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SUPERINDUSTRIA Y COMERCIO	
Radicacion : 00058243 00000004	Folios: 2
Fecha (AMD): 2003-01-21 12:29:20	
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION	
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES	

Expediente No. 00 58.243
Solicitud de Patente a nombre
de "SMITHKLINE BEECHAM
CORPORATION"
Código : 02-01-538

En relación con la solicitud contenida en el Expediente de la referencia y, en particular, con la publicación del extracto de la misma en la Gaceta de la Propiedad Industrial No. 519 de 29 de Agosto de 2002, por medio del presente escrito muy respetuosamente me permito solicitarle se sirva proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Como consecuencia de esta solicitud, acompaño el comprobante de pago por concepto de la tasa respectiva, Recibo No. 4191.

De Usted Atentamente,

GERMAN CASTILLO GRAU
C.C. 17.017.671 de Bogotá
TP 2.908 del C.S.J.

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Industria y Comercio**SUPERINTENDENCIA**

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO Folios: 2
 Radicacion : 00038243 00000004
 Fecha (RAD): 2003-01-21 12:29:20
 Trámite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
 Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 03 - 4,191
 FECHA : ENERO 21 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	8771307	21/01/2003	832,000.00

***** CONCEPTO *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	DE EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
	TOTAL :	\$ 335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE N°. _____

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D1 87

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07C 253/30, 255/36, 255/37, 255/38, 255/41, 255/46, A61K 31/275	A1	(11) International Publication Number: WO 95/24381 (43) International Publication Date: 14 September 1995 (14.09.95)
(21) International Application Number: PCT/US95/02965 (22) International Filing Date: 8 March 1995 (08.03.95) (30) Priority Data: 9404706.5 11 March 1994 (11.03.94) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate, Intellectual Property, WW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BORDAS-NAGY, Joseph [CA/US]; Apartment 0102, 655 South Fair Oaks, Sunnyvale, CA 94086 (US). GORYCKI, Peter [US/US]; 1801 Butler Pike #121, Conshohocken, PA 19428 (US). WEBB, Kevin, Scott [US/US]; 1415 Powder Horn Drive, Phoenixville, PA 19460 (US). (74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, PT, RO, RU, SD, SG, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: CYANO COMPOUNDS AND PREPARATIONS THEREOF (57) Abstract This invention relates to compounds of formula (I) which are useful as PDE IV inhibitors and for treating diseases related thereto. (I)		

CYANO COMPOUNDS AND PREPARATIONS THEREOF

Field of the Invention

The present invention relates to novel phenylcyclohexan-1-ylcarboxylic acids, pharmaceutical compositions containing these compounds, the use of these compounds in
5 treating allergic and inflammatory diseases and to the use of these compounds to inhibit 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.
10 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 components of chronic bronchial asthma.

An alternative to the "mediator approach" is to regulate the activity of cells
15 responsible for the pathophysiology of asthma. Cyclic AMP (cAMP, adenosine cyclic 3',5'-monophosphate) modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. 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
20 degranulation, and (5) inhibition of monocyte and macrophage activation. Cyclic AMP has been shown to mediate cellular responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973].

One potential means to regulate the activity of cells responsible for the
25 pathophysiology of asthma is to control the intracellular levels of cyclic AMP. Cellular cAMP levels are elevated when an appropriate agonist binds to particular cell surface receptors, thereby activating adenylate cyclase to convert Mg^{+2} -ATP to cAMP at an accelerated rate. 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
30 as cyclic nucleotide phosphodiesterases (cyclic nucleotide phosphodiesterase hereinafter "PDE"s). 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.

It has been shown that a distinct PDE isozyme, PDE IV, is responsible for cAMP
35 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

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degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. The beneficial effects of PDE IV inhibition are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids. Thus, PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E₂ and prostacyclin (both activators of adenylate cyclase) are elevated. PDE IV inhibitors offer a unique approach to the pharmacotherapy of bronchial asthma, and possess significant therapeutic advantages over agents currently on the market. The compounds of this invention have the ability to inhibit PDE IV.

The compounds of this invention also inhibit the production of TNF, a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of undesirable physiological conditions, such as diseases, and 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, human acquired immune deficiency syndrome (AIDS), cachexia secondary to AIDS, AIDS related complex (ARC), 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 erythematosus.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified: 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 a T lymphocyte requires prior T lymphocyte activation. Once an activated T lymphocyte has been infected with HIV, the T lymphocyte must be maintained in an activated state in order to permit HIV gene expression and/or HIV replication.

Cytokines, including TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication as playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity in an HIV-infected individual, such as by inhibition of TNF production, aids in limiting the maintenance of T cell activation, and thereby mitigates the progression of HIV infection to previously uninfected cells. When HIV infection of previously uninfected cells is diminished, a slowing or elimination of the progression of immune dysfunction caused by HIV infection results.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in the maintenance of HIV infection. These cells, like T cells, are targets for viral replication, where the level of viral replication is dependent upon the

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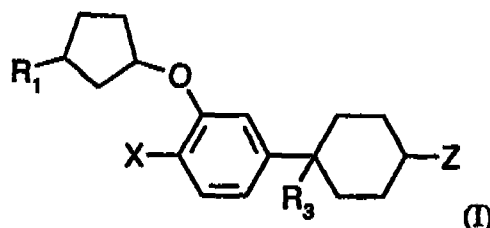
activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli *et al.*, Proc. Natl. Acad. Sci., 87:782-784, 1990], therefore, 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. TNF is also associated with yeast and fungal infections.

Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells. [See Riipi *et al.*, Infection and Immunity, 58(9):2750-54, 1990; and Jafari *et al.*, Journal of Infectious Diseases, 164:389-95, 1991. See also Wasan *et al.*, Antimicrobial Agents and Chemotherapy, 35(10):2046-48, 1991; and Luke *et al.*, Journal of Infectious Diseases, 162:211-214, 1990].

Summary of the Invention

This invention relates to certain compounds of Formula I



wherein

R₁ is OH or an ether or ester thereof,

X is YR₂, halogen, nitro, NR₄R₅ or formyl amine;

Y is O or S(O)_m, where m is 0, 1 or 2;

R₂ is methyl or ethyl, where either methyl or ethyl may be optionally substituted by 1 or more halogens;

R₃ is hydrogen, halogen, C₁₋₄alkyl, CH₂NHC(O)C(O)NH₂, halo-substituted C₁₋₄alkyl, -CH=CHR₈R₈', cyclopropyl optionally substituted by R₈', CN, OR₈, CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or -C≡CR₈;

R₄ and R₅ are independently hydrogen or C₁₋₂ alkyl;

R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is optionally substituted one or more times by C₁₋₂ alkyl optionally substituted by one to three groups selected from -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(=O)R₈, -C(=O)OR₈, -OR₈, -CN, -C(=O)NR₁₀R₁₁, -OC(=O)NR₁₀R₁₁, -OC(=O)R₈, -NR₁₀C(=O)NR₁₀R₁₁, -NR₁₀C(=O)R₁₁, -NR₁₀C(=O)OR₉, -NR₁₀C(=O)R₁₃, -C(=NR₁₀)NR₁₀R₁₁, -C(=N-

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CN)NR₁₀R₁₁, -C(=N-CN)SR₉, -NR₁₀C(=N-CN)NR₁₀R₁₁, -NR₁₀S(=O)₂R₉,
-S(O)_mR₉, -NR₁₀C(=O)C(=O)NR₁₀R₁₁, -NR₁₀C(=O)C(=O)R₁₀, thiazolyl, imidazolyl,
oxazolyl, pyrazolyl, triazolyl or tetrazolyl;

R₈ is -H or R₉;

5 R₈' is R₈ or fluorine;

R₉ is C₁₋₄ alkyl optionally substituted by one to three -F;

R₁₀ is OR₈, hydrogen, or C₁₋₄alkyl optionally substituted by one to three
fluorines;

R₁₁ is -H or C₁₋₄ alkyl optionally substituted by one to three -F; or when R₁₀ and
10 R₁₁ are as NR₁₀R₁₁ 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;

R₁₂ is C₃₋₇ cycloalkyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazolyl,
1-imidazolyl, 2-imidazolyl, thiazolyl, triazolyl, pyrrolyl, piperaziny, piperidiny,
morpholinyl, furanyl, 2-thienyl, 3-thienyl, 4-thiazolyl, 5-thiazolyl, quinolinyl, naphthyl or
15 phenyl;

R₁₃ is a heterocyclic ring selected from oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl,
triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl or
thiadiazolyl, where R₁₃ is appended to a compound of Formula (I) through a carbon atom
of the heterocyclic ring, and where each heterocyclic ring may be unsubstituted or
20 substituted by one or two C₁₋₂ alkyl groups;

R₁₄ is H or R₇, or when R₁₀ and R₁₄ are as NR₁₀R₁₄, they may together with the
nitrogen atom form a 5 to 7 membered ring optionally containing at least one additional
heteroatom selected from O, N or S;

m' is 0, 1 or 2;

25 q is 0, 1 or 2.

Y' is O or S;

Z is C(=Y')R₁₄, C(=O)OR₁₄, C(=Y')NR₁₀R₁₄, C(=NR₁₀)NR₁₀R₁₄, CN,
C(=NOR₈)R₁₄, C(=O)NR₈NR₈C(=O)R₈, C(=O)NR₈NR₁₀R₁₄, C(=NOR₁₄)R₈,
C(=NR₈)NR₁₀R₁₄, C(=NR₁₄)NR₈R₈, C(=N-CN)NR₁₀R₁₄, C(=N-CN)SR₉, 2-
30 imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 4-
triazolyl[1,2,3], 5-triazolyl[1,2,3], 3-triazolyl[1,2,4], 5-triazolyl[1,2,4], 5-tetrazolyl, 2-
oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-
oxadiazolyl[1,2,4], 5-oxadiazolyl[1,2,4], 2-oxadiazolyl[1,3,4], 2-thiadiazolyl[1,3,4], 2-
thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolidinyl, 4-oxazolidinyl, 5-oxazolidinyl, 2-
35 thiazolidinyl, 4-thiazolidinyl or 5-thiazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, or 5-
imidazolidinyl; wherein all of the heterocyclic ring systems may be optionally substituted
one or more times by R₁₄;

Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈,
CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈ ;

or

a pharmaceutically acceptable salt thereof.

5 This invention also relates to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable excipient.

This invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of Formula
10 (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method for the treatment of allergic and inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

15 This invention also relates to a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention further relates to a method of inhibiting TNF production in a mammal, including humans, which comprises administering to a mammal in need of such
20 treatment, an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. This method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states effected thereby.

This invention further relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which method comprises administering to a human
25 in need of such treatment, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF, or will elicit TNF production *in vivo*.

30 Detailed Description of the Invention

Definitions

As used herein, the following terms and expressions have the indicated meaning.

"Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. The alkyl
35 chain is meant to include both straight or branched chain radicals of 1 to 4 carbon atoms.

The term "C₁₋₂ alkyl", "C₁₋₄ alkyl", "C₁₋₆ alkyl" or "alkyl groups" includes both straight or branched chain radicals of 1 to 10 carbon atoms, unless the chain length is

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otherwise limited thereto, including, but not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like.

The term "C₃₋₇ cycloalkyl" means groups of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl.

5 "Cytokine" means any secreted polypeptide that affects the functions of cells, and is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. The cytokine inhibited by the present invention for use in the treatment of an HIV-infected human must be a cytokine which is
10 implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

"Halo" includes all halogen radicals, i.e., chloro, fluoro, bromo, or iodo.

"Heteroaryl" means an aromatic ring system containing one or more heteroatoms,
15 such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl.

"Inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

a) a decrease of excessive *in vivo* IL-1 or TNF levels in a human, to normal levels or below normal levels by inhibition of the *in vivo* release of IL-1 by all cells,
20 including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcriptional level, of excessive *in vivo* IL-1 or TNF levels in a human, to normal levels or below normal levels;
or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF
25 levels as a postranslational event.

"Percentage" and "%" refers to percentage by weight of a component or ingredient based on the weight of the total composition containing such component or ingredient.

"TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for
30 instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin), and since each induces similar biologic responses and binds to the
35 same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

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This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically

5 acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion
10 injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and central nervous system disorders such as depression and multi-infarct dementia.

The viruses contemplated for treatment herein are those that produce TNF as a
15 result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

20 This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may also be used in association with the veterinary
25 treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anemia virus, caprine arthritis virus, visna
30 virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis. Additionally, a compound of Formula (I) may be administered in conjunction with other
35 drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymycins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such

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as fluconazole, and itranazole, and the class of compounds called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

- 5 A compound of Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of Formula (I) to a mammal in need of such treatment. Preferably, a compound of Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Preferred Compounds

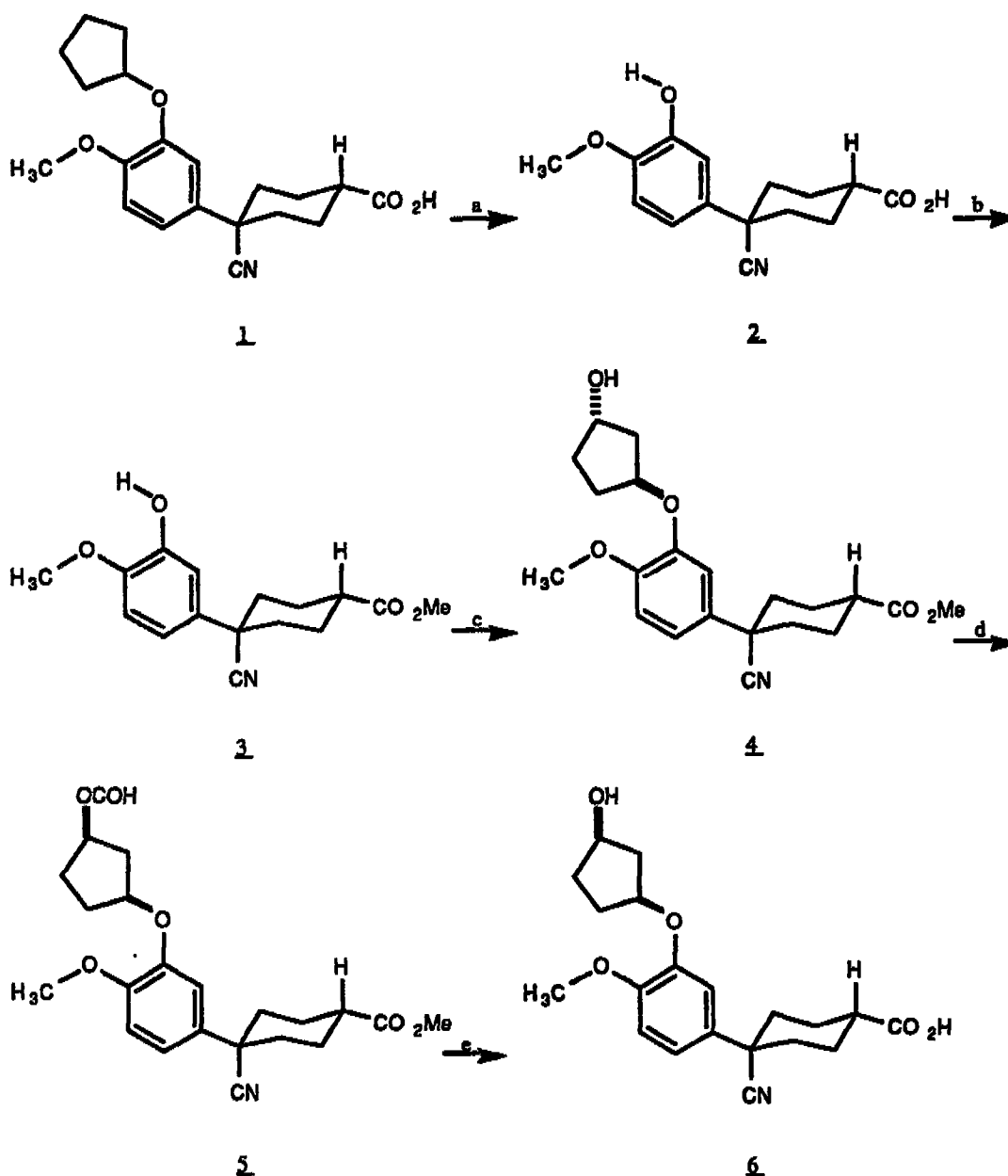
- 10 The preferred compounds of this invention are those where R_1 is OH or -COOH, X is YR_2 particularly where Y is O and R_2 is methyl substituted by 1 or more halogens; R_3 is CN or $-C\equiv CH$ and Z is a carboxylic acid derivative such as a $-C(O)OH$, a salt thereof or an ester or amide derivative such as $C(=Y)R_{14}$, $C(=O)OR_{14}$, $C(=Y)NR_{10}R_{14}$, $C(=NR_{10})NR_{10}R_{14}$. In addition, it is preferred that the R_3 group be axial and the Z group be equatorial.

- 15 The specific compounds disclosed herein are:
cis-{4-cyano-4-[3-(cis-3-hydroxycyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid};
cis-{4-cyano-4-[3-(cis-3-formyloxycyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid}, and
20 cis-{4-cyano-4-[3-(trans-3-hydroxycyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid}.

Syntheses

- Preparation of the compounds of Formula (I) can be carried out by one of skill in the art according to the procedures outlined reaction scheme set forth below and the specific chemistries set out in the Examples, *infra*. While the scheme and the examples illustrate the preparation of the cis/cis isomer(s), the cis/trans isomer(s) can be prepared by the same set of chemistries, with a nominal change in the treatment of compound 4; saponifying compound 4 provides the cis/trans compound namely the cis-{4-cyano-4-[3-(trans-3-hydroxycyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid} or the
30 corresponding compounds as defined by Formula I. The preparation of any remaining compounds of the Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

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Example 1

Preparation of cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]1(a) (3-Cyclopentyloxy-4-methoxyphenyl)acetonitrile

To a solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (20 g, 90.8 mmol) in acetonitrile (100 mL) was added lithium bromide (15 g, 173 mmol) followed by the dropwise addition of trimethylsilylchloride (17.4 mL, 137 mmol). After 15 min, the reaction mixture was cooled to 0° C, 1,1,3,3-tetramethyldisiloxane (26.7 mL, 151 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature. After stirring for 3 h, the mixture was separated into two layers. The lower layer was

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removed, diluted with methylene chloride and filtered through Celite®. The filtrate was concentrated under reduced pressure, dissolved in methylene chloride and refiltered. The solvent was removed in vacuo to provide a light tan oil. To a solution of this crude a-bromo-3-cyclopentyloxy-4-methoxytoluene in dimethylformamide (160 mL) under an argon atmosphere was added sodium cyanide (10.1 g, 206 mmol) and the resulting mixture was stirred at room temperature for 18 h, then poured into cold water (600 mL) and extracted three times with ether. The organic extract was washed three times with water, once with brine and was dried (K₂CO₃). The solvent was removed in vacuo and the residue was purified by flash chromatography (silica gel, 10% ethyl acetate/hexanes) to provide an off-white solid (m.p. 32-34° C); an additional quantity of slightly impure material also was isolated.

1(b) Dimethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)pimelate

To a solution of (3-cyclopentyloxy-4-methoxyphenyl)acetonitrile (7 g, 30.3 mmol) in acetonitrile (200 mL) under an argon atmosphere was added a 40% solution of Triton-B in methanol (1.4 mL, 3.03 mmol) and the mixture was heated to reflux. Methyl acrylate (27 mL, 303 mmol) was added carefully, the reaction mixture was maintained at reflux for 5 h and then cooled. The mixture was diluted with ether, was washed once with 1N hydrochloric acid and once with brine, was dried (MgSO₄) and the solvent was removed in vacuo. The solid residue was triturated with 5% ethanol/hexane to provide a white solid (m.p. 81-82° C); an additional quantity was also obtained from the filtrate. Anal. (C₂₂H₂₉NO₆) calcd: C 65.49, H 7.25, N 3.47. found: C 65.47, H 7.11, N 3.49.

1(c) 2-Carbomethoxy-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one

To a suspension of sodium methoxide (350 mL, 1.55 mol, 25% w/w in methanol) in toluene (2.45 L) heated to 80° C under a nitrogen atmosphere was added a solution of dimethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)pimelate (350.0 g, 0.87 mol) in toluene (1.05 L) over 10 min. The reaction was heated to 85° C by distilling away 250 mL of solvent and was vigorously stirred under nitrogen for 2 hours. The reaction was cooled to 50° C and was quenched with 3N (aq) HCl (700 mL, 2.1 mol). The organic layer was isolated, was washed once with deionized water (700 mL) and once with brine (700 mL). The organic layer was concentrated via low vacuum distillation to afford crude 2-carbomethoxy-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-one in toluene. This was dissolved in 4.2 L of dimethyl sulfoxide and used in the next step.

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1(d) 4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one

To a suspension of sodium chloride (315 g, 5.39 mol) and deionized water (315 mL) was added the dimethyl sulfoxide (4.2 L) solution of 2-carbomethoxy-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-one (323 g, 0.87 mol) and the resulting suspension was heated to 155° C for 1.75 h. The reaction was cooled to 40° C, was quenched into 8 L of iced water (2° C) and was extracted with ethyl acetate (3.5 L). The aqueous layer was isolated and re-extracted with 2.5 L of ethyl acetate. The combined organic extract (6 L) was washed two times with deionized water (2 x 1 L) and once with brine (1 L). The organic layer was isolated and concentrated in vacuo to afford a residue.

This residue was dissolved in refluxing isopropanol (500 mL), was cooled to 0° C and held at this temperature for 1 hour. The crystals were isolated by filtration, were washed with 250 mL of isopropanol (0° C), and were dried in a vacuum oven (45° C at 20 inches) to produce 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one. m.p. 111-112° C; Anal. (C₁₉H₂₃NO₃) calcd: C 72.82, H 7.40, N 4.47; found: C 72.72, H 7.39, N 4.48.

1(e) 2-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexylidene]-1,3-dithiane

To a solution of 2-trimethylsilyl-1,3-dithiane (9.25 mL, 48.7 mmol) in dry tetrahydrofuran (80 mL) at 0° C under an argon atmosphere was added rapidly n-butyllithium (2.5M in hexanes, 19.2 mL, 48 mmol). After 10 min, the mixture was cooled to -78° C and a solution of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (7.53 g, 23 mmol) in tetrahydrofuran (40 mL) was added. After 10 min, aqueous sodium chloride was added, the mixture was allowed to warm to room temperature and was diluted with water. This mixture was combined with the product of three substantially similar reactions conducted on ketone (3.04, 6.01 and 6.1 g, 48.3 mmol total), the combined mixture was extracted three times with methylene chloride, the extract was dried (MgSO₄) and evaporated. Purification by flash chromatography (silica gel, 10% ethyl acetate/hexanes) provided a white solid. m.p. 115-116° C.

1(f) cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]

To a suspension of 2-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexylidene]-1,3-dithiane (140.0 g, 0.34 mol) in acetonitrile (500 mL) and deionized water (140 mL) under nitrogen was added trifluoroacetic acid (136 g, 1.19 mol). The suspension was heated to 65° C for 1.25 h followed by the addition of 20% sodium hydroxide (420 g, 2.1 mol). The solution was heated at 70 to 75° C for an additional 1.25 h, was cooled to 45° C, deionized water (420 mL) was added followed by 3N (aq) HCl (392 mL, 1.18 mol). The suspension was cooled to 5° C and held for 1 h. The suspension was filtered, was washed with cold (5° C) deionized water (200 mL), and was dried in a vacuum oven (40° C at 20 inches) to obtain crude cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]. This material was assayed at 98.5% and was found to be a 98.8:1.2 mixture of cis-to-trans isomers, which was contaminated with

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0.1% of residual 1,3-propanedithiol. This material was purified via an oxidative workup as follows.

To a hot solution (65° C) of crude cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] (85 g, 0.247 mol) in acetonitrile (425 mL) was added 1M sodium hydroxide (425 mL, 0.425 mol). To the solution (60° C) was added 4.25 g of calcium hypochlorite and the suspension was vigorously stirred for 2 h. The reaction was concentrated by distilling out 320 mL of solvent, followed by the addition of ethyl acetate (425 mL). The reaction was again concentrated by distilling out 445 mL of solvent, was cooled to 55° C followed by the addition of ethyl acetate (1.0 L) and 6N (aq.) HCl (100 mL). The organic layer was isolated, was washed three times with deionized water (3 x 300 mL), was filtered and was concentrated by distilling out 530 mL of solvent. To the solution was added ethyl acetate (635 mL) with continued distillation to remove 750 mL of solvent. The solution was cooled to 65° C followed by the addition of hexane (340 mL). The suspension was cooled to 5° C, held at this temperature for 1 hour, was filtered and was washed with cold (5° C) 10% ethyl acetate/hexane (200 mL). The solid was collected and was dried in a vacuum oven (40° C at 20 inches) to obtain cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]. This material was found to contain no trans isomer. Anal. (C₂₀H₂₅NO₄) calcd: C 69.95, H 7.34, N 4.08; found: C 69.90, H 7.35, N 4.02.

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Example 2

Preparation of cis-[4-cyano-4-[3-(trans-3-hydroxycyclopentyloxy)-4-methoxyphenyl]-cyclohexane-1-carboxylic acid]

2(a) cis-[4-Cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]

To a solution of boron tribromide in dichloromethane (0.1M, 335 mL, 33.5 mmol) under an argon atmosphere at -78° C was slowly added a solution of cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] (4.03 g, 11.7 mmol) in dichloromethane (180 mL). The mixture was stirred for 5 min, 15% sodium methoxide in methanol was added to pH 8-9 and the reaction was warmed to RT. Water (100mL) was added and the mixture was acidified with 3N aqueous hydrochloric acid to pH 1-2. The organic layer was separated, was dried (MgSO₄/Na₂SO₄), was filtered and was evaporated. The residue was twice dissolved in chloroform and the solution was evaporated to yield a white solid. ¹H NMR(400 MHz, CDCl₃) δ 7.01 (d, J=2.4 Hz, 1H), 6.96 (d of d, J=2.4, 8.5 Hz, 1H), 3.89 (s, 3H), 2.31 (m, 1H), 2.21 (br t, J=13.6 Hz, 4H), 1.98 (m, 2H), 1.77 (m, 2H); mp 190-193° C.

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2(b) Methyl cis-[4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexane-1-carboxylate]

p-Toluenesulfonic acid monohydrate (0.015 g, 0.08 mmol) was added to a solution of the compound of Example 2(a) (0.70 g, 2.54 mmol) in dry methanol (20 mL) under an argon atmosphere and the reaction was stirred for 6 h at 45-50° C. The reaction was

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Preparation of cis-[4-cyano-4-[3-(cis-3-hydroxycyclopentyloxy)-4-methoxyphenyl]-cyclohexane-1-carboxylic acid]

3(a) Methyl cis-[4-cyano-4-[3-(cis-3-formyloxy-cyclopentyloxy)-4-methoxyphenyl]-cyclohexane-1-carboxylate]

5 The compound of Example 2(c) (0.68 g, 1.83 mmol) was dissolved in tetrahydrofuran (20 mL) under an argon atmosphere and was treated with triphenylphosphine (0.96 g, 3.66 mmol) and formic acid (0.17 g, 3.66 mmol). Diethyl azodicarboxylate (0.64 g, 3.66 mmol) was added and the mixture was stirred at RT for 16 h. The solution was evaporated, ether was added and the white solid was removed by
10 filtration. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, 65% hexane/ethyl acetate) to yield the title compound as a clear colorless oil. ¹H NMR(400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.0 (d of d, J=2.4, 8.2 Hz, 1H), 6.99 (d, J=2.4 Hz, 1H), 6.87 (d, J=8.2 Hz, 1H), 5.48 (m, 1H), 4.95 (m, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 2.31-2.40 (m, 2H), 2.13-2.28 (m, 7H), 1.96-2.06 (m, 3H), 1.74-1.87 (m,
15 3H).

3(b) cis-[4-cyano-4-[3-(cis-3-hydroxycyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid]

The compound of Example 3(a) (0.52 g, 1.31 mmol) was dissolved in 5:5:2 tetrahydrofuran/methanol/water (20mL), sodium hydroxide (0.32 g, 8.0 mmol) was added
20 and the mixture was stirred at RT for 2.5 h. The solvent was evaporated and the aqueous residue was acidified to pH 1-2 with 3N aqueous hydrochloric acid. The white solid product was collected, was washed with water and was dried in vacuo to afford the title compound as a white solid. MS(Cl/NH₃) m/e 377 [M + NH₃]⁺; ¹H NMR(250 MHz, CDCl₃) δ 6.98 (m, 2H), 6.86 (d, J=8.2 Hz, 1H), 4.97 (m, 1H), 4.59 (m, 1H), 3.85 (s, 3H),
25 1.64-2.47 (m, 17H); mp 143-145° C.

METHODS OF TREATMENT

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be used neat though a preferred technique is to present them with a carrier/diluent accordance with standard pharmaceutical practice. Any formulation
30 compatible with the chosen method of delivery and the stability of the compound may be used. One skilled in the art will be able to select and prepare an acceptable formulation in accordance with standard practices in the field of the formulary arts.

The compounds of Formula (I) or may be administered orally (when active by this route), oral, intravenous, intraperitoneal, and intramuscular administration, topically,
35 parenterally, or by inhalation in conventional dosage forms prepared by combining such agent with standard pharmaceutical carriers according to conventional procedures in an amount sufficient to produce the desired therapeutic activity.

United States Patent [19]

Christensen, IV

[11] Patent Number: 5,552,438
[45] Date of Patent: Sep. 3, 1996

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[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

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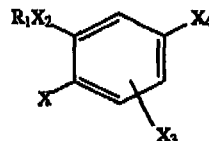
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Primary Examiner—Jacqueline Haley
Attorney, Agent, or Firm—James M. Kanagy; Stuart R. Suter; Edward T. Lentz

[57] ABSTRACT

Novel compounds of Formula (I)



where X₄ 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

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iodide or trimethylsulfonium iodide and an appropriate base, such as sodium hydride, to provide the exo-epoxide followed by treatment with aqueous potassium hydroxide in, e.g., dimethylsulfoxide and oxidation of the resulting primary alcohol to the carboxyl provides compounds of the Formula (1) wherein R_3 is H, CN, OR, C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2 , amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15} and X_5 is OH, the double bond is absent, and R_{15} is H or simple alkyl; the R_5 hydroxyl may be alkylated and these compounds then may be converted by standard procedures with proper manipulation (protection/deprotection) of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (1).

Alternatively, reaction of a compound of the Formula (2) with, e.g., 2-lithio-2-(trimethylsilyl)-1,3-dithiane followed by acidic hydrolysis with a mercury salt, such as mercury (II) chloride, or reaction of a compound of the Formula (2) with, e.g., sodio-[diethyl]-butoxy(cyano)methyl phosphonate followed by treatment with acetic anhydride and a zinc halide and then followed by treatment with an alkoxide provides compounds of the Formula (1) wherein R_3 is H, CN, OR, C_{1-4} alkyl or C_{1-4} halosubstituted alkyl, wherein X and X_3 are other than Br, I, NO_2 , amino, formyl amine or S(O)m' when m' is 1 or 2, wherein Z is CO_2R_{15} , the double bond is not present, and R_{15} is H or simple alkyl and R_5 is H; these then may be converted by standard procedures with proper manipulation (protection/deprotection) of any chemically sensitive functional groups to the corresponding ester, amide, nitrile, oxazolidinone, etc., Z groups of the Formula (1).

Preparation of such compounds of the Formula (1) wherein R_3 is C(=Z')H proceed in an analogous fashion from the compound of the Formula (2) wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by aldehyde deprotection and subsequent manipulation by standard procedures known to those of skill in the art to the remaining compounds of the Formula (1) wherein Z' is other than O or R_3 is other than H, CN, OR, C_{1-4} alkyl or C_{1-4} halosubstituted alkyl.

With proper manipulation (protection/deprotection) of any chemically sensitive functional groups:

- a) Compounds of the Formula (1) wherein X or X_3 are formyl amine may be formed at the last step, by formylating a compound wherein X or X_3 is NH_2 , obtained by removal of a protecting group from the amine functionality; such protective groups are well known to those skilled in the art. See Greene, T. and Wuts, P. G. M., Protecting Groups in Organic Synthesis, 2nd Ed., John Wiley and Sons, New York (1991).
- c) Compounds of the Formula (1) wherein X or X_3 are Br or I may be prepared from a similarly deprotected amine by diazotization of the amine and diazonium displacement.
- d) Compounds of the Formula (1) wherein X or X_3 are NO_2 may be prepared from a similarly deprotected amine by oxidation of the amine to the nitro group.
- e) Compounds of the Formula (1) wherein Y is S(O)m' when m' is 1 or 2 may be prepared from the compounds of the Formula (1) wherein Y is S by oxidation of the SR_2 moiety under conditions well known those skilled in the art

Compounds of the Formula (2) may be prepared in turn by the processes described in co-pending application U.S. Ser. No. 07/862,083 filed 2 April 1992 and the corresponding continuation-in-patent application filed on even date herewith.

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It will be recognized that compounds of the Formula (1) may exist in two distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods.

The following examples and methods are provided to illustrate how to make and use the invention. These materials are not intended to limit the invention in any manner; please refer to the claims appended hereto for determining what has been reserved to the inventors hereunder.

SYNTHETIC EXAMPLES

EXAMPLE 1

Methyl

4-Cyano-4-(3-Cyclopentylloxy-4-Methoxyphenyl)
Cyclohex-1-ene-1-Carboxylate
4-Cyano-4-(3-Cyclopentylloxy-4-Methoxyphenyl)-1-Cyclohexenyl
Trifluoromethylsulfonate

To a solution of diisopropylamine [1.95 milliliters (hereinafter mL), 13.9 millimoles (hereinafter mmol)] in tetrahydrofuran (12 mL) at 0° C. under an argon atmosphere was added n-butyllithium (5.8 mL of 2.5M solution, 14.15 mmol), the resulting solution was stirred for 25 minutes (hereinafter min) and then was cooled to -78° C. To this was added a solution of 4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexan-1-one [2 grams (hereinafter g), 6.64 mmol] in tetrahydrofuran (9 mL). The resulting mixture was stirred at -78° C. for 2 hours (hereinafter h), at which time N-phenyl-trifluoromethylsulfonamide (4.98 g, 13.9 mmol) was added. The mixture was allowed to warm slowly to room temperature and after 5h, the mixture was poured into water and extracted with methylene chloride. The organic extract was dried (potassium carbonate) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 4:1 hexanes/ethyl acetate, to afford an oil (1.09 g, 37%).

Methyl 4-Cyano-4-(3-Cyclopentylloxy-4-Methoxyphenyl)Cyclohex-1-ene-1-Carboxylate

To a solution of 4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)-1-cyclohexenyl trifluoromethylsulfonate (1.0 g, 2.24 mmol) in 1:1 methanol/N,N-dimethylformamide (8 mL) were added methylamine (0.66 mL, 4.72 mmol) and tetrakis(triphenylphosphine)palladium (0.13 g, 0.11 mmol). The resulting mixture was stirred at room temperature in the dark under a carbon monoxide atmosphere for 3h. The mixture was partitioned between water and ethyl acetate, the organic extract was washed three times with water, once with brine, was dried (potassium carbonate) and was evaporated.

Purification by flash chromatography, eluting with 3:1 hexanes/ethyl acetate, provided an off-white solid (0.64 g, 80%); m.p. 128°-129° C.

Analysis Calc. for $C_{21}H_{25}NO_4 \cdot \frac{1}{2}H_2O$: C 70.52, H 7.12, N 3.92; found: C 70.45, H 6.93, N 3.87.

EXAMPLE 2

4-Cyano-4-(3-Cyclopentylloxy-4-Methoxyphenyl)
Cyclohex-1-ene-1-Carboxylic Acid

To a solution of methyl 4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate (0.07 g, 0.18 mmol) in methanol (0.5 mL, containing just enough tetrahydrofuran to solubilize the ester) under an argon atmosphere

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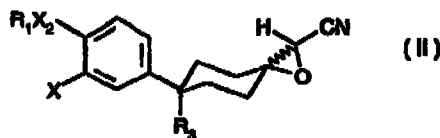
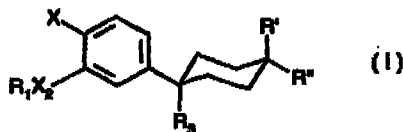


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K	A2	(11) International Publication Number: WO 98/34584 (43) International Publication Date: 13 August 1998 (13.08.98)
(21) International Application Number: PCT/US98/02749 (22) International Filing Date: 12 February 1998 (12.02.98) (30) Priority Data: 60/037,608 12 February 1997 (12.02.97) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ALLEN, Andrew [US/US]; 121 Neyland Court, Exton, PA 19341 (US). DIEDERICH, Ann, Marie [US/US]; 106 Kaiser Drive, Downingtown, PA 19335 (US). LIU, Li [US/US]; 153 Hunsicker Drive, Collegeville, PA 19426 (US). MENDELSON, Wilford [US/US]; 592 General Learned Road, King of Prussia, PA 19406 (US). (74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	

(54) Title: COMPOUNDS AND METHOD FOR PREPARING SUBSTITUTED 4-PHENYL-4-CYANOCYCLOHEXANOIC ACIDS

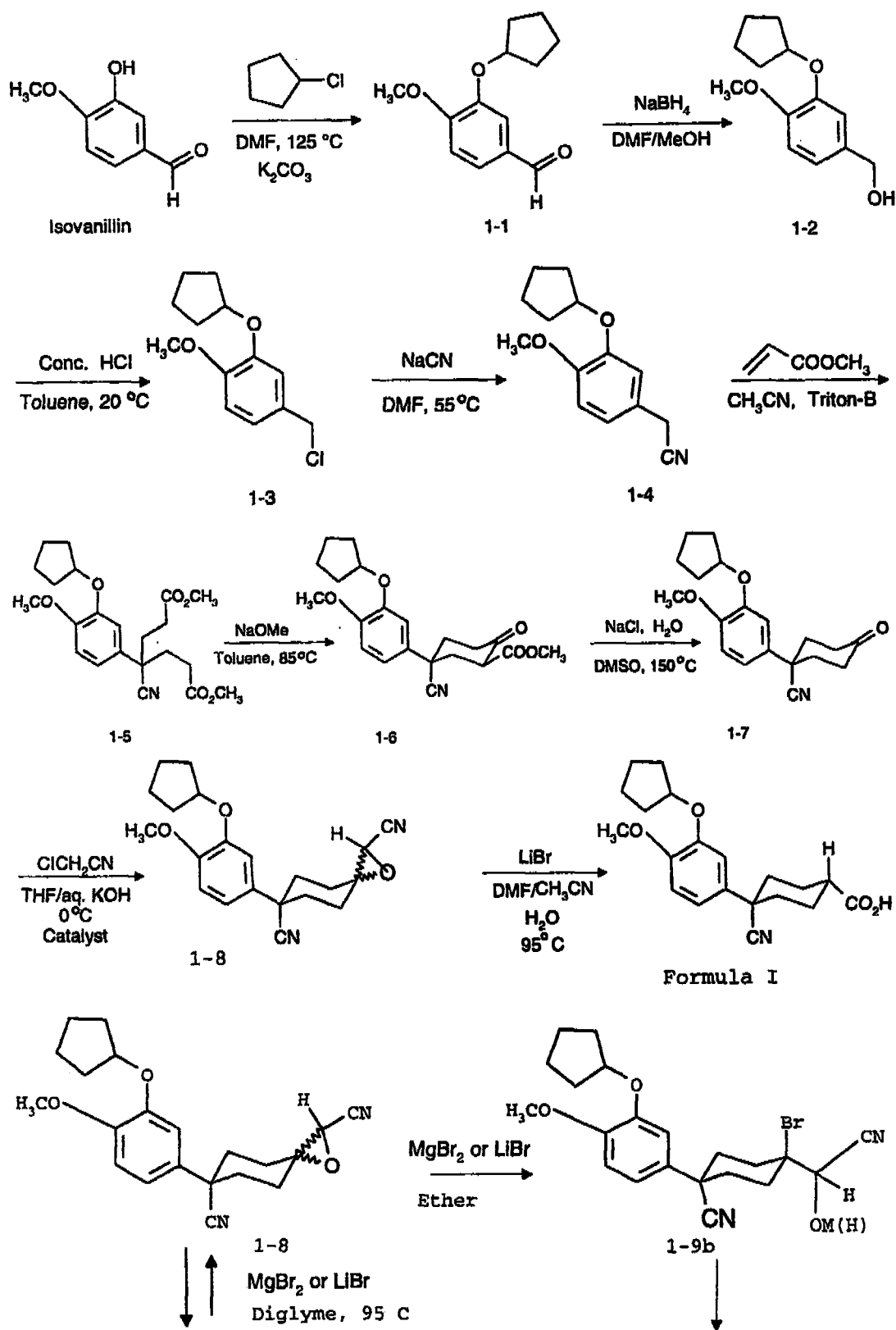


(57) Abstract

This invention relates to a method of preparing a compound of formula (I) by treating a compound of formula (II) with lithium bromide, magnesium bromide and the like.

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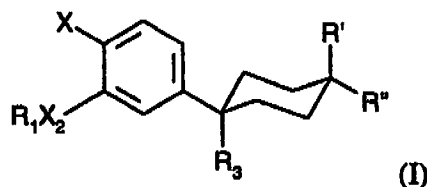
Scheme I



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What is claimed is:

1. A method for making a compound of formula I



- 5 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;
- 10 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, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl,
- 15 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
- 20 $b)$ 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;
- 25 $e)$ 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, NH_2 , or formyl amine;
- X_2 is O or NR_8 ;
- Y is O or $S(O)_{m'}$;
- 30 m' is 0, 1, or 2;
- R_2 is independently selected from $-CH_3$ or $-CH_2CH_3$ optionally substituted by 1 or more halogens;
- R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, $-CH=CR_8R_8'$, cyclopropyl optionally substituted by R_8' , CN, OR_8 ,
- 35 CH_2OR_8 , NR_8R_{10} , $CH_2NR_8R_{10}$, $C(Z)H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C\equiv CR_8'$

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R_8 is hydrogen or C_{1-4} alkyl optionally substituted by one to three fluorines;

R_8' is R_8 or fluorine;

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

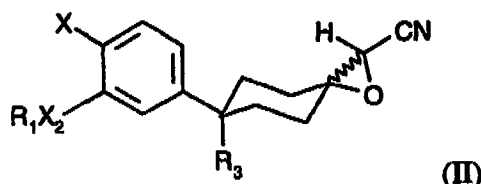
R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines;

5 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 $C(-CN)C(O)NR_8R_8$;

R' and R'' are independently hydrogen or $-C(O)OH$;

which method comprises treating a compound of formula II



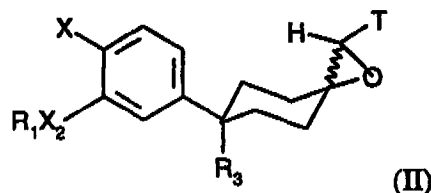
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where R_1 , R_3 , X_2 and X are the same as for formula (I), with lithium bromide in a polar solvent at a temperature between about 60° and 100° C, optionally under an inert atmosphere for a time sufficient for the reaction to go to completion.

2. The method of claim 1 wherein R_1X_2 is cyclopentyloxy and X is

15 methoxy

3. A compound of formula II



20 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;

25 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, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, 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

30 optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

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- a) when R₆ is hydroxyl, then m is 2; or
 b) when R₆ is hydroxyl, then r is 2 to 6; or
 c) when R₆ is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl,
 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
 5 d) when R₆ 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 R₆ is other than H in
 $-(\text{CR}_4\text{R}_5)_n\text{O}(\text{CR}_4\text{R}_5)_m\text{R}_6$;
 X is YR₂, halogen, nitro, NH₂, or formyl amine;
 10 X₂ is O or NR₈;
 Y is O or S(O)^{m'};
 m' is 0, 1, or 2;
 R₂ is independently selected from -CH₃ or -CH₂CH₃ optionally substituted by
 1 or more halogens;
 15 R₃ is hydrogen, halogen, C₁₋₄ alkyl, CH₂NHC(O)C(O)NH₂, halo-substituted
 C₁₋₄ alkyl, -CH=CR₈'R₈', cyclopropyl optionally substituted by R₈', CN, OR₈,
 CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or C≡CR₈'
 R₈ is hydrogen or C₁₋₄ alkyl optionally substituted by one to three fluorines;
 R₈' is R₈ or fluorine;
 20 R₁₀ is OR₈ or R₁₁;
 R₁₁ is hydrogen, or C₁₋₄ alkyl optionally substituted by one to three fluorines;
 Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈,
 CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈, and
 T is CN or SO₂R where R is C₁₋₆alkyl or C₀₋₃alkylphenyl.
 25 4. The compound of claim 3 wherein in the resulting compound R₁X₂ is
 cyclopentyloxy and X is methoxy.
 5. An invention as described herein comprising either a process for making
 a compound of formula I as described in claim 1 or any intermediated or intermediate
 step in that process.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Noviembre 29 de 2005

Doctor
GERMAN CASTILLO GRAU

ASUNTO	Radicación No.	00 058 243
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	11702
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

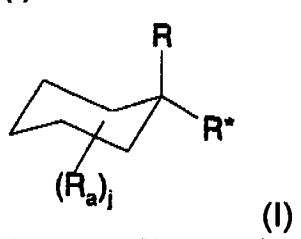
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 4 - 15 y el nuevo capítulo reivindicatorio de los folios 16 - 23 de la solicitud en estudio.

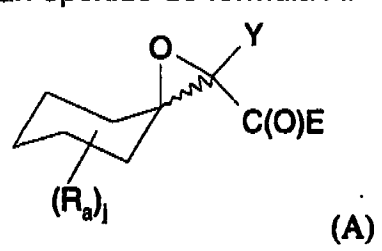
2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

La reivindicación 1 se refiere a un procedimiento para preparar ácidos ciclohexanóicos de fórmula (I):

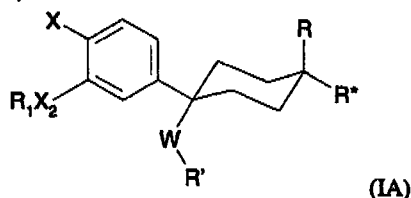


que consiste en tratar un epóxido de fórmula A:

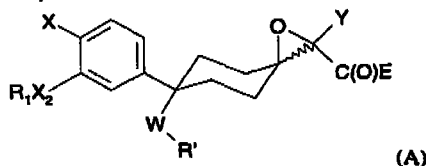


con dimetilsulfóxido y una sal de metal alcalino.

Las reivindicaciones 2 – 12 se refieren a un procedimiento para obtener un compuesto de fórmula (IA):

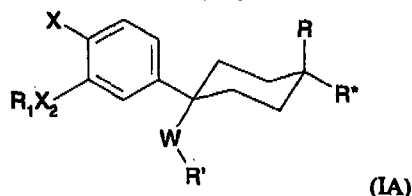


que consiste en tratar un epóxido de fórmula A:



con dimetilsulfóxido y una sal de metal alcalino.

Las reivindicaciones 13 - 16 se refieren a un procedimiento para enriquecer la forma cis de un compuesto de fórmula (IA):



que consiste en tratar el éster de alquilo inferior, el tioéster de alquilo inferior ó la mezcla de anhídridos de la fórmula (IA) con una base de alcóxido.

Las reivindicaciones 17 - 19 se refieren a
 2-cloro-6-ciano-6-[3-(ciclopentiloxi)-4-metoxifenil]-1-oxaspiro[2,5]octano-2-carboxilato de alquilo inferior,
 2-cloro-6-ciano-6-[3-(ciclopentiloxi)-4-metoxifenil]-1-oxaspiro[2,5]octano-2-carboxilato de metilo, y
 ácido 2-cloro-6-ciano-6-[3-(ciclopentiloxi)-4-metoxifenil]-1-oxaspiro[2,5]octano-2-carboxilato de alquilo inferior.

El problema planteado en esta solicitud es la necesidad de proporcionar un método para preparar ácidos ciclohexanóicos que son útiles como inhibidores de la fosfodiesterasa 4.

Para resolver este problema técnico la solicitud en estudio proporciona un método para preparar ácidos ciclohexanóicos a partir de las ciclohexanonas a través de un alfa-haloepoxi-éster.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: C 07 C 255/00 // 69/76 // 235/00 // 41/00; C 07 D 303/38.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 147 576 de agosto 6 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Claridad de la Solicitud

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero se observa que:

- (a) las reivindicaciones 1 y 2 hacen referencia a "un compuesto A" que es diferente en cada caso. "A" debería tener un solo significado.
- (b) la reivindicación 1 menciona a $(R_a)_1$ pero debe aclararse en qué consiste porque dice que R_a es "un grupo que contiene carbono", lo cual no define a este grupo caracterizante.
- (c) las reivindicaciones 2 - 12 deberían ser dependientes de la reivindicación 1 para que sea evidente que se mantiene el principio de la unidad de invención; si es que hay unidad de invención entre los dos procedimientos reivindicados, porque uno de ellos consiste en obtener ácidos ciclohexanóicos de fórmula (I) y el otro consiste en obtener compuestos de fórmula (IA).
- (d) Las reivindicaciones 13 - 16 se refieren a un procedimiento para enriquecer la forma cis de un compuesto de fórmula (IA), que consiste en tratar un compuesto de fórmula (IA) con una base de alcóxido. Quizá lo que quiere decir es "un procedimiento para obtener un compuesto de fórmula (IA) enriquecido en la forma cis, que consiste en tratar un compuesto de fórmula ...". Además no se puede partir de un compuesto (IA) y tratarlo con una base de alcóxido para convertirlo en el mismo compuesto (IA). Hacer las aclaraciones, porque en la forma que está escrito, no tiene mucho sentido.
- (e) La expresión "alquilo inferior" no define claramente los sustituyentes alquil que se quieren reivindicar, los cuales se pueden definir mencionando el número de carbonos que los conforman.

Las anteriores observaciones también son válidas para la descripción.
Deben hacer las aclaraciones necesarias

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "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.

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es agosto 6 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	WO 95 24381	Ciano compuestos y preparaciones de ellos	Sept 14, 1995
D2	US 5 552 438	Compuestos útiles para tratar enfermedades alérgicas e inflamatorias	Sept 3, 1996
D3	WO 98 34584	Compuestos y método para preparar ácidos 4-fenil-4-cianociclohexanóicos sustituidos	Ago 13, 1998

5. 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, se procedió a evaluar el cumplimiento de 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 Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará 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."*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40".

La reivindicación 1 se refiere a un procedimiento para preparar **ácidos ciclohexanólicos** de fórmula (I), que consiste en tratar un **epóxido** de fórmula A con **dimetilsulfóxido** y una sal de metal alcalino.

Las reivindicaciones 2 – 12 se refieren a un procedimiento para obtener un compuesto de fórmula (IA) que consiste en tratar un **epóxido** de fórmula "A" con **dimetilsulfóxido** y una sal de metal alcalino.

Las reivindicaciones 13 - 16 se refieren a un procedimiento para enriquecer la forma cis de un compuesto de fórmula (IA) que consiste en tratar el **éster** de alquilo inferior, el **tioéster** de alquilo inferior ó la mezcla de **anhídridos** de la fórmula (IA) con una **base de alcóxido**.

Las reivindicaciones 17 - 19 se refieren a
2-cloro-6-ciano-6-[3-(ciclopentiloxi)-4-metoxifenil]-1-oxaspiro[2,5]octano-2-carboxilato de alquilo inferior,
2-cloro-6-ciano-6-[3-(ciclopentiloxi)-4-metoxifenil]-1-oxaspiro[2,5]octano-2-carboxilato de metilo, y
ácido 2-cloro-6-ciano-6-[3-(ciclopentiloxi)-4-metoxifenil]-1-oxaspiro[2,5]octano-2-carboxilato de alquilo inferior.

D1 enseña la reacción de esterificación del ácido y el posterior tratamiento de este compuesto **éster** con una **base de alcóxido**, para reforzar la forma cis del ácido. En la pág 11 enseña que el 98.8 % de la mezcla de isómeros es el isómero cis.

D2 enseña compuestos IA como p. ej. el ácido **4-ciano-4-(3-ciclopentiloxi-4-metoxifenil)ciclohexen-1-carboxílico**.

D3 enseña **compuestos IA y "A"**, en la página 7.

Se observa que el objeto de esta solicitud que consiste en tratar un **epóxido** con **dimetilsulfóxido** y un compuesto **éster** con una **base de alcóxido**, con el fin de lograr una mezcla enriquecida en el isómero **cis**, no es nuevo porque ya se conocía en D1.

También eran conocidos en D2 y D3, los intermediarios IA y "A". Por lo cual no puede considerarse que el objeto de las reivindicaciones 1 - 19 sea nuevo.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Se observa que el objeto de esta solicitud: tratar un **epóxido** con **dimetilsulfóxido** y un compuesto **éster** con una **base de alcóxido**, con el fin de lograr una mezcla enriquecida en el isómero **cis**, era obvio para una persona conocedora de la materia, de acuerdo con lo enseñado en D1.

También eran obvios los intermediarios IA y "A", de acuerdo con lo enseñado en D2 y D3. Por lo cual no puede considerarse que el objeto de las reivindicaciones 1 - 19 tenga nivel inventivo.

Estas anterioridades sugieren a un técnico medio enfrentado al problema de proporcionar un método para preparar ácidos ciclohexanóicos que son útiles como inhibidores de la fosfodiesterasa 4, el adaptar las enseñanzas del Estado de la Técnica más cercano (D1, D2, D3) para lograr el procedimiento para preparar **ácidos ciclohexanóicos** de fórmula (I), que consiste en tratar un **epóxido** de fórmula A con **dimetilsulfóxido**, **tal como se reivindica**.

Se observa que la combinación de las enseñanzas de las anterioridades; sugiere los procedimientos de las reivindicaciones 1 - 19. Las reivindicaciones no mencionan una característica que conceda un efecto diferente o especial a los procedimientos, así que estos son obvios y evidentes para una persona versada en la materia. Entonces debido a que: (a) la etapa de tratar un epóxido con dimetilsulfóxido era conocida en las anterioridades, para una persona versada en la materia era evidente el realizarla de manera similar; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial al procedimiento porque igual en la anterioridad d1 ya se enseñaba que este tipo de reacción favorece la obtención de un alto porcentaje del isómero **cis**, así que es obvio para una persona versada en la materia y (c) el problema planteado en esta solicitud que era la necesidad de un método para preparar ácidos ciclohexanóicos que son útiles como inhibidores de la fosfodiesterasa 4 se resuelve proporcionando un método para preparar ácidos ciclohexanóicos a partir de las ciclohexanonas a través de un alfa-haloepoxi-éster, es decir de manera similar a como se resolvía en las anterioridades; las reivindicaciones son obvias y evidentes para una persona versada en la materia. De manera que no tienen **nivel inventivo**.

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5. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 95 24381	1 - 19	Novedad y Nivel inventivo
D2	US 5 552 438	1 - 19	Novedad y Nivel inventivo
D3	WO 98 34584	1 - 19	Novedad y Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

~

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
09 DIC. 2005

CONCEPTO TÉCNICO No. 1906	EXAMINADOR TÉCNICO Código 202007
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-58243

EDICTO No. 5696

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió **Resolución No. 6922 de 23-MAR-2006**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "PROCEDIMIENTO PARA PREPARAR ACIDOS A TRAVES DE ALFA-CLOROEPXI-ESTERES".

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 **23 MAR. 2006**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E).


GIANCARLO MARCENARO JIMENEZ

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 **10-ABR-2006**
Secretaría General Ad-Hoc
EDICTO No. 5696

Este edicto se desfija hoy **25-ABR-2006** a las cinco (5:00 p.m.)