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

SUPERINDUSTRIA Y COMERCIO
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Trámite : 002 PATENTES D 1 REGISTRAR/ 538 PETICION
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

Re.: Código 02-01-538
Expediente No. 00-83.427
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 \$ 335.000.00, recibo No. 03-52.084.

De Ustedes Atentamente,

GERMAN CASTILLO GRAU
T.P. # 2.978 del C.S.J.

82 48

SUPERINDUSTRIA Y COMERCIO
Radacion : 0003427 0000003
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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 32,084
FECHA : JULIO 25 DE 2003

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	16383607	23/07/2003	1,619,000.00

C O N C E P T O

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	09 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 No. _____

53 49

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 00-83427

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION FUE PUBLICADO

EN LA GACETA DE PROPIEDAD INDUSTRIAL No 526, DE FECHA 31 DE MARZO DE 2003, EL

TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL 01 DE JULIO DE 2003.

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

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.:** 313,894

[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.** 514/528; 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 Kermes 562/469
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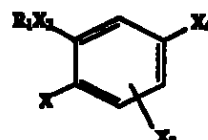
OTHER PUBLICATIONS

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 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

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 hyperactivity 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, adenylylase 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 adenylylase 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 adenylylase 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 adenylylase) 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 rejection, 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 pyrexia, 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, 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 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.

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 pharmaceutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier 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, allicates, 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 0.01 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 carrier 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 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 trachea. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torphy and Ciechanowski, 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 Ciechanowski, Mol. Pharmacol., 37:206-214, 1990. Positive IC_{50} 's in the nanomolar to μ M range for compounds of the working examples described herein for Formula (I) have been demonstrated.

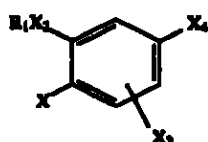
EXAMPLE D

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 μ M) of PDE inhibitors for one minute and 1 μ M 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., Radioimmunoassay 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 have demonstrated a positive EC_{50} in the μ M range in the above assay.

What is claimed is:

1. A compound of Formula (I):

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wherein:

R_1 is $-(CR_2R_3)_mC(O)O(CR_4R_5)_nR_6$,
 $-(CR_2R_3)_mC(O)NR_7(CR_4R_5)_nR_6$,
 $-(CR_2R_3)_mO(CR_4R_5)_nR_6$, or $-(CR_2R_3)_mR_6$ 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;

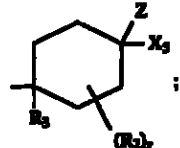
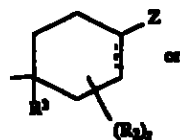
R_4 and R_5 are independently selected from hydrogen or a
 C_{1-3} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted
 aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3}
 alkyl, indenyl, indenyl, C_{7-11} polycycloalkyl, tetrahy-
 drofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetra-
 hydrothienyl, thienyl, tetrahydrothiopyranyl, thiopy-
 ranyl, C_{3-6} cycloalkyl, or a C_{3-6} 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; orb) when R_6 is hydroxyl, then r is 2 to 6; orc) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopy-
 ranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl,
 then m is 1 or 2; ord) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopy-
 ranyl, 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
 $-(CR_2R_3)_mO(CR_4R_5)_nR_6$;X is YR_7 , halogen, nitro, NR_8R_9 , or formyl amine;Y is O or $S(O)_m$;

m' is 0, 1, or 2;

 X_2 is O or NR_{10} ; X_3 is hydrogen or X; X_4 is

X_2 is H, R_{10} , OR_{10} , CN, $C(O)R_{10}$, $C(O)OR_{10}$, $C(O)NR_{10}R_{11}$, or
 $NR_{10}R_{11}$;

R_{10} 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_{11} is CN;

Z' is O, NR_{12} , NOR_{12} , NCN , $C(-CN)_2$, $CR_{12}CN$, $CR_{12}NO_2$,
 $CR_{12}C(O)OR_{12}$, $CR_{12}C(O)NR_{12}R_{13}$, $C(-CN)NO_2$,
 $C(-CN)C(O)OR_{12}$, or $C(-CN)C(O)NR_{12}R_{13}$;

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Z is $C(Y)R_{14}$, $C(O)OR_{14}$, $C(Y)NR_{10}R_{14}$,
 $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_{10})R_{14}$,
 $C(O)NR_{10}NR_{10}C(O)R_{14}$, $C(O)NR_{10}NR_{10}R_{14}$,
 $C(NOR_{10})R_{14}$, $C(NR_{10})NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$,
 $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_{10}$, (2-*A* or 5-imida-
 zolyl), (3-*A* or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]),
 (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-*A* or 5-oxa-
 azolyl), (3-*A* or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,
 2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]),
 (2-*A*, or 5-thiazolyl), (2-*A*, or 5-oxazolidinyl), (2-*A*,
 or 5-thiazolidinyl), or (2-*A*, or 5-imidazolidinyl);
 wherein all of these heterocyclic 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 $-(CR_2R_3)_mR_{12}$ or C_{1-6} alkyl wherein the R_{12} or
 C_{1-6} alkyl group is optionally substituted one or more
 times by C_{1-3} alkyl optionally substituted by one to
 three fluorines, $-F$, $-Br$, $-Cl$, NO_2 , $-NR_{10}R_{11}$,
 $-C(O)R_{10}$, $-C(O)OR_{10}$, $-OR_{10}$, $-CN$,
 $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_{10}$,
 $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$,
 $-NR_{10}C(O)OR_{10}$, $-NR_{10}C(O)R_{11}$,
 $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$,
 $-C(NCN)SR_{10}$, $-NR_{10}C(NCN)SR_{10}$,
 $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_{10}$,
 $-S(O)_2R_{10}$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$,
 $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl,
 pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_2-C_7 cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl,
 pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl,
 pyrrolyl, piperaziny, piperidinyl, morpholinyl, furanyl,
 (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naph-
 thyl, or phenyl;

 R_8 is independently selected from hydrogen or R_{10} ; R_9 is R_{10} or fluorine;

R_{10} is C_{1-4} alkyl optionally substituted by one to three
 fluorines;

 R_{11} is OR_{10} 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
 $NR_{10}R_{11}$ 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, tria-
 zolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidi-
 nyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each
 of these heterocyclic rings is connected through a
 carbon atom and each may be unsubstituted or substi-
 tuted 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-piperaziny, N-piperidinyl, or N-mor-
 pholinyl, then q is not 1;

or the pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is:

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

4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclo-
 hex-1-ene-1-carboxylic acid;

methyl trans-[4-cyano-4-(3-cyclopentylloxy-4-methox-
 yphenyl)cyclohexane-1-carboxylate];

methyl cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-cyclohexane-1-carboxylate];
 methyl trans-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-cyclohexane-1-carboxylate];
 [cis-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]];
 cis-[4-cyano-4-(3-cyclopentylloxy-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-cyclopentylloxy-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-cyclopentylloxy-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-1-tris(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-1-carboxylic acid];
 cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide];
 methyl cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxy-cyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];
 cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];
 trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxaldehyde];
 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-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-carboxamide acid];
 N-methyl-cis-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-carboxamide acid];
 cis-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];
 cis-[1-(2-cyanoethyl)-5-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexyl]tetrazole]; and
 cis-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].

3. A compound according to claim 1 wherein R₁ is CH₂cyclopropyl, CH₂-C₃₋₆cycloalkyl, C₄₋₆cycloalkyl, C₇₋₁₁polycycloalkyl, (3- or 4-cyclopentyl), phenyl, tetrahydrofuran-3-yl, benzyl or C₁₋₃alkyl optionally substituted by 1 or more fluorines, -(CH₂)₁₋₃C(O)O(CH₂)₀₋₂C₂, -(CH₂)₁₋₃O(CH₂)₀₋₂CH₃, and -(CH₂)₂₋₄OH.

4. A compound of claim 3 wherein R₁ is -CH₂cyclopropyl, cyclopentyl, methyl or CH₂H, R₂ is CN, X₂ is oxygen, X₃ is hydrogen and R₃ is CF₃H 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-cyclopentylloxy-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.

* * * * *

[54] TOPICALLY ADMINISTRABLE
PHARMACEUTICAL COMPOSITIONS
CONTAINING ANTI-INFLAMMATORY
STEROIDS

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[21] Appl. No. 308,581

[22] Filed: Oct. 5, 1981

[30] Foreign Application Priority Data

Oct. 6, 1980 [GB] United Kingdom 8032111

[51] Int. Cl.³ A61K 31/06

[52] U.S. Cl. 424/243

[58] Field of Search 424/243; 260/397.45

[56] References Cited

U.S. PATENT DOCUMENTS

3,856,828 12/1974 Phillips et al. 424/243

4,070,463 1/1978 Ecker 424/243

Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

Pharmaceutical compositions such as ointments and creams are provided by admixture of anti-inflammatory steroids active on topical application with a liquid oily phase containing at least one oil possessing a viscosity less than 10 centistokes and in which the steroid has a solubility of at least 0.5% by weight at 25° C., the degree of unsaturation of the steroid in the liquid oily phase of the composition at 25° C., being at least 3. Examples of steroids which may be used are betamethasone, beclomethasone and clobetasol derivatives. Suitable oils include esters of mono- and dibasic aliphatic acids. The compositions may include further oils such as liquid paraffin and conventional additives used in the preparation of ointments and creams. The local anti-inflammatory effect of the steroids is maintained in such formulations but systemic side effects are decreased.

14 Claims, No Drawings

TOPICALLY ADMINSTRABLE PHARMACEUTICAL COMPOSITIONS CONTAINING ANTI-INFLAMMATORY STERIODS.

The present invention relates to novel pharmaceutical compositions containing anti-inflammatory steroids.

Anti-inflammatory steroids such as clobetasol 17-propionate are commonly formulated for topical application in solution in relatively polar solvents such as propylene glycol which, in the case of ointments, may be dispersed in white soft paraffin. Such formulations permit some penetration of the active steroid into the skin to exert a topical anti-inflammatory effect. It is thought to be particularly important that the steroid should not, however, be so completely absorbed that it can exert a systemic effect which would be likely to lead to the various unwanted side effects observed with anti-inflammatory steroids such as cortisol suppression.

The use of isopropyl and butyl adipates as well as of ethyl lactate and ethanol as vehicles for the topical formulation of triamcinolone acetonide and its dicumaryl ester is described in a paper by Altmeppen and Zaun in Arch. Derm. Forsch 1974, 248, 387-390. The effects of these vehicles on the vasoconstrictor properties of the compounds is discussed, and it is concluded that the base in which a corticosteroid is administered determines to a great extent its penetration rate, strength and duration of topical anti-inflammatory activity. There is no discussion, however, of the possible dangers of enhanced penetration in increasing systemic absorption. As far as can be determined, the solutions of triamcinolone acetonide concerned were saturated or even supersaturated which we believe would have tended to maximize release of the steroid into the aqueous body fluids.

We have now found that the systemic side effects produced by anti-inflammatory steroids on topical administration can be significantly decreased if they are applied in solution in certain oils, provided that the degree of unsaturation of the steroid in the oil is relatively high, but that the local anti-inflammatory effect and clinical efficacy of the steroids are not correspondingly reduced. Consequently, it is possible to apply about the same amount of the steroid to achieve the same local anti-inflammatory effect but to correspondingly reduce unwanted systemic effects.

The formulations according to the invention comprise an anti-inflammatory steroid dissolved in a liquid oily phase as defined hereinafter. The quantity of the liquid oily phase in relation to the quantity of steroid and the solubility of the steroid in the liquid oily phase have been found to be particularly important: the solution of the steroid in the liquid oily phase of the composition should be not more than one third saturated at 25° C., i.e. have a degree of unsaturation at 25° C. of at least 3. This means that the quantity of the liquid oily phase present should be sufficient to dissolve, at 25° C., at least three times the amount of steroid which is actually present.

Thus, according to the present invention we provide pharmaceutical compositions comprising an anti-inflammatory steroid active on topical application dissolved in a liquid oily phase containing at least one oil possessing a viscosity less than 10 centistokes and in which the steroid has a solubility of at least 0.5% by weight at 25° C., the degree of unsaturation of the steroid in the liquid oily phase of the composition at 25° C. being at least 3.

Examples of steroids which can benefit by this type of formulation are Beclomethasone 17,21-dipropionate, Betamethasone 17-valerate, Betamethasone 17,21-dipropionate, Clobetasol 17-propionate, Clobetasone 17-butyrate and chloromethyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxocandrost-1,4-diene-17 β -carboxylate.

Formulations containing betamethasone 17-valerate, beclomethasone 17,21-dipropionate and clobetasol 17-propionate are preferred. Formulations containing clobetasol 17-propionate are particularly preferred since incidence of dermal atrophy has been shown to be significantly reduced in healthy volunteers when this formulation is used.

Suitable oils for inclusion as solvents for the steroids include esters of mono- and dibasic aliphatic acids, such esters having, for example, 6 to 18 carbon atoms, such as the butyl and isopropyl esters of adipic, lauric, palmitic and myristic acids. Dibutyl adipate is particularly useful. Mixtures of the above esters can also be employed.

The compositions according to the invention may contain a mixture of the solvent oil with one or more further oils in which the steroid is soluble and/or one or more oils in which the steroid is substantially insoluble, such as hydrocarbon oils, e.g. liquid paraffin. The liquid paraffin can either be the standard, relatively viscous kind (viscosity about 100 centistokes) or may more advantageously be a light paraffin having a much lower viscosity, for example about 7 centistokes. Use of such light liquid paraffin improves the penetration of the liquid oily phase into the skin.

It will be appreciated that when the principal solvent oil, such as dibutyl adipate, is present in admixture with a non-solvent oil such as a hydrocarbon, the solubility of the steroid in the liquid oily phase will not be a linear function of the concentration of the solvent oil in the mixture. The solubility of the chosen active steroid in any mixture of solvent and non-solvent oils can readily be determined by experiment.

The following Tables illustrate typical solubility values, at 25° C., of various steroids in various mixtures of solvents.

TABLE I

Mixture A: dibutyl adipate + liquid paraffin	
% dibutyl adipate in mixture	% solubility of Clobetasol 17-propionate in mixture
25	0.025
28	0.07
36	0.22
50	0.45
66	0.65
75	1.2
85	1.5
100	1.9

TABLE II

Mixture A: dibutyl adipate + isopropyl myristate		
Mixture B: dibutyl adipate + liquid paraffin		
% dibutyl adipate in mixture (A or B)	% solubility of Clobetasone 17-butyrate in mixture	
	A	B
0	0.45	0.02
10	0.70	—
20	1.02	0.08
30	1.6	0.15
40	2.1	0.45

TABLE II-continued

Mixture A: dibutyl adipate + isopropyl myristate		
Mixture B: dibutyl adipate + liquid paraffin		
% dibutyl adipate in mixture (A or B)	% solubility of Clobetasone 17-butyrate in mixture	
	A	B
50	2.55	0.8
60	2.95	2.0
70	3.5	2.75

TABLE III

Mixture: dibutyl adipate + liquid paraffin		
% dibutyl adipate in mixture	% solubility in mixture of	
	Clobetasone 17-butyrate	Clobetasol 17-propionate
25	0.15	0.085
50	2.45	0.75
65	2.85	1.25
75	2.95	1.45
85	4.4	2.1
100	7.0	3.0

Table IV shows the solubility of betamethasone 17-valerate at 25° C. in two solvent oils:

TABLE IV

Solvent Oil	% Solubility of Betamethasone 17-valerate
Dibutyl adipate	0.9
Dibutyl adipate	1.4

The degree of unsaturation appears to be particularly important in relation to the absence of systemic side effects, and while it should be above 3 it is not necessary for the degree of unsaturation to exceed about 5.0, although higher values may not be disadvantageous.

The concentrations of the active steroids in the formulations according to the invention are conveniently in the range 0.02% to 0.5%, e.g. 0.05% to 0.25% by weight, although higher percentages e.g. up to 1.5% may be employed. Preferably the compositions contain 0.05% to 0.50% by weight of active steroid.

The compositions of the invention may, for example, take the form of ointments or creams. In ointments, solid wax will commonly be present. Such an ointment may, for example, contain 55 to 90% by weight of liquid phase and 10-45% of solid wax, more usually 65-80% by weight liquid phase and 20-35% by weight of solid wax. Cream formulations will normally be emulsions, commonly oil-in-water or water-in-oil emulsions, containing 10-80%, more usually 20-60%, by weight of oil phase. Such creams can also contain emulsifying agents, which may be surfactants or emulsifying waxes, for example, cetostearyl alcohol, Cetomacrogol 1000 or self-emulsifying monostearin, as well as preservatives, buffers, stabilisers etc.

The foregoing formulations for topical application to the skin may be used for the treatment of inflammatory dermatoses of humans and animals, for example eczema, which are normally responsive to corticosteroid therapy, and also of less responsive conditions such as psoriasis in humans. The preparations may be administered by one or more applications per day to the affected area, over skin areas occlusive dressings may often be used with advantage.

The following examples are given by way of illustration only:

EXAMPLE 1

Ointment	% w/w
Clobetasol 17-propionate	0.05
Dibutyl adipate	25.00
Microcrystalline Wax 140/145	30.00
Liquid paraffin BP	to 100.00

The ointment formulation in Example 1 contains 0.07% of clobetasol 17-propionate in its liquid oily phase (dibutyl adipate+liquid paraffin). As can be seen from the solubility values in Table I above, to dissolve that level of clobetasol 17-propionate requires 28% of dibutyl adipate in the liquid oily phase. The liquid oily phase in fact contains about 36% of dibutyl adipate which as indicated in Table 1 is sufficient to dissolve 0.22% of clobetasol 17-propionate, i.e. more than 3 times the amount of steroid which is actually present in the formulation. Similarly the formulations of Examples 2-10 may be arrived at from the solubility values given in the tables or else the values may be determined by experiment.

EXAMPLE 2

Ointment	% w/w
Clobetasol 17-propionate	0.05
Dibutyl adipate	40
Beeuwax	15
Isopropyl myristate	to 100

EXAMPLE 3

Ointment	% w/w
Clobetasone 17-butyrate	0.1
Microcrystalline wax 140/145	40.0
Dibutyl adipate	25.0
Ultra light liquid paraffin	to 100.0

EXAMPLE 4

Cream	% w/w
Clobetasol 17-propionate	0.05
Dibutyl adipate	30.0
Microcrystalline wax 140/145	7.5
Cetostearyl alcohol	7.5
Cetomacrogol 1000	1.0
Sodium citrate	0.05
Citric acid	0.05
Chlorocresol	0.1
Water	to 100.0

EXAMPLE 5

Cream	% w/w
Clobetasol 17-propionate	0.05
Dibutyl adipate	30.0
Beeuwax	7.0
Cetostearyl alcohol	7.0
Self-emulsifying monostearin	1.0
Sodium citrate	0.05
Citric acid	0.05
Chlorocresol	0.1
Water	to 100.0

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EXAMPLE 6

Ointment	% w/w
Betamethasone 17-valerate	0.13
Dibutyl adipate	80
Microcrystalline Wax 140/145	20
Beeuwax	10
Liquid paraffin	to 100

EXAMPLE 7

Ointment	% w/w
Beclomethasone 17,21-dipropionate	0.025
Dibutyl adipate	37.5
Microcrystalline Wax 140/145	30
Liquid paraffin	to 100

EXAMPLE 8

Cream-like ointment	% w/w
Clobetasol 17-propionate	0.05
Dibutyl adipate	22.0
Microcrystalline Wax 140/145	30.0
Beeuwax	3.0
Cetomacrogel 1000	3.0
Titanium dioxide	2.0
Ultra-light liquid paraffin	to 100.0

EXAMPLE 9

Ointment	% w/w
Chloromethyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrost-1,4-diene-17 β -carboxylate	0.1
Dibutyl adipate	84.9
Beeuwax	15.0

EXAMPLE 10

Ointment	% w/w
Betamethasone 17,21-dipropionate	0.05
Beeuwax	10.00
Microcrystalline wax 140/145	20.00
Dibutyl adipate	to 100.00

The method used for making up the formulations is as follows: the steroid is dissolved in a portion of or all of the dibutyl adipate. The other ingredients are mixed together at 60°-70° C. and the steroid solution added to

the mixture which is then stirred and cooled until semi-solid.

We claim:

1. A pharmaceutical composition comprising an anti-inflammatory steroid selected from beclomethasone 17,21-dipropionate, betamethasone 17-valerate, betamethasone 17,21-dipropionate, clobetasol 17-propionate, clobetasone 17-butyrate and chloromethyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrost-1,4-diene-17 β -carboxylate dissolved in a liquid oily phase containing at least one oil possessing a viscosity less than 10 centistokes and in which the steroid has a solubility of at least 0.5% by weight at 25° C., the degree of unsaturation of the steroid in the liquid oily phase of the composition at 25° C. being at least 3.
2. A pharmaceutical composition according to claim 1 wherein the liquid oily phase contains at least one oil selected from the esters of mono- and dibasic aliphatic acids, the said esters having from 6 to 18 carbon atoms.
3. A pharmaceutical composition according to claim 2 wherein the liquid oily phase contains at least one oil selected from the butyl and isopropyl esters of adipic, lauric, palmitic and myristic acids.
4. A pharmaceutical composition according to claim 3 wherein the liquid oily phase contains dibutyl adipate.
5. A pharmaceutical composition according to claim 4 which contains clobetasol 17-propionate.
6. A pharmaceutical composition according to claim 4 which contains betamethasone 17-valerate.
7. A pharmaceutical composition according to claim 4 which contains beclomethasone 17,21-dipropionate.
8. A pharmaceutical composition according to claim 1 wherein the liquid oily phase contains further oils.
9. A pharmaceutical composition according to claim 8 wherein the liquid oily phase contains liquid paraffin having a viscosity of about 7 centistokes.
10. A pharmaceutical composition according to claim 1 wherein the degree of unsaturation of the steroid is in the range 3.0 to 5.0.
11. A pharmaceutical composition according to claim 1 wherein the concentration of the steroid is from 0.02 to 1.5% by weight of the composition.
12. A pharmaceutical composition according to claim 1 in the form of an ointment or cream.
13. A pharmaceutical composition according to claim 12 containing, as additional ingredients, substances selected from solid wax, emulsifying agents, preservatives, buffers, stabilisers and other conventional additives.
14. A method of treatment of inflammatory dermatoses of humans and animals comprising topically administering to the affected skin a pharmaceutical composition according to claim 1.

* * * * *

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**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

PATENT NO. : 4,370,322

DATED : January 25, 1983

INVENTOR(S) : BUSSE et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 19, change "6 to 18" to --6 to 20--.

Claim 2, line 4, change "6 to 18" to --6 to 20--.

Signed and Sealed this

Thirty-first **Day of** *May* 1983

[SEAL]

Attest:

DONALD J. QUIGG

Attesting Officer

Acting Commissioner of Patents and Trademarks

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Marzo 9 de 2006

Doctor
GERMÁN CASTILLO GRAU

ASUNTO	Radicación No.	00 083 427
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	3105
	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 – 16 y el capítulo reivindicatorio del folio 17 de la solicitud en estudio.

2. Objeto de la Invención

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

Las reivindicaciones 1 – 2 se refieren a un método para tratar la enfermedad pulmonar administrando un inhibidor PDE4 (p. ej. ácido cis-4-ciano4-(ciclopentiloxi-4-metoxifenil)ciclohexano-1-carboxílico) y un corticosterolde antiinflamatorio (p. ej. dexametasona, fluticasona, beclometasona, budesonida, flunisolida, furoato de mometasona, acetónido de triamcinolona).

El problema planteado en esta solicitud es la necesidad de proporcionar un método para tratar la enfermedad pulmonar.

Para resolver este problema técnico la solicitud en estudio proporciona el método que consiste en administrar un inhibidor PDE4 (p. ej. ácido cis-4-ciano4-(ciclopentiloxi-4-metoxifenil)ciclohexano-1-carboxílico) y un corticosterolde antiinflamatorio (p. ej. dexametasona, fluticasona, beclometasona, budesonida, flunisolida, furoato de mometasona, acetónido de triamcinolona).

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/185 // 31/573 // 31/40 // 31/56.

También se reivindica prioridad de la Solicitud de Patente US 60 163 158 de noviembre 2 de 1999, con respecto a la cual la fecha de presentación de la

actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) 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"*

Las reivindicaciones 1 – 2 se refieren a un método para tratar la enfermedad pulmonar administrando un inhibidor PDE4 (p. ej. ácido cis-4-ciano4-(ciclopentiloxi-4-metoxifenil)ciclohexano-1-carboxílico) y un corticosteroide antiinflamatorio (p. ej. dexametasona, fluticasona, beclometasona, budesonida, flunisolida, furoato de mometasona, acetónido de triamcinolona).

Se observa que el método de tratamiento que comprende administrar un inhibidor PDE4 (p. ej. ácido cis-4-ciano4-(ciclopentiloxi-4-metoxifenil)ciclohexano-1-carboxílico) y un corticosteroide antiinflamatorio (p. ej. dexametasona, fluticasona, beclometasona, budesonida, flunisolida, furoato de mometasona, acetónido de triamcinolona), de las reivindicaciones 1 - 2, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables. Y porque además se trata de compuestos ya conocidos en el estado de la técnica.

En conclusión, el método de tratamiento que comprende administrar un inhibidor PDE4 y un corticosteroide antiinflamatorio de las reivindicaciones 1 - 2, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

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 2 de noviembre 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
D1	US 5 552 438	Método y composiciones para tratar enfermedades pulmonares	Mayo 10, 2001
D2	US 4 370 322	Composiciones farmacéuticas administrables tópicamente que contienen esteroides antiinflamatorios	Ene 25, 1983

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5. Evaluación de los requisitos de Patentabilidad

El compuesto inhibidor PDE4 (p ej ácido cis-4-clano4-(ciclopentiloxi-4-metoxifenil)ciclohexano-1-carboxílico) mencionado en esta solicitud ya era conocido en la técnica (ver D1 en el folio 58, columna 33)

Los corticosteroides antiinflamatorios (p ej beclometasona) también eran conocidos en la técnica (ver D2 en el folio 62, columnas 5 y 6)

6. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5 552 438	1 - 2	Novedad
D2	US 4 370 322	1 - 2	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 quinto del título primero de la Circular Unica No 10 de 2001


ALIX CARMONA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
15 MAR. 2005

CONCEPTO TÉCNICO No 377	EXAMINADOR TÉCNICO Código 202007
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16/03/008