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 17.5% perchloric acid, the pH was neutralized by the addition of 1 M potassium carbonate and camp content was assessed by RIA. A general protocol for this assay is described in Brooker et al., Radioimmunassay of cyclic AMP and cyclic GMP., Adv. Cyclic Nucleotide Res., 10:1–33, 1979. The compounds of the working examples as described herein for Formula (I) have demonstrated a positive EC_{50s} in the μM range in the above assay.

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected from hydrogen or a C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

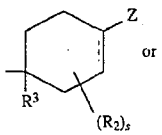
Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

X_2 is O or NR_8;

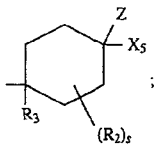
X_3 is hydrogen or X;

X_4 is



(a)

or



(b)

;

X_5 is H, R_9, OR_8, CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8;

R_2 is independently selected from the group consisting of $-CH_3$ and $-CH_2CH_3$ optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is CN;

Z' is O, NR_9, NOR_8, NCN, $C(=CN)_2$, CR_8CN, CR_8NO_2, $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(=CN)NO_2$, $C(=CN)C(O)OR_9$, or $C(=CN)C(O)NR_8R_8$;

Z is $C(Y')R_{14}$, $C(O)OR_{14}$, $C(Y')NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_8)R_{14}$, $C(O)NR_8NR_8C(O)R_8$, $C(O)NR_8NR_{10}R_{14}$, $C(NOR_{14})R_8$, $C(NR_8)NR_{10}R_{14}$, $C(NR_{14})NR_8R_8$, $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_9$, (2-,4- or 5-imidazolyl), (3-,4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-,4- or 5-oxazolyl), (3-,4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-,4-, or 5-thiazolyl), (2-,4-, or 5-oxazolidinyl), (2-,4-, or 5-thiazolidinyl), or (2-,4-, or 5-imidazolidinyl); wherein all of these heterocylic ring systems may be optionally substituted one or more times by R_{14};

the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, —F, —Br, —Cl, NO_2, $-NR_{10}R_{11}$, $-C(O)R_8$, $-C(O)OR_8$, $-OR_8$, —CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_3–C_7-cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R_8 is independently selected from hydrogen or R_9;

R_8, is R_8 or fluorine;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as NR_1R_{11} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen;

provided that:

f) when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1;

or the pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is:

methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl) cyclohex-1-ene-1-carboxylate;

4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid;

methyl trans-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

methyl trans-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

[cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate], tris(hydroxymethyl)ammonium methane salt;

cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl) cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

methyl cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylate];

methyl trans-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];

trans-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carbohydrazide];

cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-(2-acetylcarbohydrazide)];

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5yl)cyclohexane};

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5yl)cyclohexane};

cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5yl)cyclohexane};

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1tris(methylthio)methylcyclohexane];

methyl cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1carboxamide];

methyl cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1carboxamide];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1carboxaldehyde];

methyl trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];

methyl trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide acid];

N-methyl-cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];

cis-[1-(2-cyanoethyl)-5-{4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl}tetrazole]; and

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].

3. A compound according to claim **1** wherein R_1 is CH_2cyclopropyl, CH_2—C_{5-6}cycloalkyl, C_{4-6}cycloalkyl, C_{7-11}polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C_{1-2}alkyl optionally subsitituted by 1 or more fluorines, $—(CH_2)_{1-3}C(O)O(CH_2)_{0-2}C_3$, $—(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and $—(CH_2)_{2-4}OH$.

4. A compound of claim **3** wherein R_1 is $—CH_2$-cyclopropyl, cyclopentyl, methyl or CF_2H, R_3 is CN, X_2 is oxygen, X_3 is hydrogen and R_2 is CF_2H or methyl.

5. A pharmaceutical composition comprising a compound of Formula (I) according to claim **1** and a pharmaceutically acceptable excipient.

6. A method for treating an allergic or inflammatory disease which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim **1** alone or in combination with a pharmaceutically acceptable excipient.

7. A compound according to claim **1** which is:

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising the compound of claim **7** and a pharmaceutically acceptable excipient.

9. A method for treating an allergic or inflammatory disease which method comprises administering to a subject in need thereof an effective amount of the compound of claim **7** alone or in combination with a pharmaceutically acceptable excipient.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-14625** EDICTO No. **6001**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **9684** de **29-ABR-2005**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "METODO PARA TRATAR COPD".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, o a quien haga sus veces, en su calidad de apoderado de Smithkline Beecham Corporation., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 29 ABR. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIME RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **23-MAY-2005** Este edicto se desfija hoy**07-JUN-2005** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. **6001**