CAVELIERABOGADOS COLO-14890-841-002-7 ID-122246

S

All

SULkj I LNDLNCA DL ’DJSIk;A Y OCMLRCJC

Industria Comercio

SUPEFNTENDENCIA

FORMULARIO UNICO DE

0 SOLICITUD DE:

LI CorrecciOn de Error Material X Modificaciôn a una solicitud
Nombre: KOWA CO., LTD.

Sociedad constituida existente bajo las Ieyes 2 de Japón. IDENTIFICACION SOLJCITANTE

DirecciOn: 6-29 Nishiki 3-chome,

Naka-ku, Nagoya-shi, cc. LI NIT LI

Aishi 460-8625 C.E. Otro Ja on

Domicilio: Aishi, NUmero:
Japon
TelØfono: 546 09 70 Fax: 249 40 70
E-mail: cIientesc2cavelier.com
IDE NTIFICACION
3

Nombre: Emilio FERRERO

EI NIT LI Dirección: Carrera 4a No. 72-35 C. C.
REPRESENTANTE TelØfono: 347 36 11 Fax: 21792 11 C. E. LI Otro LI
OAPODERADO E-mail: caveliercaveIier.com NUmero: 438.019 TP
31.929

0 Nümero de expediente: 07-053.244

0 Descripción de la corrección o modificación solicitada:

Presento a este Despacho Nuevo Pliego Reivindicatorio que consta de 3 reivindicaciones para ser
tenido en cuenta al momento de realizar el Estudlo do Patentabilidad.

Comprobante de pago No. 08-23,318 Fecha: 17 de marzo de 2008

(7 Anexos "’ LI Comprobante de pago de la tasa por $1 03.000.00
LI] Poderes, si fuere el caso
LI Documento que acredita la existencia representación legal de las partes, cuando
sean personas jurIdicas.

8 NOMBRE: EMILIO FERRERO FIRMA:

C.C. 438.019 de UsaquØn T.P.A. 31.929

AHP

REIVINDICACIONES

1. Un agente para el tratamiento a prevenciOn de glaucoma que comprende

(S)-(-)-1 -(4-fluoro-5-isoquinolinasulfonil)-2-metil homopiperazina 0 su sal y Æcidofosfórico o su sal.

2. Un agente para tratamiento a prevención hipertensiOn ocular que
tornp rende

S

(S)-(-)-1 -(4-fluoro-5-isoquinolinasulfonil)-2-metil homopiperazina o su sal y
à cido fosfórico o su sal.

3. Gotas para los ojos que comprenden

(S)-(-)-1 -(4-fluoro-5-isoquinolinasulfonil)-2-metil homopiperazina o su sal y
à cido fosfórico o su sal.

’.;\

lw

SUPERINTENMENCILA BE INDUSTRIA V COHERCIO

NIT 800176039-2

RECIBO OFICIAL BE CAJA 08 -. 270.31C
FECHA : NRZ0 17 BE 2008

SUPERiNTENDENCIA DE I NDUSTRIAY COMERCIQ

-: -

- ONALI

- -

BEPOSIThNTE TIPO P480 84NC0 CUENT4 No. P460 FECH# P60 Yr. P460 ---

C4VELIER 48064808 RECIBO BE C4J4 23181 17/0312008 48.718000.00

**U C 0 N C E P 1 0

CANT. REFITISTICO CONCEPTO TOTAL CONCEPTO --

1 50005-01-03 C4MBIO BE N084L1048 V HODIFIC4 12 MARCAS V LEAS CONERCIALES 103,000.00
TOTAL; 103.000.00
30FI CIENTO IRES NIL PESOS

RESPONSABLE

RECIBO BE CAJA APLICADO AL EXFEDIENTE No.

/4’q04f002

CC))
Industria y Comercio
S U P E R I N T E N D E N C I A

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE No. 07-53244

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 580 DE

FECHA 28 DE SEPTIEMBRE DE 2007 EL TERMINO HABIL SEALADO POR

LA LEY EXPIRA EL 27 DE DICIEMBRE DE 2007

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS,

SI NO X

Canadian

Intellectual Property
Office

An Agency of
Industry Canada

(12)

(21) 2 327 276

(22) 23.04.1998

Office de la Propri,t,
Intellectuelle
du Canada

Un organisme
d’Industrie Canada

(11) CA 2 327 276

(40) 28.10.1999
(43) 28.10.1999

–:L04(13) Al

(51) Int. Cl6: C07D 217102, C07D 401/12,
C07D 217/24, A61 31/495,
A61 31/55

(85) 03,10.2000

(66) PCT/JP98/0 1868

(87 W099154306

(71) (72)
HIDAKA, HIROVOSHI, HIDAKA, HIROYOSHI (JP).
3-A,607 Otokikiyama MURAMATSIJ, HIROSHI (JP).
Tenpaku-ku, Aichi 468-0063, NAGOYA-
SHI, XX (JP). (74)
GOWLING LAFLEUR HENDERSON LLP

(54) DERIVES ISOQUINOLINESULFONAMIDE ET MEDICAMENTS INTEGRANT CES DERIVES COMME PRINCIPE AChE
(54) ISOQUINOLINESIJLFONAMIDE DERIVATIVES AND DRUGS CONTAINING THE SAME AS THE ACTIVE INGREDIENT

(57)
Compounds represented by general formula (1),
their salts, or solvates of both, and drugs containing
the same, wherein A represents linear or branched
alkylene; Ri represents hydrogen, hydroxy, alkoxy, alkyl, etc.; R2 represents hydrogen, alkyl, etc.; R3

represents hydrogen, alkyl, etc.; and R4 and R5 are the same or different and each represents hydrogen, lower alkyl, etc. Because of having an inhibitory effect on the growth of viruses, these compounds are useful as

remedies for AIDS

CA 02327276 2000-10-03 i4

- 3-

HIV, and are useful as virus proliferation inhibitors
and AIDS therapeutics, leading to the completion of the
present invention.
Namely, the present invention provides an
5 isoquinolinesulfonamide_derivative represented by the
following formula (1)

R2 S02N NR3

R1 R4

(1)

wherein A represents a linear or branched alkylene
group, R- represents a hydrogen atom, a halogen atom, a
10 hydroxyl group, an alkyl group, an alkoxy group, an
aryloxy group, a benzylcxy group which may be substituted by one or more halogen atoms, an alkylthio
group, an amino group, an alkylamino group, a dialky].-
amino group or -0(CH2)NH2 in which n stands for an
15 integer of from 2 to 6, R2 represents a hydrogen atom,
a halogen atom, an alkyl group or a cyano group,
represents a hydrogen atom, an alkyl group, an acetyl
group or a benzyioxycarbonyl group, and R4 and R5 may
be the same or different and individually represent
20 hydrogen atoms or lower alkyl groups; an N-oxide or
salt thereof; or a solvate thereof.
The present invention also provides a pharma-

CA 02327276 2000-10-03

- 4-

ceutical which comprises as an active ingredient an isoquinolinesulfonamide derivative represented by the formula (1), an N-oxide or salt thereof, or a solvate thereof.

5 The present invention also provides an AIDS
therapeutic which comprises as an active ingredient an isoquinolinesulfonaniide derivative represented by the formula (1), an N -oxide or salt thereof, or a solvate thereof.

10 Moreover, the present invention also provides a
viral proliferation inhibitor which comprises as an
active ingredient an isoquinolinesulfonamide derivative represented by the formula (1), an N -oxide or salt
thereof, or a solvate thereof.
15 The present invention also provides a pharma-
ceutical composition which comprises an isoquinoline-sulfonamide derivative represented by the formula (1),
an N-oxide or salt thereof, or a solvate thereof and a pharmacologically acceptable carrier.
20 The present invention also provides use of an
isoquinolinesulfonarrtide derivative represented by the formula (1), an N-oxide or salt thereof, or a solvate thereof as a pharmaceutical.
The present invention also provides use of an
25 isoquinolinesulfonamide derivative represented by the

CA 02327276 2000-10-03

- 13 -

conversion of the compound (1-6) into the compound (1-
7) can be conducted by reacting the compound (1-6) and
an amine, if necessary, in the presence of a base.
The compound (1) obtained as described above has
5 p24 protein production inhibiting activity and inhibits
proliferation of viruses such as lily, and can be used
as pharmaceuticals such as an viral proliferation
inhibitor and an AIDS therapeutic.
The compound (1) can be formula toctherwitli
10 pharmacologically accept.ab.le.. carriers.into.
pharmaceutical compositions of various preparation
forms by methods known per se in the art. Its
administration form is not specifically limited but can
be selected as desired depending on the object of
15 treatment. For example, its administration form can be
any one of an oral preparation, an injection, a suppository and the like. These preparation forms can
be obtained by formulation methods known to and commonly employed by those skilled in the present field
20 of art.
To formulate a solid oral preparation, an
excipient and, if necessary, a binder, a disintegrant,
a 6›-6-6-ioring matter, a taste corrigent, a
smell corrigerit and/or the like can be added to the
25 compound (1), and the resultant mixture can then be

CA 02327276 2000-10-03

44

- 14 -

formed into tablets, coated tablets, granules, powder, capsules or the like by a method known per in the
art. Such additives can be those commonly used in the
present field of art, including, for example,
5 excipients such as lactose, sucrose, sodium chloride,
glucose, starch, calcium carbonate, kaolin, micro-crystalline cellulose and anhydrous silicic acid;
binders- such as water, ethanol, propanol, sucrose
solution, glucose solution, starch solution, gelatin
10 solution, carboxyiiethylcellulose, hydroxypropyl-
cellulose, hydroxypropyistarch, nethylcellulose, ethyl -
cellulose, shellac, calcium phosphate and polyvinyl-pyrrolidorie; clisinteqrators such as dry starch, sodium alginate, powdered agar, sodium bicarbonate, calcium
15 carbonate, sodium laurylsulfate, stearic acid
onoglyceride and lactose; lubricants such as purified
talc, stearate salts, borax and polyethylene glycol;
and taste corrigents such as sucrose, bitter orange
peel, citric acid and tartaric acid.
20 To formulate a liquid oral preparation, a taste corrigent, a buffer, a stabilizer, a smell corrigent
and the like can be added to the compound (1), and the resultant mixture can then be formed into a solution
for internal use, a syrup, an elixir or the like. In
25 this case, the taste corrigent can be those mentioned

CA 02327276 2000-10-03

above, the buffer can be sodium citrate or the like,
and the stabilizer can be tragacanth, gum arabic,
gelatin or the like.
To formulate an injection, a pe1atarn
5 buffer, a stabilizer, an isotonicity, a local
anesthetic and the like can be added to the compound
(1), and the resultant mixture can then be formed into
a subcutaneous, intramuscular or intravenous injection
by a method known per se in the art. Examples of the pH
10 regulator and buffer can include sodium citrate, sodium
acetate, and sodium phosphate. Examples of the
stabilizer can include sodium pyrosulfite, EDTA, thio-glycolic acid, and thiolactic acid. Illustrative of
the local anesthetic can be procaine hydrochloride and
15 lidocaine hydrochloride. Illustrative of the iso-
tonicity can be sodium chloride and glucose.
To formulate suppositories, a pharmaceutical
carrier known in the present field of art, for example, polyethylene glycol, lanolin, cacao butter, a fatty
20 acid triglyceride or the like and, if necessary, a
surfactant such as Tween (trade mark) can be added to
the compound (1), and the resulting mixture can then be formed into suppositories by a method known per se in

the art.

25 The amount of the compound (1) to be incorporated

CA 02327276 2000-10-03

- 63 -

0. 79-0. 96 (3H, m)
Mass (FB) rn/z for C22H33N303S: 420 (M --H)
Example 54
1-(4-1’luoro-5-isoquinolinesulfonyl)-2-methyl--
5 hexahydro-1H-1,4-diazepinc
j
Using the 4-fluoro-5-isoquinolinesulfonyl chloride obtained in Referential Example 4 and the l-t-butoxyc.arbonyl-3-methylhexahyclro-1H-1,4-diazepine synthesized in Referential Example 11, treatments were conducted as in Example 1, whereby 20.0 mg of the target compound were obtained.
1H-NMR (270 MHz, CDC) 5:
8.83 (111, d, J7.59Hz)
8.57(iH,d,.J4.62Hz), 8.22(lH,d,J8.58Hz),
15 7.73(1H,t,J=7.92Hz), 3.92-4.11(2H,m),
3.12-3.33(3H,rn), 2.63-2.79(1H,rfl), 2.4(lH.dd,J14.52,8.91Hz), 1.59-2.08(2H,m)

Mass (FAB) in/z for C15F118FN302S: 324 (M+H+)
20 Example 55
1-(4-Fluorc-5--isoquinolinesulfonyl)hexahydrO-1H-1,4 diazepine
Using 4-f1uoro--5isoquinolinesulfony1 chloride
and hexahydro-114-1,4-diazepine, treatments were

25 conducted as in Example 7, whereby 120.0 mg of the

Ll

S

(12) United States Patent Kapin et at.

(54) USE OF CERTAIN
ISOQUINOLINESULFONYL COMPOUNDS
FOR THE ’I’REAI’MEN’I’ OF GEAL.JCOMA
AND OCUlAR ISCHEMIA

(75) Inventors: Michael A. Kapin, Arlington; Louis M.
Desantis, Jr., lor1 Worth, both of TX
(US)

(73) Assignee: Alcon Laboratories, Inc., Fort Worth, TX (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35
U.S.C. 154(h) by 0 days.

(21) App!. No.: 99/077,575

(22) PCT Filed: Dec. 20, 1996

(86) PCT No.: PCT/US96/20197

§ 371 Date: Jan. 19, 1999

§ 102(e) Date: Jan. 19, 1999

(87) PCT Pub. No,: W097/23222

PUT Pub. Dale: Jul. 3, 1997

Related U.S. Application Data
((iO) Provisional application No. 60/009,351, tiled on Dec. 21,
1995.

(51) mt. C1.7...A6IK 31155
(52) U.S. Cl...........................514/21S; 514/912; 514/913
(58) Field of Search......................................14/218, 912,
514/913

(56) References Cited

U.S. I’A[ENT DOCUMENt’S

4,525,589 6/1985 Ilidaka et al.

11111 11111111 01111011111111111111111111 liii 11111 11111 111111 11111111 fill (JS006271 224131
(10) Patent No.: US 6,271,224 BI
(45) Date of Patent: Aug. 7, 2001

4,541,408 9/198 Lloyd
4,678,783 7/1987 Ilidaka et at.
4,730,013 3/1988 Bondi Ct at.
4,911,920 3/1990 Jani el al.
5,212,162 5/1993 Mii,sct eL at.
5,552.403 9/1996 Burke et al.
5,573,758 11/1996 Adorante et at.
Dl 4,678,783 4/1995 Ilidaka ci at.

FOREIGN PATENT DOCUMENTS

7277979 10/1995 (JP)
WO 93/23082 11/1993 (WO)
WO 94/13275 6/1994 (WO)
WO 95/15958 6/1995 (WI))
WI) 95/19968 7/1995 (WI))
WO 96/17608 6/1996 (WO)

OTHER PUBLICATIONS

Derwent Abstract, JP 7238071 (Sep. 12, 1995), DIALOGfi File No. 351, Accession No, 10447021.

Drugs of the Future, "Fasudil Hydrochloride" 17(12):1132-1133 XP 000617424 (1992).

Primary Exa,ninerZohreh Fay
(74) Attorney, Agent, or FirmBarry L. Copeland

(57) ABSI’RAC’l’

The present invention relates to the field of ophthalmology. In particular the invention relates to the field of ocular disorders including visual field loss and glaucoma using an isoquinohnesullonyl compound, which lowers intrancu jar

pressure (LOP) and produces dilation of ocular blood ves- sels,

. Claims, No Drawings

El

LA

US 6,271,224 BI

USE OF CER1A1N
ISOQUINOLINESULFONYL COMPOUNDS
FOR THE TREATMENT 01 (IAUCOMA
AND OCUlAR ISCHEMIA

’Misapplication is a 371 of l’CT/US96/20 197 flied on Dec, 20, 1996. This application claim benefit to Provisional Application No. 600)9,351 filed Dec. 21, 1995,

BACKGROUND OF THE INVENTION

Although the underlying causes of glaucoma are not fully understood at this lime, glaucoma is characterized by dam-age to the optic nerve head, accompanied by a decrease in the normal visual field. One risk factor for glaucomatous visual field loss is elevated lOP. In fact, glaucoma has historically been treated by drug and/or surgical therapy to lower elevated lOP. While elevated lOP has been positively correlated with the rate of progression of visual field loss in glaucoma, visual field loss may occur at levels of lOP which are considered within the normal range. Thus, other factors, alooc or in addition to elevated lOP, may influence the occurrence and rate of progression of visual IlcId loss. To remain healthy and function normally, the retina and the optic nerve head fibers (neurons) must receive a proper supply of nutrients and oxygen, and must have their carbon dioxide and other metabolic waste products removed. This is accomplished by the nucrocirculation in these tissues. As used herein, the term "niicrocirculation" refers to the blood low through Ihe nutritive blood vessels, across whose walls nutrients, gases and waste products move. Blood flow to the eye depends upon the pension pressure (tile systemic blood pressure may the lOP). Some tissues have the ability to maintain (i.e., autoregulale) blood flow through a range of perfusion pressures such that an increase in systemic blood pressure may cause a reduction in the caliber of the blood vessel lumen. Conversely, reduction in systemic pressure in such tissues can result in vessel dilation; however, there is a point where perfusion pressure falls to such a level that the vessel is maximally dilated. Any further fall in perfusion pressure results in a reduction of blood flow to the tissue (ischemia), lschemia may also result from obstruction, vasospasm, increased vascular resistance, or other interfer-ence with microcirculation. Prolonged ischeniia ultimately can result in tissue necrosis or neuronal cellular apoptosis. In the ease of the optic nerve head or retina, a stale of visual dysfunction may precede the death of the neurons. hence, if ischemia is involved in the death of optic nerve fibers due to glaucoma or some other ischcniic-bornc rctinopathics or optic neuropathies, then its prevention could protect the neurons from death or loss of function.

The vasodilatory and spasmolytic activities of certain isoquinolinesulfonyl compounds have been described with respect to non-ocular tissues. See, e.g., EP 0 17 371 BI, which corresponds to U.S. Pat, No. 4,675,783. These vas-cular attributes are likely associated with inhibitition of myosin-light chain kinase activity. Myosin-light chain kina.se is an enzyme necessary for the excitation-contraction coupling of contractile activity in vascular smooth muscle. Inhibition of this enzyme results in vascular smooth muscle relaxation (i.e., vasodilation) which can produce an increased blood flow.

SUMMARY OF ’11111 INVENTION

2

visual field loss. While bound by no theories, the inventors postulate that compounds which enhance oxygen and nutri-ent delivery by enhancing ocular blood flow may he hen-eticial in preventing optic nerve head injury and may sub-sequently prevent or alter the rate of progression of visual field loss associated with glaucoma and ischemic optic neuropathies.
The present invention provides compositions and meth-
ods useful in the treatment of glaucoma (with or without 10 ocular hypertension) and ocular ischcmia, which may result in retinopathies and optic neuropathics. The compositions contain an isoquinolincsullonyl compound which is effec-tive in reducing or preventing optic nerve head or retinal damage as well as reducing lOP toward normal levels and

1.5 thus, in reducing or preventing visual field loss.
In an alternative embodiment of the compositions and mcthods of the present invention, the above compositions may further include a mucomimetie polymer, a gelling polysaccharide, a finely divided drug carrier substrate

(defined below), or a combination of these components. 20 ’l’hese additional components provide compositions which
enhance comfort and provide sustained release and delivery of the drug to the eye.
DETAILED DESCRIPTION OF TIlL
INVENTION
Elevation of lOP is associated with clinical manifestations characteristic of glaucomatous optic neuropathy. Optic nerve dysfunction may be the result of pressure-induced changes in the structure of the optic nerve head and/or reduced circulation to the optic nerve head and retina. in addition to affecting vascular resistance and blood flow, the inventors have discovered that certain isoquinolinesulfonyl compounds also lower intraocular pressure.
The isoqui nolinesulfonyl compounds of the present invention are the compounds of formula (I) shown below, as well as their pharmaceutically acceptable salts.

52

40 \\. I.

oj

45

R’

wherein

cc

60

The inventors believe that microcirculatory disturbances 65 that restrict nutritive blood flow to the chorcrid, retina arid optic nerve head are likely involved in the progression of

U

R represents a hydrogen atom, a chlorine atom or a hydroxyl group; and when R’ represents a hydrogen atom,

A represents an ethylene group unsubstituted or substi-tuted with an alkyl group having 1 to 6 carbon atoms, a phenyl group or a bcnzyl group,
R2 and R3 are directly bonded with each other, thereby forming a trimethylene group unsubstitutcd or substi-tuted with an alkyl group having 1 to 6 carbon atoms,
a phenyl group or a benzyl group, and
R represents a hydrogen atom or an alkyl group having I to 6 carbon atoms; and
when

R1 represents a chlorine atom or a hydroxyl group,
A represents an alkylcne group having 2 to 6 carbon atoms, said group being unsubstituteci or substituted with an alkyl group having 1 to 6 carbon atoms,

LI

I

US 6,271,224 BI

3
R2 and R3 arc not bonded with each other and each independently represent a hydrogen atom or an alkyl group having I to 6 carbon atoms, or R2 and R3 are directly bonded with each other, thereby lorming an ethylene group unsubstituted or substituted with an alkyl group having 1 to 6 carbon atoms or a trirneth-ylene group unsubstituted or substituted with alkyl group having 1 to 6 carbon atoms, and
R4 represents a hydrogen atom, an alkyl group having I to 6 carbon atoms or an amidino group;
and pharmaceutically acceptable salts thereof. With respect to the above-mentioned alkyl groups, they may be a straight chain group or a branched chain group. ’liicse compounds and methods of their syntheses are disclosed in U.S. Pat. No 4,678,783, the entire contents of which are incorporated herein by this reference. Other isoquinolinesulfonyl deriva-tives and methods of their syntheses are disclosed in U.S. Pat. No. 4,525,589, the entire contents of which arc likewise incorporated herein by this reference.
The preferred isoquinohnesulfonyl compound of the present inveniion is hexrrhydro I (iqiJinf1tinyli(ffciiiyT 11-1 1 4 Tia7cp also knownaf(isoquinolanesulfonyl) homopiperazine and shown below is Cdt’npdond T1), as we as its pharmaceutically acceptable
-salts.

("__)NH

Most preferred is the hydrochloride salt of Compound (11). The hydrochloride salt of Compound (11), known as lasudil, AT-877, and HA-1077 is manufactured by Asahi Chemical Industry Co., Ltd. (Japan).
Alternatively, Compound (II) and a preferred metabolite thereof may be represented the following formula:

ME
R

oI N\
NH

wherein RH or Oil.
In general, for topical administration an amount of an isoqu inolinesu I fonyl compound between about 0.001 and about 10.0 percent by weight (wt %) is used in the compo-sitions of the present invention. It is preferred that between about 0.01 and about 3.0 wt % is used, and it is especially preferred to use an amount between about (1.1 and about 2.0 wt %.

’liTre compositions of the present invention may addition-ally include components to provide sustained release and/or

"? 9

91

comfort. Such components include mucomimelic polymers,
gelling polysaccharides and finely-divided drug carrier sub-
strates. These components are discussed in greater detail in
U.S. Pat. No. 4,911,920 issued Mar. 27, 1990 and in U.S.
s Pat. No..5,212,162 issued May IS, 1993. The entire contents
of these two patents are incorporated herein by reference. For purposes ui this invention, the term "mucomimetic polymers" includes carhomers (discussed below), muco-polysaccharicles (e.g. hyaluronic acid and cliondroitin 10 sulfate) and cellulosic polymers (e.g. methyl cellulose, hydroxy propyl methyl cellulose, hydroxyethyl cellulose, carhoxy methyl cellulose, and hydroxy propyl cellulose). The preferred mueomimetic polymers useful in the present invention are anionic and have a molecular weight is between about 50,000 and 6 million daltons. These preferred polymers are characterized as having carboxylic acid func-tional groups and preferably contain between 2 and 7 carbon atoms per functional group. ’the gels which form during preparation of the ophthalmic polymer dispersion have a
’ viscosity between about 1,000 to about 300,(X)0 centipoise
(cps). Suitable polymers are carboxy vinyl polymers, prel-crably those called carhomers, e.g., (’ARI3OPOI.fi J (Goodrich Co., Cleveland, Ohio). Specifically preferred are CARBOPOI.Ofi 934 and 940. Such polymers will typically
25 be employed in an amount between about 0.05 and about 8.0
WI %, depending on the desired viscosity of the composition. Pourable liquid compositions generally comprise art amount of the polymer between about 0.05 and about 2.0 WI
As used herein, the term "finely-divided drug carrier
30 substrate’ (or "DCS") means finely-divided solids, colloidal
particles, or soluble polymers and/or polyclectrolytes which are capable of selective adsorption or binding with drug molecules. Examples of I)(S include, but are not limited to: finely divided silica, such as fumed silica, silicates and .s benkunites; ion exchange resins, which can he anionic, cationic or non-ionic in nature; and soluble polymers, such as, alginc acid, pectin, soluble carragccnans, CA1BOPOI.fi, and polystyrene sulfonie acid. In general, the DCS component is used at a level in the range of about
40 ().05 to about 100 WI %. For particulate DCS, the average
particle size diameter ranges from about I to about 20 microns. The amount of DCS and its characteristics (e.g., amount of cross-linking, particle size) may he varied in order to produce the desired time-release profile for the
45 chosen drug,
11reierred lit’S are the ion exchange resins. Some resins which are used in chromatography make ideal l)(S for binding drugs in the compositions of the present invention. Such resins are readily available, for example, from Rohm
50 & Haas (Philadelphia, Pa.) under the name AMHERI.ITEfi
and from Dow Chemical Co. (Midland, Mich.) under the name DOWEX. The average particle size diameter of the commercially available forms of the resins is about 40 to about 150 microns. Such commercially available particles 5z) are most conveniently reduced to a particle size range of about 1.0 to about 25 microns by ball milling, according to known techniques. At least 9517t, of the resulting spheroidal particles will preferably have a diameter less than 20 microns, l’he ion exchange resins will typically he present in
6) an amount between about 0.05 and about 10.0 WI % and will have an average particle size diameter between about I and about 20 microns.
In addition to the above -described principal ingredients,
the compositions of the present invention may further corn-
o5 prise various formulatory ingredients, such as antimicrobial
preservatives and tonicity agents. Examples of suitable antimicrobial preservatives include: benzalkoniuni chloride,

US 6,271,224 Ri

5

thimerosal, chlorohutanol, methyl paraben, propyl parahen, phenylethyl alcohol, cdcta te disodiu m, sorbic acid, polyquaternium 1 and other agents equally well-known to those skilled in the art. Such preservatives, if utilized, will typically be employed in an amount between about 0.001 and about IA) WI. Examples of suitable agents which may he utilized to adjust the tonicity or osmolality of the formu-lations include: sodium chloride, potassium chloride, mannitol, dextrose, glycerin and propylene glycol. Such agents, if utilized, will typically be employed in an amount between about 0.1 and about 10.0 wt %
As will be appreciated by those skilled in the art, the compositions may he formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels and erodible solid ocular inserts. The compositions are preferably aqueous, have it p11 between about 3.5 and about 8.0 and an osmolality between about 280 and about 320 milliOsmoles per kilogram (mOsm/kg).
[lsc compositions of the present invention may also comprise non-aqueous formulations such as: substantially non-aqueous liquids, substantially non-aqueous semi-solid compositions, and solid compositions or devices. The first class, substantially non-aqueous liquids, includes a iso-quinolinesulfonyl compound dissolved or suspended in one or more of the following: vegetable and mineral oils, such as liquid petrolatum, corn oil, castor oil, sesame oil, and peanut oil; triglycerides, such as the capric/caprylic triglycerides commonly used in foods and cosmetics: liquid lanolin and lanolin derivatives; and perthiorohydrocarbons. The second class, semi-solid compositions, comprises an isoquinoline-sulfonyl compound dissolved or suspended in one or more of the following: various types of petrolatum, such as white, yellow, red, and Sc> on; lanolin and lanolin derivatives; gelled mineral oil having a hydrocarbon base, such as Pl.ASl’l-

HASUSfi; petrolatum and ethylene carbonate mixtures; pet- rolatum in combination with surfactants and polyglycol,
such as iolyoxyl 40 stearate and polyethylene glycol. The third class, solid compositions or devices, includes an isoquinolinesulfonyl compound in association with (i) non-erodible devices which are inserted into the conjunctival sac of the eye and later removed, such as the Ali.a-type ditlu.sion or osmotic pressure controlled polymer membranes; and (ii) bioerodible polymers which do not have to he removed from the conjunctival sac, such as essentially anhydrous but water soluble polymers and resins (e.g., celluloses, polycarboxylic acids, and so on). Especially preferred are the biocrodible inserts described and detailed in U.S. Pat. No. 4,540,408 (Lloyd) and U.S. Pat. No. 4,730,013 (Bondi et al.), wherein isoquinolinesulfonyl compounds of the present invention would be entrained in a non -aqueous matrix consisting essentially of polyvinyl alcohol. The entire contents of these two patents are incorporated herein by reference.
As will further be appreciated by those skilled in the art, the isoquinolinesulfonyl compounds of the present invention

,_D
may also he administered iniraocularly, periocularly or sys-icinically (e.g. parenterally or orally).
Intraocular or periocular administration may he effected
by incorporating a isoquinolinesulfonyl compound in a
5 surgical irrigating solution used in ophthalmic surgery, or,
preferably, by intravitreal or periocular injection. Such injec-tion therapy will typically require from about 0.1 tiM to about 1 mM (approximately 0.02 ng to.500 gig) of a isoquinolinesulfonyl compound for each eye treated. It is preferred that between about 200 nM and about 160 jiM (approximately 40 rig to 80 >g) per eye he used in such therapy-
The preferred routes of systemic administration are oral
and intravenous. Oral dosing of an isoquinolinesulfonyl

compound in accordance with this invention will typically 15 range from about 1.0 to about 1000 mg, one to four times per
clay.’I’ll(; preferred closing range of oral administration is front about 10 to abotit 250 tug two to three times per day. Intravenous dosing of an isoquinolinesulfonyl compound in

accordance with this invention will typically range from 20 about 0.01 to about 100 mg, one to four times per day. The
preferred dosing range for intravenous administration is from about 1.0 to about 30 mg, two to three times per day. The present invention is also directed to methods of treating glaucoma and other ophthalmic diseases and abnor-
25 malitics associated will> vial field loss. The treat may be
effected by administering a therapeutically effective amount of an isoquinolinesulfonyl compound topically, ntraocularly, periocularly or systemically. The preferred methods comprise topically applying to the affected eye(s)
30 of the patient a therapeutically effective amount of it com-
position according to the present invention. The frequency and amount of dosage will be deterniintccl by the clinician based on various clinical factors. The preferred methods will typically comprise topical application of one or two drops

(or an equivalent amount of a solid or semi-solid dosage form) to the affected eye as needed, preferably one to three
times per day.
The following examples are presented to further illustrate various aspects of the present invention, but arc not intended

to limit the scope of the invention in any respect. 40
EXAMPLE 1

The hydrochloride salt of Compound II, also known as
- fasuclil hydrochloride or just fasudil, was topically admin-
istered to eyes of ocular hypertensive monkeys, New Zealand Albino (NZA) and Dutch Belted (CB) rabbits. The results are presented in fable 1. As presented, Compound II effectively lowered lOP in both ocular normotensive and hypotcnsivc (laser-induced) primates. In NZA rabbits, lOP
51) was marketedly lowered below base line for the four hour dose response. Compound If also lowered lOP in the 1)13 rabbit; however, the reduction in lOP was not sustained as it)
the NZA rabbit study.

IAHI.E 1

F.Iti’xi OF FASUOt), ON TOP RFDtJrIION IN THF Odl LAS
HYPEWt1-NSIVU AND NOI(MOTF)NStVF MONKEYNEW
ZEALAND ALBINO AND I)>) IL:tt LItILIE)t) RAt>>>>>’

ANLMAI. Baseline IJIRCENi CHANCE tROM ltASt.l.INu.

MODEl. (iurnHg) I 115 2 HR 3 HR 4 us 6 OR

t.aeied MtOP 32.1 3.2 21.9 r 6.7 14.4 5.51 23.4 4.41 (’I 9)4
1.,mercd MIOP 34.2 3.3 1 59 681 14.1 4.81 7.1 – 4.91 (I> 9)

US 6,271,224 BI I

7 8

TABLE 1 -continued

1.I1IICI’ OF lASUDIL ON 1011 RLiL)IJCI’ION IN ’FF111 OCULAR
HYPERTENSIVE AND NORMOTENSIVE MONKEY, NEW
ZEAIANL) ALBINO AND DUTCH BEEFED RABBIT

ANIMAL Baseline PERCENr CHANC3E FROM BASELINE

MODEL TOP (mmHg) 1 HR 2 HR 3 HR 4 HR 6 HR

Normal MIOP 20.4 1,4 18.9 551 21.7 –,5.21
(a- 51)

Dutch Belted 37.4 0.6 33.7 2.11 18.0 3.71 10.8 5.21 11,11 3.91 Rabbit (a 7)tt

Dutch lJeJLed 32.1 a 0.4 33.1 a 2.71 25.2 a 3.51 111.7 a 3.91.11.7 s4.01
Rabbit (n 7)tt
NZA Rabbit 27.2 13.3 36.2 3.71 35.513,61 26.1 391 22.5 3.61
(a 7)1t

All drugs wcrc administered to eves in a topical manner at a dose = 500 pg (2 s 25 pl). Fastidil was for.
, mulaled in phosphate buffered saline containing 0.01% hencalkoniuni chloridn. 11 No significant change in lop from baseline values was observed in the coirtralaleral untreated ocular nol-niotersive aye or in ii
vehicle treated ocular hypertensive eye. 55 No significant change in TOP from baseline values were
observed ill the coniralateral untreated eve. MIOP - monkey intraocular pressure. a - sninbcr of animals
in study.

EXAMPLE 2

Compound Ii (hydrochloride) was administered topically 25
to the eyes of Dutch Belted (DB) rabbits in doses of 75 and
150 /rg. The results are presented in Table 2.

’JABLE 2

DOSE-RESPONSE STUDIES oF FASUDI!. ON TOP
IN ’DIE DUTCH BELTED RABBIT

Baseline
101’ Percent Chanec from Baseline

Compound (mailIg) 11.5 hr 1 hr 2 hr .5 hr 4 hr

Oroap 1 33.0 a 0.8 8.8 3.81 1 1.5 3.21 14.6 351 3.4 2.71 0.5 3.2f
Fasud ii

lS(lpg OD
Group 1 338 0.6 3.6 a.191 3.7 a 2Aj 5.7 a 2.6 11 a 2.41 2.1 a 3.2f
Vehicle
OS

Groap 2 34.3 0.8 3.2 a 2.81 3.3 e 1.91 1.7 a 2.71 5.2 a 2,21 2.9 2.11

Fnstidll

75 pg 051 41 (Irotip 2 33.6 t 0.6 1.1 a 0.6, 5.9 2.bt (vU a 3,111 4.5 1.9f 131

Vehicle
OS

All drugs were administered to eyes in a topical rtianncr (1 a 30 pl) All compounds weJc
formulated in a phosphate bttnred suture containing 9.01% henzalkoaiunr chloride. N 11
anserats/groapi OD - drug treated eye; OS = vehicle treated eoatinlalnral rye.

EXAMPLE 3 (hydrochloride) was administered in a topical ocular fashion

in doses of 50, 125 and 25(1 g. The results of this study are A dose study similar to that described in Example 2 was
conducted with the NZA rabbit. Compound 11 presented in Table 3.

tAft!-) 3

DOSE-RESPONSE S’tlil)tt.S 01 lAST:1)11. 05 tot’ IN tElL NEW ZEALAND ALBINONO }lALiLtrI
Baseline

lop Petceni Ctaane from baseline

Compound (as nilIg) 0.5 hr I hr 2 hr 3 Iii 4 hr

C/map I 213.6–11.3 5.5 a 6.71 21.1 a 5.41 24.9 – 6.11 25.1 – 4(4 i6.3a4.04
Frisadil
250 /IS Oil

US 6,271,224 BI

9 10

fABLE 3-continued

DOSI1-RJ)SPONSL JS’ SIUDIL1S 01 FASUDIL ON LOP
N IHE NEW 7JAI AND ALBINO RABBIT

Baseline
Percent Change from Baseline

Compound (lrilnHg) 0.5 hr 1 hr 2 hr 3 hr 4 hr

Group 2 21.2.5 1.1 3.74 4.4 3.41 2.7.3.21 2.7 3.91 5.4 3.h Vehicle
Os

Group 2 20.4 a.7 2.8 3.8t 11.0 a 2.94 11.0 4.74 7.0 a 4.84 5.1 –2.74 lins,nJ,1
125 pg OD

Group 2 21.3.6 5.3 a 2.6f 8.3 6.01 7.3– 4.61 7.2 5.31 17.1 6.51 Vehicle
OS

Group) 21.3.8 1.6 3.04 3.2 3.11 2.1 4.71 1.7 4.34 1021 a 5.71 Fnsudil
50 pg

Group)

21.4.8 6.7 4.11 9.1 1.71 3.6 3.31 9.8 7.61 7.4 4.51 Vehicle
OS

All drugs were administered to eyes in a to1,ica! manner (1 a 30 pI). All compounds were forms- sled in a phosphate hullered saline containing 0.01% beazalkoninni chloride. N 6 animals/group;

(II.) drag treated eye; OS vehicle treated cottttnlaterttl eye.

EXAMPLE 4 EXAMPlE 6

The effect of repeated doses of Compound ii on the
and duration of TO-P

reduction was evaluated in lhpical Ophthalmic Formulation With Sustained Release
ocular normotensive monkeys. As shown in Table 4 a blat

of 900 ig of Compound IT (hydrochloride) administered in Lngrcdicnt .6 (w/v)

three doses, ten minutes apart, resulted in significant 101’ Compound II (hydrochloride) 1.0 reduction. 35

C:arbontcr 9341’ or Carhomcr 9741’ 0.5
Nat) 0.4

1,5,131,E 4 Manni1l 2.4

bFIl (1 OF RFPFAT10 DOSES OF FAnIJIlIl (IN lOP IN Tfl L)isodium cdctatc 0.01
OCIJ1 AR NORMOTFNSIVF CYNOMOI,GIIS MONKEY 40 BAC 13.1)1

Water for Injection q.s. to 00 Baseline
Percent Change &ont Baseline Na(Ill or LID to adjust pI I q.s.

Compound (ittttillg) 1 hr 3 hr 5111

Fasudil 20.6–0.8 23.1 2.84 23.1 3.34 19.3 a 3.24 45
900 pg OS

Vehicle 20.2 a 0.8 4.1 1.84 0.3 4.41 1.1 3.74.1 a 30 pl EXAMPLE 7 Os
Fasudil was ad:ninjslnied 3 a 301d topically (1 a 30#1, 10 minutes apt,,!). 50
N 10 for drag treated and N 5 tot Vehicle. Fasudil was formulated in
a phosphate buttered saline containing 0.01% heezalkoniuni chloride. Systeittic Formulation (Uroll

Weight
Ingredient Proportion
so

EXAMPLE h Composed II (hydrochloride) 513

Sodium Ciliate 20
Alginic Acid
Folyvinylpyrrolidone 15
Magnesium Slenratc 5
...Igvjcal Ohthn1mic Formulation hO

Ingredient (w/v)

Compound If (hydrochloride) 1.5

Benznlkoniam chloride 0.01 Preparation: The dry composition is thoroughly blended,
Phosphate buffeted saline q.s. 10 1013 65 tablets are punched from the resulting mixture, each tablet
being of such size that it contains 10 iiig of Compound II
(hydrochloride).

US 6,271,224 131
11
EXAMPLE 8

Intraocular or Periucular Forniulatjort
(For Itttittvitreal Cur Pcriocrajrtr Injection)

Ingredient (w/v)

Compound IT (hydruch)oridc) 0.002
Sterile balanced salt solution q.S to 100

EXAMPLE 9

Method of Treatment (Topical)

A patient suffering from elevated lOP and/or visual Ibid loss is treated by the topical administratration of the formu-lation of Example 5. (Inc 30 p1 drop of the formulation is administered one to tour times per day to the affected eye(s) thereby reducing the lOP and/or the progression of visual
field loss.

12
EXAMPLE 10

Method of Treatment (Systemic)
A patient suffering from elevated lOP and/or visual held loss is treated by the oral administration of the formulation of Example 7. One or more tablets of the formulation are administered orally Ito 4 times per day thereby reducing the lOP and/or the progression of visual field loss.

EXAMPLE ii 10 Method of Treatment (intraocular or Periocular)
A patient suffering from elevated lOP and/or visual held
loss is treated by the intravitreal or periocular administration of the formulation of Example 8. Ten to twenty-live micro-is liters of the formulation are administered I time per itiotith to the affected eye(s) thereby reducing the 101’ and/or the progression of visual field loss-

EXAMPLE ossEXAMPLE 12

20 Other isoquinolinesulfonarnides were topically adminis-
tered to the eyes of New Zealand Albino (NZA) rabbits-The
results are presented in Table 5 below.

TABLE 5

EFFECT OF OTtILiO ISOQUINOI,INFSULEONAMIDES ON lOP IN TIlE NZA RABBIT

Baseline

lOP Percent Change tram Baseline

Compound (mniHg) 1 hr 3 hr 5 hr

o rThht
o,\

20.4 0.8 146.t 2.0 7.3 a 4.1 1 0.(? j 35 1

19.5–0.5 7.7–4.31 14.5a0.51 0.8–2.31

15.6 –0.5 16.8 a 5.7 1 10.0 a 5.7 t 370 – 4.1

10.2 – 0.3 9.9 a 3.5 1 9.4 – 12) 1 3.3 a 38 1

US 6,271,224 BI
13

All drugs were administered to eyes in a topical manner at a dosc500 itg (2x25 p1). All compounds were formulated in
phosphate buffered said containing -0_.-0.F% beni ilkoniurn chloride, and in all instances N7.
The invention has been described by reference to certain preferred embodiments; however, it should he understood that it may he embodied in other specific forms or variations thereof without departing from its spirit or essential char-acteristics. The embodiments described above are therefore considered to he illustrative in all respects and not.1 restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.
What is claimed is:

1. A method of treating glaucoma, ocular hypertension, ocular ischemia and related disorders in a patient with one I or more ofsuch conditions, comprising administering to said patient a composition comprising an ophthalmically effec-tive amount of a compound of formula:

(I) 20

wherein R1 represents a hydrogen atom, a chlorine atom or a hydroxyl group; and

when

R’ represents a hydrogen atom,
A represents an ethylene group unsubstituted or sub-stituted with an alkyl group having 1 to 6 carbon
atoms, a phenyl group or a benzyl group, R2 and R3 are directly bonded with each other, thereby forming
a trimethylene group unsubstituted or substituted

with an alkyl group having 1 to 6 carbon atoms, a phenyl group or a benzyl group, and
R4 represents a hydrogen atom or an alkyl group having
1 to 6 carbon atoms; with the proviso that the following compound be excluded:

when

R’ represents a chlorine atom or a hydroxyl group,

14

A represents an alkylene group having 2 to 6 carbon atoms, said group lcrng unsubstitutcd or substituted with an alkyl group having 1 to 6 carbon atoms,
R and R3 are not bonded with each other and each independently represent a hydrogen atom or an alkyl

group having I to 6 carbon atoms, or R2 and R3 are directly bonded with each other, thereby forming an

ethylene group unsubstituted or substituted with an

alkyl group having I to 6 ca rt,on atoms or a I ri met h - ylenc group unsuhstituted or substituted with alkyl

group having 1 to 6 carbon atoms, and
R4 represents a hydrogen atom, an alkyl group having
to 6 carbon atoms or an arri idmo group;
and pharmaceutically acceptable salts thereof; and an oph-thalmically acceptable carrier therefore.
2. A method of treating glaucoma, ocular hypertension,

ocular ischemja and related disorders in a patient with one or more ofsuch conditions, comprising administering to said
patient a composition consisting essentially of an ophthalmi-cally acceptable carrier and an ophthalmicahly effective amount of a compound of formula:

It 25

30 0

.10

wherein R1›1 or Oil;
and pharmaceutically acceptable salts thereof.
3. The method of claim 2, wherein the administration of
40 the composition is effected topically.
4 the method ol claim 2, wherein Rll.
5 The method I claim 4, wherein the final composition concentration of the compound is between about 0.001 and about 10.0 wt %.

45 6. The method of claim 5, wherein the final composition concentration of the compound is between about 0.01 and about 30 wt %.

7. The method of claim 6, wherein the final composition concentration of the compound is between about 0.1 and about 2.0 wt % and the pharmaceutically acceptable salt is hydrochloride.
8. The method of claim 2, wherein the composition further comprises a sustained release component.
9. The method of claim 8, wherein the sustained release

55 component is selected from the group consisting of muco- mimetic polymers, gelling polysaceharides, finely-divided

drug carrier substrates, and combinations thereof.

S

85
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

2020

Bogota, D.C., 22/01/2011

Abogado
Emilio Ferrero
(Apoderado)

ASUNTO RadicaciOn 0753244
Trªmite 002
Evento 001
Actuaciôn 430
Oficlo
Folios 005

Patente de Invención Patente de Modelo de Utilidad 71

Via Nacional

Via PCT (fase nacional) Cap. I M Cap. II LII

No, Solicitud Internacional PCT/JP05/023570
Fecha de Presentación Internacional 22/Diciembre/2005

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

1. Documentos estudiados

DescripciOn: Folios: 38 a 53

Reivindicaciones: Folios: 54 y 55
Folio: 67 Memorial de 27/03/2008

Prioridad: US60/638,118 de 23/12/2004

2. Objeto de la invención

Titulo de la solicitud: Agente Preventivo o TerapØutico contra glaucoma

El problema planteado en esta solicitud es la necesidad de un agente capaz de tratar el glaucoma, reduciendo solo la presión intraocular de niveles normales.

Una vez catalogada la invenciOn Østa se clasificO en la sección: A 61 K 31/551 //31/495 de la ClasificaciOn Internacional de Patentes.

pIl

3. De la Solicitud de Patente

Reivindicaciones (art 30 D. 486, art. 22 PCT)

Las clªusulas I y2 del capitulo reivindicatorlo allegado mediante memorial de fecha 27/03/2008 se encabezan en la forma de "Agente para el tratamiento prevenciOn de glaucoma", al respecto es pertinente seæalar que eltØrmino Agente no define de forma inequivoca el producto que se pretende proteger.

De acuerdo con los elementos esenciales que definen el producto, dicha reivindicaciOn corresponde a una composición farmacØutica constituida porel agente
activo: (S)-(-)-1-(4-fluoro-5-isoquinolinasulfonil)-2-metil-homopiperazina o su sal y
por Æcido fosfOricoa su sal.

Par otra parte, el encabezado de la clªusula incluye la actividad farmacologica del
ingrediente activo incorporado en la composición como si Øste fuese un elemento

S caracterIstico de la formulaciOn. Al respecto es pertinente seæalarque la aplicaciOn

farmacolOgica no debe incluirse en la reivindicación, como quiera que las eventuales
ventajas tØcnicas asociadas a la materia reivindicada solo se pueden especificar
dentro de la memoria descriptiva de la solicitud.

En consecuencia, esta Superintendencia requiere al seæor solicitanteen los tØrminos
del presente examen tØcnico para que precise el contenido y alcance de la materia
reivindicada y modifique el encabezado de las clÆusulasde tal suerte que definan una composiciOn farmacØutica, lo anterior, en virtud de las disposiciones normativas del art. 30 D. 486 sobre definiciOn clara y precisa de la materia reivindicada.

4. Determinación del Estado de la TØcnica

El Estado de la TØcnica relacionado con la invenciOn se determinO con base en la fecha de prioridad reivindicada por la solicitud de patente en fase nacional . 23/12/2004.

Y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

N Documento Titulo Fecha de

Publucacion

"Isoquinoline sulfonamide derivatives and
Dl CA2327276 drugs containing the same as the active 28/10/1999
ingredient"
"Use of certain isoquinolinesulfonyl
D2 US6271224 compounds for the treatment of glaucoma 07/08/2001
and ocular ischemia"

Anterioridades Dl y D2 en los folios 70 a 84.

S. AnÆlisis depatentabilidad (artIculo 14 D. 486)

Novedad (art 16 D. 486)

S

La novedad del objeto
identidad tØcnica entre
tØcnica:

87

reivindicado se evaluO mediante comparaciOn y anâlisis de
sus elementos esenciales y los revelados por el estado de Ia

- La reivindicación I consiste en un Agente para el tratamiento o prevención de
glaucoma que comprende:

i) (S)-(-)-1-(4-fluoro-5-isoquinolinasulfonil)-2-metil-homopiperazina o su sal y
ii) Æcido fosfórico o su sal

- El estado del arte previo a la invención presenta los siguientes documentos:

La publicaciOn Dl revela derivados de isoquinolin-sulfonamida de fOrmula general (I):
R2 A

I S02N’ NR3

R1-f(Y 54 4

NLJ R R

Y el Ejemplo 54 de la citada referencia presenta el compuesto:

I -(4-fluoro-5-isoquinolinsulfonil)-2-metil-hexahid ro-I H-I,4-diazepina que corresponde al compuesto incorporado en la composicion reivindicada (ver folio 76). El mencionado compuesto puede formularse en una preparaciOn liquida oral acompaæada de un sistemabuffer o regulador de pH y dentro de los sistemas de elecciOn se encuentra el de fosfato de sodio (ver folio 75 de DI).

Tabla 1. ComparaciOn de elementos tØcnicos

Materia Reivindicada Antecedente Dl
(CA2327276)
Agente para el tratamiento o prevenciOn de Composiciones antivirales (VIH) que
glaucoma que comprende: comprenden:

i) (S)-(-)-i -(4-fluoro-5-isoquinolinasulfonil)-2- (Ver folio 76 ejemplo 54)1
metil-homopiperazina 0 su sal -(4-fluoro-5-isoquinolinsulfonil)-2-metil-

hexahidro-1 H-i,4-dipina

ii) Acido fosfórico (Ver folio 75 linea 11)

fosfato de sodio

Nivel Inventivo (Art18 D486)

- La reivindicaciOn 1 consiste en un Agente para el tratamiento o prevención de
glaucoma que comprende:

i) (S)-(-)-I-(4-fluoro-5-isoquinolinasulfonil)-2-metil-homopiperazina o su sal y
ii) Æcidofosfórico o su sal

- El estado del arte previo a la invenciOn presenta los siguientes documentos:

La publicaciOn D2 revela el uso de compuestos isoquinolinsulfonilo para el tratamiento de glaucoma e isquemia ocular. En el documento se establece que los compuestos hexahidro-I-(5-isoquinolinsulfonil)-I H-I,4-diazepina tambiØn denominados 1 -(5-isoquinolinsulfonil)-homopiperazina pueden formularse junto con un buffer fosfato (ver folio 84 columna 13 lIneas 1 a 4 de D2).

[:1;]

Tabla 2. ComparaciOn de elementos tØcnicos

Materia Reivindicada Antecedente D2
(US6271 224)
Agente para el tratamiento oprevención de Composiciones para el tratamiento de
que glaucoma que comprenden:

I) (S)-(-)-1 -(4-fluoro-5-isoquinolinasulfonil)-2- (Ver folio 79 columna 3 lineas 19 a
22)Compuestos metil-homopiperazina o su sal hexahidro-1 -(5-

isoguinolinsulfonil)-1 H-i,4-diazepina

ii) Acido fosfOrico (Ver folio 84 columna 13 lineas 2

Buffer fosfato 37)
AnÆlisisde Diferencias TØcnicas:

Con respecto a D2 la diferencia tØcnica estriba en que el compuesto formulado corresponde a (S)-(-)-i-(4-fluoro-5-isoquinolinasulfonil)-2-metil-homopiperazina, mientras que en el estado del arte divulgado en D2 se mencionan en general algunos derivados de hexahidro-i -(5-isoquinolinsulfonil)-1 H-i,4-diazepina.

Del problema tØcnico objetivo y del efecto inesperado:

De acuerdo con Ia memoria descriptiva de la solicitud el problema tØcnico objetivo consiste en la necesidad de suministrar un compuesto con capacidad para reducir los eventuales incrementos de la presiOn intraocular caracterIsticos del glaucoma.

Para ello suministra un Agente definido en tØrminos de su nombre IUPAC, el cual para su administraciOn requiere ser combinado con ÆcidofosfOrico.

Al respecto es pertinente seæalar que el compuesto (S)-(-)-1-(4-fluoro-5-isoq uinolinasulfonil)-2-metil-homopiperazina se encuentra divulgado por el estado del arte, asI como sus combinaciones con cido fosfOrico, tal y como se demostró en el acâpite de novedad por medio del contenido de la divulgación Dl. Y la aplicaciôn de esta clase compuestos para el tratamiento del glaucoma se encuentra divulgada en el antecedente D2.

En consecuencia, una persona del oficio, normalmente versada en la materia se encontraba en capacidad de anticipar los elementos caracteristicos del Agente reivindicado, en virtud de las enseæanzas de los documentos Dl y D2, por lo que esta Superintendencia infiere razonablemente que Ia materia carece de altura inventiva.

Por las razones expuestas anteriormente esta dependencia encuentra que la materia reivindicada no cumple las disposiciones normativas seæaladas enel articulo 18 de la Decision comunitaria 486.

6. Conclusion:

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

N° Documento N° Reivindicaciones Requisito que Afecta Afectadas
Dl CA2327276 I a 3 Novedad yNivel

I nventivo
D2 US6271224 1 1 a 3 Nivel Inventivo

En cumplimiento del artIculo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dias contados a partir de la fecha de notificación de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, 0 si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegarÆ la patente.

Notifiquese el presente oficio conforme a 10 dispuesto en el numeral 5.2, literal e), del capItulo quinto deltItulo primero de la Circular Unica N° 10 de 2001.

JOSE LUIS SALIALOPEZ

Director de Nuevas Creaciones [E]

El anterior requerimiento fue notificado par fijación en lista, de fecha

CONCEPTO TECNICO No. 296 EXAMINADOR TECNICO
Codigo No. 202044