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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES
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Solicitud de Patente a nombre de FcI,os 2
Novartis AG y Mitsubishi Pharma Corporation

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogota, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada
de las sociedades Novartis AG y Mitsubishi Pharma Corporation, con domicilios en Basilea, Suiza y Osaka, Japón, solicitantes de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en ci expecliente de la referenda, es patentable.

Adjunto al presente memorial el recibo No. 07 - 84,097 de 11 de octubre de 2007, pot la suma de $404.000.00, con lo cual queda cubierta la tasa oficial correspondiente
a dicho estudio.

SeæorSuperintendente,

JIMENA U 9’TRTBE
C.C.39.779.452 de UsaquØn
T.P. 68.228

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(54) 2.AM1NOPROPANE-1,3-DIOL COMPOUNDS, MEDICINAL USE THEREOF, AND
INTERMEDIATES IN SYNTHESIZING THE SAME

(57) The present invention relates to a compound of the general formula

CH2OR3 0
J=\

ii-(CH2)4__0 (I)

CH2OR4

wherein R1, R2, R3 and A4 are each a hydrogen or an acyl, a pharmaceutically acceptable acid addition salt thereof or
a hydrate thereof; a pharmaceutical comprising this compound; a pharmaceutical composition comprising this com-pound and a pharmaceutically acceptable carrier; and 2.amino.2(2.(4.(1.hydroXY-5-PheflYlPentYDPhenY0ethYI)Pro
CI pane-i,3-diol or 2-amino-2-(2.(4iormylphenyl)ethYl)ProPafle-1.3-diOl, the derivatives of the two compounds whose amino group and/or hydroxy group are(is) protected or a salt thereof. The compound of the present invention shows superior immunosuppressive action with less toxicity and higher safety, and is useful as a drug for prevention or sup-pression of rejection of organs or bone marrow transplantation, or as a drug for prevention or treatment of various
0 autoimmune diseases or allergic diseases.
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tis), necrotizing enterocolitis), or intestinal lesions associated with thermal bums.
[0174] Further, the compounds of the present invention are also useful for treating or preventing renal diseases
including interstitial nephritis. Goodpasture’s syndrome, hemolytic uremic syndrome and diabetic nephropathy; nervous diseases selected from multiple myositis, Guillain-BarrØ syndrome. MØniŁre’s diseaseand radiculopathy, endocrine die-
5 eases including hyperthyroidism and Basedow’s disease; hematic diseases including pure red cell aplasia, aplastic
anemia, hypoplastic anemia, idiopathic thrombocytopanic purpura, autoimmune hemolytic anemia, agranulocytosis and anerythrcplasia; bone diseases including osteoporosis; respiratory diseases including sarcoidosis, fibroid lung and idiopathic interstitial pneumonia; skin diseases including dermatomyositis, vitiligo vulgans, ichthyosis vulgaris, photoal-lergic sensitivity and cutaneous T cell lymphoma; circulatory diseases including arteriosclerosis, aortitis, polyarteritis
10 nodose and myocardosis; collagen disease including scieroderma, Wegener’s granuloma and SjOgren’ syndrome; adi-
posis; eosinophillc fasciltis; periodontal disease; nephrotic syndrome: hemolytic uremic syndrome: and muscular dys-trophy.
(0175] Further, the compounds of the present invention are indicated in the treatment of diseases including intesti-
nal inflammations or allergies such as Coeliac disease, proctitis, eusinophilic gastroenteritis, mastocytosis. Crohn’s die-
15 ease or ulcerative colitis; and food related allergic diseases which have symptomatic manifestation remote from the
gastrointestinal tract, for example migraine, rhinitis and eczema.
101761 The compounds of the present invention also have liver regenerating activity and/or activity in promoting
hypertrophy and hyperplasia of hepatocytes. Therefore, they are useful for the treatment and prevention of hepatic die-eases such as immunogenic diseases (e.g. chronic autoimmune liver diseases including autoimmune hepatitis, primary
20 biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins,
viral hepatitis, shock or anoxia), viral hepatitis type B, non-Nnon-B hepatitis and cirrhosis.
[0177] The compounds of the present invention are also indicated for use as antimicrobial agents, and thus may be
used in the treatment of diseases caused by pathogenic microorganisms and the like.
[0178] Further, the compounds of the present invention can be used in the prevention or treatment of malignant
25 rheumatoid arthritis, amyloidosis, fulminant hepatitis, Shy-Drager syndrome, pustular psoriasis, Behçet’s disease, sys-
temic lupus erythematosus, endocrine opthalmapathy, progressive systemic sclerosis, mixed connective tissue dis-ease, aortitis syndrome, Wegener’s gramulomatosis, active chronic hepatitis, Evans syndrome. pollinosis, Idiopathic hypoparathyroidism, Addison disease (autoimmune adrenalitis), autoimmune orchitis, autoimmune oophoritis, cold hemagglutinin, paroxysmal cold hemoglobinuria, pernicious anemia, adult I cell leukemia, autoimmune atrophic gas-
30 tritis, lupoid hepatitis, tubulointerstitial nephritis, membranous nephritis, amyotrophic lateral sclerosis, rheumatic fever,
poetmyocardial infarction syndrome and sympathetic ophthalmitis.
[0179] The compounds of the present invention have antifungal effect and are useful as an antifungal agent.
(01801 Moreover, the compounds of the present invention, pharmaceutically acceptable acid addition salts thereof
or hydrates thereof can be used in combination with other immunosuppressant(s), steroid(s) (prednisotone, methyl-
35 prednisolone, dexamethasone, hydrocortisone and the like) or nonsteroidal acid anti-inflammatory agent As the other
immunosuppressant, preferred is particularly selected from azathioprine, brequinar sodium, deoxyspergualin, mizorib-me, 2-morpholinoethyl mycophenolate, cyclosporin, rapamycin, tacrolimus monohydrate, leflunomide and OKT-3.
(0181] When Compound (I) of the present invention thus obtained, a pharmaceutically acceptable acid addition salt
thereof or a hydrate thereof is used as a medicament, Compound (I) is admixed with a pharmaceutically acceptable car-
40 rier (e.g., excipients, binders, disintegrators, correctives, corrigents, emulsifiers, diluents, solubilizers and the like) to
give a pharmaceutical composition or a pharmaceutical agent (tablets, pills, capsules, granules, powders, syrups, emul-sions, elixirs, suspensions, solutions, injections, transfusions or external preparations), which can be administered orally or parenterally. The pharmaceutical composition can be formulated into a pharmaceutical preparation by a con-ventional method. In the present specification, parenterally° includes subcutanous injection, intravenous injection.
45 intramuscular injection, intraperitoneal injection, transfusion and topical administration (administration through the skin,
eye, lung, bronchus, nose, rectum). The preparation for injection, such as a sterile aqueous or oily suspension for injec-tion, can be prepared using a suitable dispersing agent or a wetting agent and a suspending agent, according to a method known in the pertinent field. The sterile preparation for injection may be a sterile injectable solution or suspen-sion in a non-toxic diluent or solvent permitting parenteral administration, such as an aqueous solution. Examples of the
so vehicle and solvent which can be used include water, Ringer solution, isotonic saline and the like. In addition, sterile
nonvolatile oil can be generally used as a solvent or a solvent for suspension. For this end, any nonvolatile oil or fatty acid can be used, inclusive of natural, synthetic or semi-synthetic fatty oil or fatty acid, and natural, synthetic or semi-synthetic mono, di or triglycerides. The solid dosage form for oral administration includes the above-mentioned ones such as powders, granules, tablets, pills, capsules and the like. In these dosage forms, the active ingredient is admixed
55 with at least one additive such as sucrose, lactose, cellulose sugar, mannitol, maltitol, dextrari, starches, agar, argin-
ates, kichins, chitosans, pectins, tragacanth gums, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers and glycerides. In these dosage forms, routine additives can be added, which may be inert diluents, lubricants such as magnesium stearate, preservatives such as parabens and sorbic acid, antioxidants such as ascorbic

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acid, a-tocopherol and cysteine, disintegrators, binders, tackifiers, buffers, sweeteners, flavors, perfumes and the Oka. An enteric coating may be applied to tablets and pills. The liquid agents for oral administration may be pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, solutions and the like, which may contain inert diluents (e.g., water), which are generally used in the pertinent field.

5 [0182] The external agent applicable to Compound (I) of the present invention, a pharmaceutically acceptable acid
addition salt thereof or a hydrate thereof includes an ointment, a paste, a liniment, a lotion, a plaster, a cataplasm, an eye drop, an eye ointment, a suppository, a fomentation, an inhalant, a spray,an aerosol, a paint, a nasal drop a cream,
a tape, a patch and the like.
[0183) The external agent of the present invention contains the compound of the present invention in the form of a
10 mixture with an organic or inorganic carrier or excipient, and, for example, can be used in the form of a solid, semi-solid
or liquid pharmaceutical preparation.
[0184] The compound of the present invention can be mixed with, for example, a non-toxic and pharmaceutically
acceptable carrier which is usually employed for obtaining an external preparation for topical administration. A carrier which can be used includes water, glucose, lactose, gum arabic, gelatin, mannitol, starch paste, magnesium trisilicate,
15 talc, corn starch, keratin, colloid silica, potato starch, urea and other carriers which are suitable for preparing a solid,
semi-solid or solution composition. Further, an adjuvant, a stabilizer, a thickener, a coloring matter or a flavoring agent can be added.

[0185] The compound of the present invention as an active ingredient of the pharmaceutical composition can be
contained in an amount enough to exhibit the desired activity depending on the symptom or severity of the diseases. In
20 the case of the treatment of the symptom and diseases induced by immune disorder, the compound of the present
invention can be administered by way of a topical administration, an aerosol or a rectal administration in a form of a dos-age unit composition which contains pharmaceutically acceptable and non-toxic carrier, adjuvant and excipient. In the treatment of reversible obstructive airways disease, the compound of the present invention is preferably administered
to lung by an aerosol in a form of, particularly a powder or a solution.
25 [0186] The amount of the compound of the present invention which can be mixed with a carrier can vary depending
on the host to be treated and a specified dosage form. The specified dose of the specified patient should be determined depending on the various factors such as age, body weight, the whole condition of health, sex, meal, time for adminis-tration, administration route, rate of excretion, combination of drug and the severity of the specified diseases under
treatment.

30 [0187] When the compound of the present invention is used in the form of anointment, it is contained in an amount
of 0.01 to 10 wlw% in the ointment. The ointment base which can be used includes oleaginous base (a natural wax such as white beeswax or carnauba wax, a petroleum wax such as hard paraffin or microcrystalline wax, a hydrocarbon wax such as liquid paraffin, white petrolatum or yellow petrolatum, p!astibase. zelen 50W, silicone, a vegetable oil, lard, beef tallow, a simple ointment or lead oleate plaster), an emulsion type ointment base (an oil in water type (01W type) base
35 such as a hydrophilic ointment or a vanishing cream or a water in oil type (WI0 type) base such as a hydrophilic petro-
latum, a purified lanolin, aquahole, eucelin, neoselin, an absorptive ointment, a hydrous lanolin, cold cream, a hydrophilic plastibase), a water-soluble base (a macrogol ointment or solbase) or a suspension type ointment base (a lyogel base, e.g., a hydrogel base such as a non-fat ointment, a gelbase or lotion; or a FAPG base (a suspension of a microparticle of an aliphatic alcohol such as stearyl alcohol or cetyl alcohol in propylene glycol), and these ointment
40 bases can be used alone or in a combination of not less than two bases.
[0188] Further, when used as an ointment, the compound of the present invention is dissolved in a solubilizing and
absorptive accelerating agent and added to the above-mentioned ointment base. The solubilizing and absorptive accel-erating agent to be used means the agent in which the compound of the present invention is soluble at a concentration
of at least not less than 0.01 w/w% and which can accelerate the absorption of the compound of the present invention
45 from skin when formulated as an ointment, and includes a lower alkanediol (e.g., ethylene glycol, propylene glycol or
butylene glycol), an alkylene carbonate (e.g., propylene carbonate or ethylene carbonate), an alkanedicarboxylic acid ester (e.g., dimethyl adipate, diethyl adipate, diisopropyl adipate, diethyl pimelate, diethyl sebacate or clipropyl seba-cate), a higher alkanoic acid glycerin ester (e.g., monolaurate, dilaurate or trilaurate), a higher alkenoic acid glycerin ester (e.g., monooleate, dioleate or trioleate), a higher alkanoic acid alkyl ester (e.g., isopropyl myristate or ethyl myr-so!state), a higher unsaturated alcohol (e.g., geraniol or oleyl alcohol) or an azacycloalkane (e.g., 1-dodecylazacyclohep-tan-2-one). These solubilizing and absorptive accelerating agents can be used alone or in a mixture of not less than two agents, and can be added at a sufficient amount to dissolve the compound of the present invention. The amount gen-erally ranges from 2 parts by weight to 200 parts byweight per one part by weight of the compound of the present inven-tion. The upper amount is limited not to deteriorate the physicochemical properties of the ointment. ’
[0189] The ointment which contains the compound of the present invention may contain, in addition to the above-
mentioned ointment base, other additives such as an emulsifier (e.g., polyoxyethylene hydrogenated castor oil, glycerol monostearate, sorbitan sesquioleate or lauromacrogol); a suspending agent (e.g., polyethylene glycol, polyvinylpyrro-lidone or sodium carboxymethylcellulose); an antioxidant (e.g., a phenol or a quinone); a preservative (e.g.. paraoxy-

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DISCLOSURE OF THE INVENTION

[0009] Asa result of extensive studies on the physiological activities possessed by Si P, the present inventors have found unexpectedly that it has activity of suppressing fibrosis of organs and thereby accomplished the present Invention.
5 This is a result which cannot be expected at all In view of the prior art but confirmed for the first time by the inventors
based on experiments.
(0010] In addition, it is known that Si P receptors are expressed In each organ. For example, it Is known that S1 receptors Edg-1 Edg-3, Edg-5 and Edg-6 are expressed Irfthe lungs, and Si P receptors Edg-1, Edg-3 and Edg-5 are expressed in the liver and kidney (Genomics, 53164-169 (1998), B. B. A., 1484, 107-11 6(2000)).
10 [0011] Thus, based on these facts, it was also found that inhibition of fibrosis in various organs by S1 receptor
agonists can be fully predicted.
[0012] The present Invention relates to an anti fibrotic agent for various organs, comprising an SiPreceptor agonist
as an active ingredient. Particularly, the present Invention relates to an anti fibrotic agent for various organs, comprising
Si P as an active ingredient.
15 [0013] The SiP used In the present invention is a known substance (CAS registration number: 26993-30-6) and Is
commercially available.
[0014] Regarding the Si P receptor of the present invention, all of the receptors so far known (e.g., Edg-1, Edg-3,
AGR1 61H21 8 (Edg-5), Edg-6 and Edg-8) and which will be identified in the future are included.
(- [0015] As the Si Preceptor agonist of the present invention, all of the SiPreceptor agonist compounds so far known
20 and compounds which will be found in the future are Included.

INDUSTRIAL APPLICABILITY

(00181 It has been known that Si P is concerned in the growth of fibroblast. In general, it is considered that growth
25 of fibroblast leads to the acceleration of fibrosis in organs. However, the inventors have found a fact that S1 inhibits
fibrosis, which is a completely opposite result of the commonly known information.
[0017] Accordingly, since S1 has activity of inhibiting fibrosis In various organs, it Is useful in preventing and/or treating pulmonary fibrosis, interstitial pneumonia, chronic hepatitis, hepatic cirrhosis, chronic renal failure, renal glomarulosclerosis and the like.
30 (0018] Also, based on the fact that Si P inhibits fibrosis, it can be fully predicted that an Si P receptor agonist will
inhibit fibrosis in organs.
[00191 Accordingly, since the SiPreceptor agonist has activity of inhibiting fibrosis in various organs, it is considered
to be useful In preventing and/ortreat ng pulmonary fibrosis, interstitial pneumonia, chronic hepatitis, hepatic cirrhosis, chronic renal failure, renal glomeruiosclerosis and the like.
35

Toxicity:

[0020] Since toxicity of the SI P used in the present invention is low, it can be judged that it is sufficiently safe in
using it as a medicament.

40 Application for Pharmaceuticals

[0021] The S1 receptor agonist or S1 of the present invention mayj ally be ad ninistered systemically or
topically, usually by oral or parenteral administration.
45 [0022] The doses to be administered are determined depending upon, for example, age, body weight, symptom, the
- desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses
per person are generally from 1mg to 1000 mg, by oral mlcdattaxton, up to several times per day, and from 0.1 mg
to 100 mg, by parenteral administration (preferably intravenous administration), up to several times per day, or contin-
uous administration from I to 24 hours per day from vein.
50 [0023] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases In
which doses lower than or greater than the ranges specified above may be used.
(0024] The compounds of the present invention maybe administered in the form of, for example, solid forms for oral administration, liquid forms for oral administration, injections, liniments or suppositories for parenteral administration.
[0025] Solid forms for oral administration include compressed tablets, pills, capsules, dispersible powders, and gran-

55 ules etc. Capsules include hard capsules and soft capsules. / [0026] In such solid forms, one or more of the active compound(s) maybe admixed with vehicles (such as lactose,
mannitol, glucose, microcrystalline cellulose, starch, etc.), binders (such as hydroxypropyl cellulose, polyvinylpyrro-
lidone or magnesium metasilicate aluminate, etc.), disintegrants (such as cellulose calcium glycolate, etc.), lubricants -

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(such as magnesium stearate, etc.), stabilizing agents, and solution adjuvants (such as glutarnlc acid or aspartic acid, etc.) and prepared according to methods well known In normal pharmaceutical practice. The solid forms may, if desired,
be coated with coating agents (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phtha-late, etc.), or be coated with two or more films. And further, coating may Include containment within capsules of ab-
5 sorbable materials such as gelatin.
(0027) Liquid forms for oral administration include pharmaceutically acceptable solutions, suspensions and emul-sions, syrups and elixirs, etc. In such forms, one or more of the active compound(s) may be dissolved, suspended or emulsified into diluent(s) commonly used in the art (such as purified water, ethanol or a mixture thereof, etc.). Besides such liquid forms may also comprise some additives, such as wetting agents, suspending agents, emulsifying agents,
10 sweetening agents, flavoring agents, aroma, preservative or buffering agent, etc.
(00281 Injections for parenteral administration Include sterile aqueous, suspensions, emulsions and solid forms which are dissolved or suspended into solvent(s) for injection immediately before use. In Injections, one or more of the active compound(s) may be dissolved, suspended or emulsified Into solvent(s). The solvents may Include distilled water for Injection, physiological salt solution, vegetable oil, propylene glycol, polyethylene glycol, alcohol, e.g. ethanol, or a
15 mixture thereof, etc. Injections may comprise some additives, such as stabilizing agents, solution adjuvants (such as
glutamic acid, aspartic acid or POLYSORBATEBO (registered trade mark), etc.), suspending agents, emulsifying agents, soothing agent, buffering agents, preservative, etc. They may be sterilized at a final step, or may be prepared and compensated according to sterile methods. They may also be manufactured In the form of sterile solid forms (such
as freeze-driedproducts) which may be dissolved in sterile water or some other sterile dlluent(s) for Injection immedi-
20 ateiy before use.
(00291 Other forms for parenteral administration include liquids for external use, ointments and endermlc liniments, inhalations, sprays, suppositories and pessarles for vaginal administration which comprise one or more of the active compound(s) and may be prepared by methods known per se.
[0030] Sprays may comprise additional substances other than diluents, such as stabilizing agents (such as sodium
25 sulfate), isotonic buffers (such as sodium chloride, sodium citrate or citric acid). For preparation of such sprays, for
example, the method described in the United States Patent No. 2,868,691 or 3,095,355 may be used.

BEST MODE FOR CARRYING OUT THE INVENTION

30 (00311 The activity of S1 to inhibit fibrosis of organs was confirmed by the following test

Test Method:

Production of bleomycin-Induced lung Injury model animal:
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(0032] Using each of ICR male mice and under pentobarbital (60 mg/kg, l.v.) anesthesia, the cervical region was shaved and the skin was incised for about 4 m from under the larynx region along the median line. Next, the muscle layer covering upper trachea was peeled off to expose the trachea. Using a micro-syringe, physiological saline or bieomycin hydrochloride (0.03 mg/animal, manufactured by Nippon Kayaku) was administered trachealiy (50 Vanimal)
40 from the tracheal smooth muscle region between cricoid cartilage. After the administration, the incised region was
closed and antibiotics were administered Into the thigh intramuscularly in order to prevent infection. Si P (10 mg/5 ml!
kg, 0.5% aqueous solution of carboxymethylceilulose sodium (CMC.Na)-physiological saline, manufactured by Matreya) was Intraperitoneally administered once a day for 14 days after the bleomycln Induction. Tests on the phys-iological saline group (normal group) and bleomycin-induced groups (control group and Si P-administered group) were
45 each carried out using 10 animals. Fifteen days after the induction, each animal was sacrificed by exsanguination
under pentobarbital (60 mg/kg, lv.) anesthesia, and a lung (1 mg) tissue was excised.
[0033] Measurement of the lung fibrosis was carried out based on the lung tissue hydroxyproline content as shown
below.

(00341 The excised lung parenchyma was cut Into fine strips of about 2 to 3 mm, transferred into a heat-resistant
50 screw test tube using distilled water (0.4 ml) and then freeze-dried. After overnight freeze-drying, 6 N hydrochloric acid
(2.5 ml) was added thereto to carry out hydrolysis at 110°C for24 hours. Afterthe hydrolysis, this sample was neutralized with 6 N sodium hydroxide aqueous solution (2.5 ml). Thereafter, this was centrifuged (1,000 x g, 5 minutes) and the resulting supernatant (25 iii) was used In the determination of hydroxyproline.
[0035] The hydrolyzed supernatant (25 it1) was mixed with borate-alanine buffer (2.475 ml) separately prepared, and
55 potassium chloride (solid) was added thereto until it was saturated. To the mixture, 0.2 M chloramine 1 (0.6 ml) was
added, and Incubated at room temperature for 40 minutes for oxidation, and the oxidation was terminated with 3.6 M sodium thiosuifate (2 ml). Toluene (3 ml) was added thereto, followed by sufficiently mixing and heating for 30 minutes
in a boiling water bath. Next, the resulting mixture was cooled with tap water, followed by centrifugation (1,000 x g, 5

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minutes) to separate the toluene layer (1.5 ml). Ehrllch’s reagent (0.6 ml) was added thereto to carry out the color development at room temperature for 30 to 40 minutes. The absorbance of each sample was Immediately measured
at 560 nm, and the amount of hydroxyproline in the sample was calculated from a calibration curve. The results are shown In Table 1.

Table I

Bleomyc1n-hduced Bleomycin-Induced PhyslologkW saline-

irlduced SIP Es SI P adminIstered SIP unadminlstered unadministered group group group [B]

Hydroxyproflne 227.8–17.5 318.8 –10.2 217.3–9.3
content (tgllung)

[0036] The inhibition ratio was calculated by the following equation.
(0037] Inhibition ratio

=[{(G-B)-(S-B))-1..(C-B)]X 100(%)

S: Hydroxyproline content in bleomycin-induced + SI P-administered group
25 C: Hydroxyproilne content in bleomycin-Induced + 0.5% CIVIC Na- physiological saline-administered group
B: Hydroxyproline content in physiological saline-Induced + 0.5% CMC.Na- physiological saline-administered group

[0038] As the above result, S1 suppressed bleomycin-induced the increase of hydroxyproilne content by Ca. 90%.

30 Formulation Examples:

Formulation Example 1

(00391 The following components were mixed in the usual way and then subjected to tablet making to thereby obtain
35 100 tablets containing 50 mg of the active ingredient per tablet.

Ve

Sphingosine 1 -phosphate 5.0 g ID
Carboxymethyiceilulose calcium (disintegrator) 02 g 2
Magnesium stearate (lubricant) 0.1 g
40 Microcrystalline cellulose 4.7 g

Formulation Example 2

45 [0040] The following components were mixed In the usual way, and the solution was sterilized in the usual way,
dispensed In ml into ampuls and then free d I the usual way to thereby obtain 100 ampule containing 20 mg
of the active ingredient per ampul.

Sphingoslne 1 -phosphate 5.0 g
50 Mannitol 20 g
Distilled water 500 ml

Claims

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1. An anti fibrotic agent, comprising a sphingosine 1 -phosphate receptor agonist as an active ingredient.

2. An agent for preventing and/or treating a fibrosis, comprising a sphingosine 1 -phosphate receptor agonist as an

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

2020
Bogota, D.C.

Abogado
JIMENA ESCOBAR URIBE

ASUNTO Radicaciôn 05-102278
TrÆmite 011
Evento 379
Actuación 430

Oficio 11663
Folios 014

Patente de InvenciOn51 Patente de Modelo de Utilidad F-1

Via Nacional

Via PCT (fase nacional) Cap]F Cap. IIX]

No. Sol. Internacional PCT/EP2004/003656
Fecha de Presentaciôn Internal. 06-04-2004

Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descnpciôn: Folios 06-43 como se radicô inicialmente
1.2. Reivindicaciones: Folios 44-45 como se radicô inicialmente
1.3. Prioridad: Folio 1 US, 60/461.215, 08-04-2003

2. Objeto de la invención

TItulo de la solicitud: COMPOSICIONES FARMACEUTICAS SOLIDAS QUE COMPRENDEN UN AGONISTAS DE RECEPTOR SIP Y UN ALCOHOL DE AZUCAR (folio 65).

El objeto de la presente solicitud de patente de invención consiste en las reivindicaciones 1-10 en una composiciôn farmacØutica que comprende un agonista de receptor SI P y un alcohol de azücar.

El problema tØcnico planteado en esta solicitud esta relacionado con la necesidad de obtener composiciones farmacØuticas sôlidas de administraciôn oral que contengan un agonista del receptor SPI en baja proporción, que permitan alcanzar una uniformidad dosis adecuada en la composición.

Para solucionar este problema tØcnico la solicitud en estudio proporciona una cornposiciOn farmacØutica sólida que comprende un agonista del receptor SPI y un
alcohol de azücar.

La presente invenciOn se cataloga en A61 9/20, A61 9/48, A61 K47/26, A61 31/135 de acuerdo con la ClasificaciOn Internacional de Patentes (IPC).

3. Determinación del Estado de la TØcnica

Considerando que la fecha de presentación de Ia primera solicitud de patente es 08-04-2003, se buscaron documentos del estado de la tØcnica relacionados, con fecha de publicaciôn anterior a Østa.

N° Documento TItulo Fecha de

Publicación
2-aminopropane-1,3-diol compounds,
DI EP 1002792 medicinal use thereof, and 24-05-2000
intermediates in synthesizing the same.

02 EP1 195165 Sphingosine-1-phosphate for treating 10-04-2002 fibrosis I
Anterioridad Dl en folios 98-103 y D2 en folio 104-107.

4. AnÆlisisde patentabilidad (artIculo 14 D486)

4.1 Novedad (artIculo 16 D486)

La presente solicitud de patente busca protección en las reivindicaciones 1, 3-5 y 9-10, para una composiciôn farmacØutica sôlida que comprende un agonista del receptor SI P y un alcohol de azücar (manitol), que ademÆs puedecomprender un lubricante como estearato de magnesio, en forma de tableta o capsula.

En la reivindicaciôn 2 (en parte) solicita la anterior composiciôn cuando el agonista es 2-amino-2[2-(4(1 -oxo-7-phenyl)ethyl]propane-1,3-diol.

Al comparar elemento por elemento el objeto de la presente solicitud con el estado de la tØcnica, esta oficina encuentra que:

Dl ya enseæa formas de dosificaciOn sôlida para administración oral, como polvos, granulos, tabletas, pildoras y capsutas, de un activo agonista del receptor SI P de formula (I) mezclado con al menos un excipiente como manitol; adicionalmente, estas formas de dosificaciôn pueden tener un lubricante como estearato de magnesio (folio 99, pÆg.19). Entre los compuestos de formula (I) de Dl se encuentra el compuesto 2-amino-2[2-(4(I-oxo-7-phenyl)ethyl]propane-I,3-diol (folio 103, pªg. 48).

De manera tal, que composiciones como las reivindicadas no pueden considerarse
nuevas.

4.2Nivel inventivo (art(cuIol8 D486)

La presente solicitud de patente busca protecciôn en las reivindicaciones 1, 3-5 y 9-10, para una composiciôn farmacØutica sólida que comprende un agonista del

/10

receptor SI P y un alcohol de azücar (manitol), que ademÆs puede comprender un lubricante como estearato de magnesio, en forma de tableta o cÆpsula.

Solicitando en la reivindicaciôn 2 (en parte) la anterior composición cuando el agonista es 2-amino-2-[2-(4-octylphenyl)ethyl]propane-I, 3-diol y en las reivindicaciones 6-8 cuando en la composicion el agonista del receptor SI P estÆ entre (0,5-5)%, el alcohol de azücar entre (90-95)% y un lubricante entre (1,5-2,5)%.

En el estado de la tØcnica mas cercano se encuentra Dl que ya ensena formas de dosificaciôn sólida para administración oral como polvos, granulos, tabletas, pildoras y capsulas, de un activo agonista del receptor SI P de formula (I) en mezcla con al menos un aditivo como manitol; adicionalmente, estas formas de dosificaciôn pueden tener un lubricante como estearato de magnesio (folio 99, pÆg. 19). El compuesto 2-amino-2[2-(4(l -oxo-7-phenyl)ethyl]propane-I,3-diol se encuentra entre los compuestos de formula (I) de DI (folio 103, pÆg.48).

Asimismo, Dl divulga una composición para tabletas que contiene I mg del agonista del receptor SI P (0,83%), 90 mg de lactosa (75%), 25 mg celulosa cristalina (20%) y 4 mg de estearato de magnesio (3,3%) (folios 101-102, pÆg.39-40).

Por otra parte, el documento 02 senala que un compuesto agonista del receptor de esfingosina 1-fosfato (SIP) puede ser administrado en formas sôlidas para administraciôn oral incluyendo tabletas, pIldoras, cÆpsulas,polvos o granulados, en donde uno o mas de los compuestos activos pueden ser mezclados con un vehiculo como manitol y un lubricante como estearato de magnesio (folio 105, pÆg.3).

De esta manera, las diferencias con DI son que en la presente solicitud la composición tiene a) otro agonista del receptor SIP y b) da un rango de proporciones definidas para el activo (0,5-59) %, el alcohol de azücar (90 a 95) % y el lubricante (1,5-2,5) %. Sin embargo, estas diferencias no parecen conceder un efecto inesperado puesto que:

a) para un experto en la materia serla obvio intercambiar en las composiciones de DI el agonista del receptor SI P por otro agonista del receptor SIP, como el especificado en la solicitud y
b) ya DI da a conocer formulaciones para formas sôlidas donde un agonista del receptor SI P se encuentra en un bajo porcentaje (0,83 %), utilizando tambiØn como lubricante estearato de magnesio (folios 101-I 02, pÆg.39-40); igualmente tanto DI como 02 ya establecen que el vehIculo puede ser manitol y el lubricante estearato de magnesio.

En consecuencia, un experto en la materia teniendo en cuenta el problema tØcnico planteado de obtener composiciones farmacØuticas sôlidas de administración oral que contengan un agonista del receptor SPI en baja proporción, que permitan alcanzar una uniformidad dosis adecuada en la composición; hubiese combinado de manera obvia las enseæanzasde DI y 02 para lograr una composición como la reivindicada, sin denotar una actividad inventiva.

De forma tal que la composiciôn reivindicada puede considerarse una alternativa a composiciones que ya tienen una baja proporciôn de un agonista del receptor SPI como la seæaladapor DI.

Por lo expuesto anteriormente, se considera que la solicitud no cumple con el requisito de nivel inventivo.

5. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados asI:

N° Documento N° Reivindicaciones Requisito que Afecta Afectadas
Dl EP 1002792 1-5 9-10 Novedad
1-10 Nivel inventivo

D2 EP1 195165 1-10 Nivel inventivo

En cumplimiento del artIculo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dIas contados a partir de la fecha de notificaciôn de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesiôn, se denegara la patente.

Notifiquese el presente oficio con e a lo dispuesto en el artIculo 8 de la resoluciOn reglamentaria No. 002del 15 de enero de 2001, advirtiendo que contra Øl no procede recurso aguno;Z41a via gubernativa.

ALIX CARMENZA çESPEDES DE VERGEL
Jefe de DivisiOn de’Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha ii

CONCEPTO TECNICO EXAMINADOR TECNICO
No. 2510 COdiqo No. 202079