REYES&REYES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act 329 CTOINFORMACION Folios 18
Seæor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: Expediente 06-021-164

TITULO SOLICITADO: FORMAS CRISTALINAS DE ACIDO LR(R*, R*)J2(4
FLUOROFENlL)-,5-DlHIDROXI-5-(1 -METILETIL)-3-FENIL-4-((FENILAMINO)-CARBONIL]-1 H-PIRROL-1 -
HEPTANOICO.

PUBLICACION: Gaceta 583 NO de publicación 1031

PRIORIDAD: US 60/503,592 de 17/09/2003

SOLIC1TANTE: WARNER LAMBERT COMPANY LLC.

APODERADO: CARLOS R. OLARTE

TRAMITE: SUSTENTACION DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de ml firma, abogado en ejercicio, titular de la tarjeta profesional nUmero 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad TECNOQUIMICAS SA., dentro del trÆmite dela referenda, en ejercidlo de lo dispuesto por el artIculo 42 inciso 20 de la DecisiOn 486 de 2000, por medlo del presente escrito, procedo a sustentar y complementar la oposiciOn presentada en los siguientes tØrminos:

I. COMPLEMENTO DE INFORMACION.

La solicitud colombiana 06-021-164 en trÆmite, que se refiere al Æcido libre de atorvastatina cristalino y sus formas A y B o hidratos, carecen de los

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requerimientos fundamentales para otorgarsele el beneficio de patente de invención, tal y como se puede evidenciar a travØs de los siguientes argumentos:

4 La patente americana US 4,681,893 titulada "Trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1 -yl) alkyl] -4-hydroxypyran -2-one inhibitors of cholesterol synthesis" y publicada el 21 de Julio de 1987 describe entre otros, la preparaciOn del Æcidolibre de Atorvastatina:

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LIII Li . 1.. I I:111 I Ip I I Il
aqueous sodium3M

nd 30.5 ml of
30% aqueous __

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: - o rom temperature overnight.
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 . La patente americana US 5,273,995 titulada
13,ö-dihydroxy-5-(1 -methylethyl-3-phenyl-4-[(phenylamino) carbonyl]- I H-pyrrole-1-heptanoic acid, its lactone form and salts thereof" y publicada el 28 de diciembre de 1993 revela, como su nombre lo indica el Æcido librede atorvastatina, su forma de lactona y sales de la misma.

3p

Como vemos, estas y otras patentes revelan el Æcidolibre de atorvastatina, el cual,
luego de algunas reacciones permite obtener la respectiva lactona o las sales que comünmente conocemos y que han sido motivo de discusión en otras oportunidades; si bien es cierto en estos documentos no se hace menciôn expilcita
de su estructura externa (hÆbito) o suestructura interna (Cristalinalamorfa), no to
es menos que, esta y todos los compuestos qulmicos deben adoptar algün tipo de presentación fIsica, ademÆs, el hechode que no se mencione si se encuentra en estado cristalino no quiere decir que Østa sustancia no to sea.
Para esto es necesario recordar que los sôlidos pueden existir, de acuerdo con su estructura u ordenamiento interno, en forma cristalina o amorfa, sin que ello signifique que se estØ frente a un compuesto o sustancia qulmica diferente, como se aprecia en la figura 1:

COMPUESTO QUIMICO (Principlo Activo).

ESTRUCTURA EXTERNA ESTRUCTURA INTERNA.

HABITO CRISTALINA
AMORFA.

ENTI DAD SIMPLE. ADUCTO MOLECULAR.

POLIMORFOS. COMPUESTO DE SOLVATO
INCLUSION NO ESTEQUIOMETRICO.
ESTEQUIOMETRICO.

Figura No. 1 HÆbitosy modificaciones cristalinas del estado s6lido1

Ahora bien, frente a la supuesta novedad de la forma cristalina de Atorvastastina Acido libre, esto es, frente a la ausencia de revelaciones textuales que en gracia de discusiôn se presentarla respecto de Ia forma de presentaciôn que nos ocupa, y sin perjuicio de reconocer que cada solicitud de patente debe examinarse

Tornado de "Tecnologia FarmacØutica Volumen I", Jose Luis Vila Jato. Editorial Sintesis S.A., Madrid. PÆgina45.

separadamente, me permito ttamar la atención a algunos apartes de la decision adoptada por la Superintendencia de Industria y Comercio frente a un caso de polimorfismo, contenida en la resoluciOn No 059 del 14 de enero de 2003, por la cual se niega la patente de invención a la solicitud 96037513 "Forma III cristalina de la sal de calcio de atorvastatina". En esta decisiOn se sostiene que "evidentemente el polimorfismo corresponde a variados modos de agregación de las molØculas en diferentes configuraciones de ordenamiento en redes cristalinas o alternativamente sin orden alguno (sôlidos amorfos), modos de agregaciOn que se dan segun las condiciones en las que se encuentre, siendo este hecho extrapolable a otros estados de la misma materia mÆs simples, como son por ejemplo el liquido y el gaseoso, los cuales se presentan bajo diferentes condiciones de temperatura y/o presiOn, estados gue debido a su grado de agreqación molecular presentan, tal como los polimorfos, diferentes propiedades siendo siempre la misma sustancia." (Subrayado y negrilla fuera del texto). Continua la Resolución citada diciendo que "se debe reconocer plenamente el hecho de que en la obtenciôn de polimorfos son las condiciones las que determinan su formaciOn; es evidente que la confiquración cristalina gue adopte una sustancia, depende Unicamente de su propia naturaleza fisicoguimica y termodinÆmica quedirigirÆsu respuesta frente at ambiente y posterior confiquración cristalina, por lo tanto, es la propia molØcula la que determina su forma de cristalización en respuesta al ambiente". (Negrilla y subrayado fuera del texto). En consecuencia, la forma cristalina de Atorvastatina Acido libre que se pretende patentar mediante la solicitud en curso, corresponde a una FORMA DE PRESENTACIÔN INHERENTE A LA MOLECULA V DERIVADA AL AMBIENTE AL QUE SE EXPUSO.

Elio demuestra una vez mÆs que, enpresencia de la forma cristalina o de la forma que sea de Atorvastatina Acido libre, y sin perjuicio de las eventuales, naturales y predecibles diferencias que puedan presentarse en ciertas propiedades fisicoquImicas de una y otra, siempre se estarÆ frente ala misma sustancia. En este punto es necesario hacer notar que la pretensiOn de obtener patente sobre Atorvastatina Acido libre cristalino no es otra cosa que la pretension de patentar UNA FORMA DE PRESENTACION DE UNA SUSTANCIA CONOCIDA, POSIBILIDAD EXCLUIDA DE PLANO POR LAS NORMAS APLICABLES.

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Ahora bien, ante el predecible y ya mencionado argumento en el sentido de que
para Atorvatastina Acido libre no se habrIan revelado expresamente ordenamientos cristalinos, el simple hecho de conocer la existencia de la formas cristalinas de Atorvastatina CÆlcicadescritas en las patentes US 5,969,156 de 19
de octubre de 1999, y US 6,121,461 de 19 de septiembre de 2000 y la forma amorfa (US 6,274,740 de 14 de agosto de 2001), es decir, anteriores a la fecha de prioridad aqul invocada, constituye una motivaciôn efectiva para investigar la obtenciOn y presentaciones de la Atorvastatina Acido libre considerando que Østa es la materia prima o que fÆcilmente atravØs de reacciones Æcido-base permite obtener las sales conocidas en el estado del arte, ademÆs, quees tarea obligatoria del farmacØutico formulador de sOlidos realizar estudios profundos acerca de la ocurrencia y/o existencia de variaciôn en la estructura interna o externa de los materiales que utiliza. Una persona medianamente versada en la materia tØcnica, del conocimiento de Atorvastatina Acido libre y sus propiedades, en presencia de mØtodos experimentales adecuados, y basada en documentos generales sobre formulaciôn, podrIa combinar tales enseæanzas y derivar efectivamente (a posibilidad de obtener la forma cristalina (0 cualquier otra), o una gran variedad de formas cristalinas de (a misma sustancia.

En conclusiOn puede afirmarse que Atorvastatina Acido libre cristalina no es mÆs que una FORMA DE PRESENTACION DE UNA SUSTANCIA CONOCIDA, que no merece en consecuencia privilegio de patente.

6. Para terminar, la solicitud colombiana en trÆmitereivindica, especIficamente en su reivindicació 15, un mØtodo para tratar la hiperlipidemia, hipercoIesteroemia, osteoporosis, hiperplasia porstÆtica benigna, enfermedad de Alzheimer que comprende la adminsitración de una cantidad efectiva de un compuesto como (a Atorvastatina Acido libre cirstalina, con lo
cual, dicha solicitud, incurre directamente en una improcedencia de patentabilidad, ya que como lo expone claramente el literal d) del articulo 20 del capitulo 1 del titulo II "No serÆn patentables (...) d) los mØtodos terapØuticos o quirUrgicos para el tratamiento humano o animal, asi como los mØtodos de diagnOstico aplicados a los seres humanos o a animales"

AsI mismo, y por si no fuera suficiente, las patentes arriba mencionadas es decir la US 4,681,893 y la US 5,273,995 (entre otras), claramente describen

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que los compuestos revelados en tales documentos poseen actividad hipolipidØmica e hipocolesterolØmica, lo que evidentemente demostrarla la falta de novedad y de nivel inventivo en cuanto al uso.

Asi las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la sohcitud para que su despacho se abstenga de conceder el privileglo de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

II. ANEXOS

) La patente americana US 4,681,893 titulada "Trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-y1l) alkyl] -4-hydroxypyran -2-one inhibitors of cholesterol synthesis". Portada, columnas 1,2, 13 y 14.
> La patente americana US 5,273,995 titulada
,6-dihydroxy-5-(1 -methylethyl-3-phenyl-4-[(phenylamino) carbonyl]- I H-pyrrole-1-heptanoic acid, its lactone form and salts thereof’.

Seæor Superintend

JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de UsaquØn
T.P. 44655 del C. S de la J.

United States Patent [19]
Roth

[541 TRANS-6-[2-(3- OR
4-CARBOXAMIDO-SUBSTITUTED

PYRROL-1.YL)ALICYL].4-HYDROXYPY. RAN-2-ONE INHIBITORS OF
CHOLESTEROL SYNTHESIS

[75] Inventor: Bruce D. Roth, Ann Arbor, Mich.

[731 Assignee: Warner-Lambert Company, Morris
Plains, N.J.

[21] App!. No.: 868,867

[22] Filed: May 30, 1986

[511 mt. C1.4..................... A61K 31/40; A6IK 31/35;
CO7D 207/327

[52) U.S. Cl..................................... 514/422;514/423; 546/256; 546/275; 548/517; 548/537
[58] Field of Search................548/517, 537; 514/422,
514/423

[56] References Cited

U.S. PATENT DOCUMENTS

3,983,140 9/1976 Endo at al........................... 549/292 4.049,495 971977 Endo et a!...........................435/125 4,137.322 1/1979 Endo et al...................... 548/344 X 4,198,425 4/1980 Mitsui et al.........................514/460 4,255,444 3/1981 Oka et at.........................549/292 X 4,262,013 4/1981 Mitsui et al.................... 549/292 X 4,375,475 3/1983 Willard et at.......................514/460

[II] Patent Number: 4,681,893

[45] Date of Patent: Jul. 21, 1987

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Htilcher; Arch.!3iochem. Biophys., vol. 146, pp. 422-427,(1971).
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Brown, et al.; J. Chem. Soc. Perkin 1, (1976), pp.
1165-1170.

Journal of the Americas Medical Assoc.; (1984), vol. 251, pp. 351-364, 365-374.

Primary ExaminerJoseph Paul Brust
Attorney, Agent, or FirmJerry F. Janssen

[57] ABSTRACT

Certain trans-642-(3- or 4-carboxamido-substituted pyr-rol-1.yl)alkyl]-4-hydroxypyran-2-ones and the corre-sponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylgluraryl-coenzyme A reductase (HMG CoA reductase and are thus useful hypolipidemic or hypo-cholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharma-ceutical compositions are also disclosed.

9 Claims, No Drawings

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TRANS-6.[243. OR
4-CARBOXAMIDO-SUBSTITUTED

PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN. 2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS

BACKGROUND OF THE INVENTION

The present invention is related to compounds and 10 pharmaceutical compositions useful as hypocholestero-
lemic and hypolipidemic agents. More particularly, this invention concerns certain trans-6-[2-(3- or 4-carbox-amidosubstitutedpyrrol-1-yl)alkyl]-4-hydroxypyran-

2-ones and the corresponding ring-opened acids derived 15 therefrom which are potent inhibitors of the enzyme
3-hydroxy-3-niethylglutaryl-coenzyme A reductase (HMG CoA reductase), pharmaceutical compositions containing such compounds, and a method ofinhibiting

the biosynthesis of cholesterol employing such pharma- 20 ceutical compositions.
High levels of blood cholesterol and blood lipids are conditions involved in the onset of arteriosclerosis. It is well known that inhibitors of HMG-CoA reductase are

effective in lowering the level of blood plasma choles 25 terol, especially low density lipoprotein cholesterol
(LDL-C), in man (cf. M. S. Brown and J. L. Goldstein, New England Journal of Medicine, 305, No. 9, 515-517 (1981). It has now been established that lowering

LDL.0 levels affords protection from coronary heart 30 disease (cf. Journal ofthe American Medical Association,

251, No. 3, 351-374 (1984).
Moreover, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form, 35 mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., Proc. Soc. Exper. Biol. Med., 102: 370 (1959) and F. H. Hulcher, Arch. Biochem. Bioplzy.c., 146: 422 (1971)).
U.S. Pat. Nos. 3,983,140; 4,049,495 and 4,137,322 40 disclose the fermentative production of a natural prod-

uct, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., J. Chem. Soc. 45
Perkin 1(1976) 1 165.
U.S. Pat. No. 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having an-tilipidemic activity.
U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. 5o

disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.
U.S. Pat. no. 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibi-tors of cholesterol biosynthesis.
Published PCT application No. WO 84/01231 dis-closes certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatheroscierotic agents. 60

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided certain trans-6-[2-(3- or 4-carboxamido-sub-stituted pyrrol-1-yI)alkyl]-4-hydroxypyran-2-ones and 65 the corresponding ring-opened bydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the en-

4,681,893 2
zyme 3-hydroxy-3-methylglutaryl coenzyme A reduc-
tase (HMG-CoA reductase).
In particular, in its broadest aspect the present inven-tion provides compounds of structural formula I

wherein X is.CH2, CH2CH2, CH2CH2C-
H2 or CH2CH(CH3).
Rj is 1-naphthyl, 2-naphthyl; cyclohexyl; norborne-nyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoro-methyl; alkyl offrom one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.
Either R2 or R3 is CONR5R6 where R5 and R6 are independently hydrogen; alkyl of from one to six car-bon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substi-tuted with fluorine, chlorine, bromine, cyano, trifluoro-methyl, or carboalkoxy of from three to eight carbon atoms; and the other of R2 or R3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoro-methyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.
R4 is alkyl of from one to six carbon atoms; cyclopro-pyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoro-methyl.
Also contemplated as falling within the scope of the present invention are the hydroxy acids, and pharma-ceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of struc-tural formula I above.

In another aspect of the present invention, there is provided a method of preparing the compounds of structural formula 1 above which comprises the steps of (a) first reacting a substituted [(pyrrol-l.yl)alkyl]alde-hyde compound of the formula

with the dilithio or sodio-lithio salt of methyl acelo-acetate to form a compound of the structure

1 11

R2 OH 0

R3

R4

4,681,893
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36.8 g (80.9 mmol) of 5-(4-fluorophenyl)-2-(1-methyle-
thyl)- I -(3-oxopropyl)-N,4-diphenyl- lH-pyrrole-3-car-boxamide, from Step F above, in 100 ml of tetrahydro-
furan was added over a period of thirty minutes. The resulting solution was stirred for 30 minutes at - 78° C. and then warmed to 0° C. where it was held for an additional 60 minutes.
The mixture was then acidified by the dropwise addi-tion of 300 ml of ice-cold 3M hydrochloric acid, diluted with ether, washed successively with water and brine, dried over anhydrous magnesium sulfate, and concen-trated. Flash chromatography of the residue yielded 37.9 g of 2.(4-fluorophenyl)-&.hydroxy.5-(1-methyle-thyl)-J3-oxo-3-phenyl-4-[(phenylamino)carbonyl]-IH-pyrrole-1-heptanoic acid, methyl ester.
The 90 MHz proton magnetic resonance spectrum of the product exhibited signals at 1.50 (doublet, 6H, 3=7 Hi); 1.8 (multiplet, 211); 2.45 (doublet, 2H, 3=7 Hz); 28 (broad, 1H); 3.33 (singlet, 211); 3.5 (multiplet, IH); 3.67 (singlet, 3H); 3.8-4.0 (multiplet, 2H); and 6.8-7.3 (multi-plet, 14H) parts per million downfield from tetrame-thylsilane.
Step H. Preparation of
dihydroxy-5-(l-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl].IH-pyrrole-1-heptanoic acid and trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2.(tetrahydro-4..hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide
Air (60 ml) was bubbled via a syringe through a solu-tion of 2-(4-fluorophenyl)-8-hydroxy-5-(l-methyle-thyl)-/3-oxo-3-phenyl-4-[(phenylamino)carbonyl)- lH-pyrrole-1-heptanoic acid, methyl ester (48 g, 84.1 mmol) and 92.5 ml of 1M tributylborane in 100 ml of anhy-drous tetrahydrofuran. The mixture was stirred over-night at room temperature and then cooled to 78° C. Sodium borohydride (3.85 g, 101.8 mmol) was added to the cooled mixture in one portion. The mixture was allowed to warm slowly to 0° C. over a period of three hours, during which there was vigorous gas evolution. The dry ice-acetone bath applied to the reaction ves-sel was replaced by an ice bath and 18.3 ml of glacial acetic acid were added dropwise, followed by 204 ml of 3M aqueous sodium hydroxide solution and 30.5 ml of 30% aqueous hydrogen peroxide solution.
The mixture was vigorously stirred while being al-lowed to warm to room temperature overnight. The mixture was then partitioned between diethyl ether and water and the aqueous layer was separated, acidified, and extracted with ethyl acetate.
The ethyl acetate extract was washed with brine, dried, and evaporated to yield crude Rt,R-2-(4-fluorophenyl-/3,&-dihydroxy-5.(l.methylethyl)-3-phe-nyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid which was used without further purification. The crude acid was taken up in toluene and lacto-nized by heating under reflux for six hours. This mixture was chromatographed to provide 30 g of trans.5-(4-fluorophenyl)-2-(l-methylethyl)-N,4-diphenyl-1-[2-(tet-rahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethylj-IH-pyrrole-3-carboxamide as a foamy solid, mp 90°-97° C. Analyzed for C33H33FN204: Cale.: C, 73.31%; H, 6.15%; N, 5.18%; Found: C, 73.46%; H, 6.31%; N, 5.28%.

This material was found by HPLC analysis to com-prise a 9:1 molar ratio of the and trans-isomeric forms of the product. Recrystallization from toluene-ethyl acetate yield the essentially pure trans-form, mp 148°-149° C.

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EXAMPLE 2

Preparation of
-methyle-
5 tbyl)-3-phenyl-4-[(phenylamino)carbonyl]-]H-pyrrole-1-heptanoic acid, sodium salt

A mixture of trans-5-(4-fluorophenyl)-2-(l-methyle-thyl)-N,4-diphcnyl-I -[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran.2-yl)ethyl]-1H-pyrrole-3-carboxamide (10 g, 18.5 mmol) and 0.74 g (18.5 mmol) ofsodium hydroxide in 90 ml of a 1:2 mixture of tetrahydrofuran-water was cooled to 0’ C. This mixture was allowed to warm slowly to 25° C., after which time it was concentrated 15 and the residual solid dried under vacuum.
The infrared spectrum of the product exhibited prin-cipal absorption peaks at 3400, 1651, 1598, 1565, 1511, 1438, 1412, 1316, 1224, 1159, 844, 754, and 702 recipro-cal centimeters.

20 The 90 MHz proton magnetic resonance spectrum of a hexadeutero dimethylsulfoxide solution ofthe product exhibited signals at 1.34 (doublet, J=7 Hz, 611); 1.5 (multiplet, 4H); 1.80 (doublet of doublets, 3=15, 8 Hz, IH); 1.99 (doublet of doublets, J= 15, 4 Hz, lH); 3-4 25 (multiplet 811); 6.9-7.3 (multiplet, 12H); 7.50 (doublet, J=8 Hz, 2H); and 9.85 (singlet, lH) parts per million downfield from tetramethylsilane.

EXAMPLES 3 AND 4

30 Preparation of
trans-2-(4-fluorophenyl)-N,4-diphenyl- l-[2.(tetrahydro-4hydroxy-6oxo-2H-pyran-2-yl)ethy11-5-(triflUOrome-thyl)-pyrrole-3-carboxamide and
trans-5-(4-fluorophenyl)-N,4-diphenyl- l-[2-(tetrahydro-35 4..hydroxy..6oxo-2H-pyran-2-yl)ethyl]-2-(trifluorome-thyl)pyrrole-3-carboxamide

Step A. Preparation of a-[[2-(1,3-dioxalan-2-y1)ethyi-]aminoj-4-fluorobenzeneacetic acid.

40 a-[[2-(1,3-Dioxolan-2-yl)ethyl)aminO]-4-flUOrObefl-zeneacetic acid, ethyl ester (36.5 g, 122.8 mmol, pre-pared as described above in Example I, Step A) was dissolved in 1500 ml of a 5:1 mixture of methanol-water together with 7.6 g of sodium hydroxide. This mixture 45 was heated under reflux for a period oftwo and one-half
hours after which time the solvents were removed under vacuum.

The solid residue was taken up in 325 ml of water and
a mixture of 14 ml of glacial acetic in 28 ml of water was 50 added with stirring. After stirring for a time, an addi-tional 3 ml of glacial acetic acid were added and the mixture was chilled for 75 minutes. The solids were

collected by filtration, washed with water and then ethyl acetate and dried to yield a-[[2-(1,3-dioxalan-2-55 yl)ethyl]amino]-4-fluorobenzeneacetic acid, nip
218’-220’C.

Step B. Preparation of a mixture of 5-(4-fluorophenyl)- 1*(3oxopropyl)-N,4.-diphenyl-2-(trifluoromethyl)- 111-pyrrole-3-carboxamide and 2-(4-fluorophenyl)- 1 -(3-60 oxopropyl)-N,4-diphenyl-5-(trifluoromethYl)-1-PYr-role-3-carboxamide

a-[[2-(1,3-Dioxalan-2-yl)ethyl]amiflO]-4-flUorObefl zeneacetic acid (6.06 g, 22.5 mmol) was dissolved in 45 ml of trifluoroacetic anhydride and 7.47 g (33.8 mmol) 65 of N,3-diphenyl-2-propynamide (prepared as described above in Example 1, Step D) was added. The resulting mixture was heated under reflux for a period offive and one-half hours. The mixture was then cooled, and 1.74

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US005273995A United States Patent (’91 [UI Patent Number: 592739995
Roth [45] Date of Patent: Dec. 28, 1993

[54] (R.(RSR*)].2.(4.FLUOROPHENYL).P,&..DIHY.
DROXY-5.(1.MErHYLFrHyL.3.p}jNyL.4..

[(PHENYL&MINO) CARBONYL]. - 1H-PYRROLE-1-HEPTANOIC ACID, ITS - LACTONE FORM AND SALTS THEREOF
[75] Inventor: Bruce D. Roth, Ann Arbor, Mich.

[73] Assignee: Warner-Lambert Company, Morris
Plains, N.J.

[21] AppI. No.; 660,976

[22] Filed: Feb. 26, 1991

Related U.S. Application Data

[63] Continuation of Ser. No. 384,187, Jul. 21, 1989, aban-
doned.

[51] bit. CL.....................A61K 31140 C07D 405/06 [52] U.S. CI..................................... 514/422;514/423; 548/517; 548/537
[58] Field of Search................5 14/422, 423; 548/517,
548/537

[56] References Cited

U.S. PATENT DOCUMENTS

4,681,893 7/1987 Roth....................................514/223

OTHER PUBLICATIONS

J. Med. Chem. 1985, 28, 347-358G. E. Stokker, et al. "3-Hydroxy-3-Methylglutaryl-Coenzyme a Reduc-tase...".

Tetrahedron Letters, vol. 28, No. 13, pp. 1385-1388, 1987 "Synthesis of an HMG-COA Reductase inhibitor,

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[57] ABSTRAcr

[R(*,R*)I.2.(4..auoropheny1).$&,.dihydroy.s.((1. methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]. 111-pyrrole-1.heptanoic acid or (2R-trans)-5-(4-tluoro. phcnyl)-2-(1.methylethyl.N,4-diphenyl-1.[2.(tetrahy-dro.4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl].IH.pyrrole-3carboxainide; and pharmaceutically acceptable salts thereof.

12 Claims, No Drawings

j4l

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1 2

(R-(R’R)J-244-FLUOROPHENYL)./3,6-DIHY- 0 lb
DROXY-541-METHYLETHYL-3-PHNYL-4- /

((PHENYLAMINO) CARBONYL]- HO o
IH-PYRROLE-I-}ffPTANOIC ACID, ITS
LACTONE FORM AND SALTS THEREOF

CH o

This is a continuation of U.S. application Set. No. 10 07/384,187 filed Jul. 21, 1989, abandoned. -
BACKGROUND OF THE INVENTION

Trs.(–)-5-(4-fluorophenyl)-2-(l-methylethyl)-N,4-

diphenyl-1-[2-tetrahydro-4-hydroxy.6-oxo.2H-pyran-2- 35 11

yl)ethyl]-IH.pyrrole.3-carboxamides are among corn- apparently is required for inhibition of HMG-CoA re- pounds of U.S. Pat. No. 4,681,893 having usefulness as ductase. This is reported by Lynch et *1. in "Synthesis
inhibitors of cholesterol biosynthesis. The compounds of an HMB.CoA Reductase Inhibitor; A diastereoselec-
therein broadly include 4-hydroxypyran-2-ones and the 20 tive Aldo] Approach in Tetrahedron Letters, Vol. 28,
corresponding ring-opened acids derived therefrom. No. 13, pp. 1385-1388 (1987) as the 4R, 6R configura-
It is now unexpectedly found that the enantiomer However, an ordinarily skilled artisan may not pre-
having the R form ofthe ring-opened acid oftrans-5-(4- dict the unexpected and surprising inhibition of choles-
fluorophenyl).2-(l-methylethyl)-N,4-diphenyl-1-[2-tet. 25 terol biosynthesis of the present invention in view of
rahydro-4-hydroxy-6-oxo-2H-pyran.2.yl)ethyl]-IH- these disclosures.
pyrrolc-3-carboxarnide; that is [R.(R*,R*)]2(4fluoro SUMMARY OF THE INVENTION
phenyl)-$,8-dihydroxy-5-(1-methylethyl)-3-phenyl.4.. Accordingly the present invention provides for corn-
[(phenylamino)carbonyl]-IH-pyrrole-1-beptanoic acid, 30 pounds consisting of [R.-(R,R)]-2-(4-fluorophenyl)-
provides surprising inhibition of the biosynthesis of 8,8-5<(l-methy1ethyl).3-phenyl-4-

((phenylamino) carbonyl}-IH-pyrrole-1-heptanoic acid
cholesterol. (compound of formula I), pharmaceutically acceptable
It is known that 3-hydroxy-3-methylglutaryl coen- salts thereof and (2R-trans)-5-(4-fluorophenyl)-2-(l-
zyme A (HMG.00A) exists as the 3R-stereoisomer. 35 methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-
Additionally, as shown in the study of a series of 5-sub- 6-oxo-2H-pyran-2.yl)ethyl]-11i-pyrrole-3.carboxamide

(the lactone form ofthe heptanoic acid or compound of
stituted 3,5-dihydroxypentanoic acids by Stokker et W., formula II).
in "3-Hydroxy-3-methylglutaryl-Coenzyme A Reduc- The present invention also relates to a pharmaceutical
tate Inhibitors. 1. Structural Modification of 5-Sub- 40 composition, useful as a hypocholesterolemic agent,

stituted 3,5-Dihydroxypentanoic acids and Their Lac- comprising a hypocholesterolcnuc effective amount of
tone Derivatives," /. Med. Chem. 1985, 28, 347-358, methylethyl).3-phenyl-4-[(phenylamino)caibonyl]-1H-
essentially all of the biological activity resided in the pyrrole-1 -heptanoic acid, its pharmaceutically accept-
trans diastereomer of (E)-6-[2-(2,4-dichlorophenyl)e- 45 able salts or (2R-trans)-5-(4-fluorophenyl)-2-(1-
thenyl]-3,4,5,6-tetrahydro-4-hydroxy.21{-pyranone methylethyl.N,4-diphenyl-1-(2-(tetrahydro-4-hydroxy-
6-oxo.2H-pyran-2-yl)ethyl]-lH-pyrrole-3-carbOxan3ide having a positive rotation. Further, the absolute config- acid; and it pharmaceutically acceptable carrier. Fur-
uration for the $-hydroxy-6-lactone moiety common to ther, the present invention is also a method of treating
mevinolin of the formula (la) 50 mammals, including humans, suffering from hypercho-lesterolemia by administering to such mammal a dosage
form of the pharmaceutical composition described
0 Ii shnup

H3C

and compactin of the formula (lb)

55 DETAILED DESCRIPTION OF THE
INVENTION

The pharmaceutically acceptable salts of the inven-tion are those generally derived by dissolving the free acid orthe lactone; preferably the lactone, in aqueous or 60 aqueous alcohol solvent or other suitable solvents with an appropriate base and isolating the salt by evaporating the solution or by reacting the free acid or lactone; preferably the lactone and base in an organic solvent in which the salt separates directly or can be obtained by 65 concentration of the solution.

In practice, use of the salt form amounts to use ofthe acid or lactone form. Appropriate pharmaceutically acceptable salts within the scope of the invention are

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those derived from bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hy-

droxide, 1-dcoxy-2.(methylamino).D-glucitol, magne- sium hydroxide, zinc hydroxide, aluminum hydroxide, ferrous or ferric hydroxide, ammonium hydroxide or organic amines such as N-methylglucainine, choline,

arginine and the like. Preferably, the lithium, calcium,

magnesium, aluminum and ferrous or ferric salts are prepared from the sodium or potassium salt by adding the appropriate reagent tor a solution of the sodium or potassium salt, i.e., addition of calcium chloride to a solution of the sodium or potassium salt of the com- pound of the formula I will give the calcium salt

thereof.

The free acid can be prepared by hydrolysis of the lactone form of formula IT or by passing the salt

trans racemate

through a cationic exchange resin (H +resin) and evap-orating the water.
The most preferred embodiment ofthe present inven-tion is [R-(R’R)J.2-(4-fluorophenyl)-$,8-dihydroxy-5-5 (l.methylethyl).3-phenyl-4.[(phenylamino)carbonyl]- IH-pyrrole-1-heptanoic acid, hemicalcium salt. - Generally, the compounds I and II of the present invention can be prepared -by (I) resolving the race. mate, that is prepared by the processes described in U.S. 20 Pat. No. 4,682,893 which is incorporated by reference therefor, or (2) synthesizing the desired chiral form beginning from starting materials which are known or readily prepared using processes analogous to those which are known.
15 Specifically, resolution of the racernate may be ac-complished as shown in Scheme I (where Ph is phenyl)
as follows: - -

Scheme I -
F

HO

tOH 0t ON 0

Ph

PhHNJJii \ cE3

R

+ 02N F Ph_StepAo

> +

(:3

R

1R(RR) isomer
,NaOH

OH OH 0

Ph

(CH3
R

Stei))

Separate
NaOH
refhix in toluene

HO,

Ph CONHPII

tS(RR) isomer
,NaOH

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-continued
Scheme I
O2Na

Ph CONBPh

CO2Na

OH

OH

Ph cONHPh

The "transracemate" ofScheme I means a mixture of 20 the following: -continued

HO

#0

25 F

30
Ph CONHPh

Ph CONHPh [S(JtK’)jsomer

IR(tR)]isomer 35 The conditions of the Step I and 2 of Scheme I are
OW generally as found in the Examples 6 and 7 hereinafter. The chiral synthesis is shown in Scheme 2 (where Ph
is phenyl) as follows:

Scheme 2

Ph Mg
Ph

1

I __i. ThF-80-90 C.

I hr

PbNHC to oe 2.AcOH
U
P h 0;

1 Ph J

Ph OR 0 Ph

Ii e NsOMe

F

OH MeOH, IO’C.
I6hrs

PhN}tOC" Ph

73% (3)

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-continued
Scheme 2

Ph OH
OBu’ 8 eq
2Me C. >
5 his

75% . (4)

Ph OH 0
I.B(Et)3,N.BH4

2.58303PhNHOC

(5)78%

1, NiOR

Ph OH ON
02Bu’ 2. T. H20TI
PhNHOC

(6) 83%

F

Ph

058

PhOCO t H

[a]j23 = -- 18.07 (CHCI3)

(6)93%

Generally, conditions for Scheme 2 are as shown in

the Examples 1-5 hereinafter. 60 which is now also incorporated by reference therefor. One of ordinary skill in the art would recognize van- The CSI data of the compound I, its enantiomer the ations in the Schemes 1 and 2 which are appropriate for compound II and the racemate ofthese two compounds the preparation of the compounds of the present IflVCfl are as follows: tion.

The compounds according to present invention and 65
especially according to the compound of the formula I
inhibit the biosynthesis of cholesterol as found in the
CS! screen that is disclosed in U.S. Pat. No. 468 1,893

’C50

Compound (micromolesfliter)
fJ.(RR)] isomer 0.0044

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-continued

- Compound (In)crous/1tier)
aomer 044

*acemate 0.045

Accordingly, the present invention is the pharmaceu- tical composition prepared from the compound of the
formula I or II or pharmaceutically acceptable salts
Thereof.

These compositions are prepared as described in U.S.

Pat. No. 4,681,893 which is, therefore, again incorpo- rated by reference here. Likewise, the present invention is a method of use as bypolipidemic or hypocholesteroleinjc agents. The compounds ofthe present invention utilized in the phar- maceutical method of this invention are administered to

the patient at dosage levels offrom 10 to 500 mg per day which for a normal human adult ofapproximately 70 kg is a dosage of from 0.14 to 7.1 mg/kg of body weight

per day. The dosages may be preferably from 0.5 to 1.0 mg/kg per day.
The dosage is preferably administered as a unit dos-

age form. The unit dosage form for oral or parenteral use may be varied or adjusted from 1010 500 mg, pref- erably from 20 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other

active therapeutic agents. Determinations of optimum dosages for a particular situation is within the skill of

the art.

The compounds of the formula I and II and their

pharmaceutically acceptable salts are in general equiva- lent for the activity of the utility as described herein.
The following examples illustrate particular methods for preparing compounds in accordance with this in-vention. These examples are thus not to be read as limit-ing the scope of the invention.

EXAMPLE I

285 ml 2.2M n-butyl lithium (in Hexane) is added dropwise to 92 ml diisopropylamine in 300 ml THF at 50°-.60’ C. in a 1000 ml 1 neck flask via dropping funnel and under nitrogen. The well stirred yellow solution is allowed to warm to about -20’ C. Then it is cannulated

into a suspension of 99 g S(+)-2-acetoxy-1,l,2-tri- phenylethanol in 500 ml absolute THF, kept in a 2L-3

neck flask at -70° C. When addition is complete, the

reaction mixture is allowed to warm to -10’ C. over a period of two hours. Meanwhile, a suspension of 0.63
mol MgBr2 is prepared by dropping 564 ml (0.63 mol) of

bromine into a suspension of 15.3 g ofmagnesium (0.63 mol) in 500 ml THF plus in 3 L flask equipped with

reflux condenser, and overhead stirrer. When this is completed, the MgBr2 suspension is cooled to -78 C. and the enolate solution (dark brown) is cannulated into the suspension within 30 minutes. Stirring is continued for 60 minutes at -78’ C. 150 g 5-(4-fluorophenyl)-2.(l-methylethyl).1-(3-oxopropyl)-N,4.djphenyl-lHpyr. role-3-carbozamide in 800 ml THF absolute was added dropwise over 30 minutes; then stirred for 90 minutes at
- 78° C., then quenched with 200 ml AcOH at -78’ C. This is removed to a cool bath, 500 ml of H20 is added and the mixture concentrated in vacuo at 40°-50° C. 500

ml of 1:1 EtOAc/Heptane is added to the yellowish slurry and filtered. The filtrate is washed extensively with 0.511 MCI, then several times with H20 and finally with EtOAc/Heptane (3:1) that was cooled with dry

10
ice to -20° C. The light brown crystalline- product (Example IA) is dried in vacuum oven at 40’ C. The yield is 194g.
The product 1A is recrystallized from EtOAc at
5 -10. C. to yield 100 g to yield product lB and then recrystallized from acetone/pentane to yield 90 g to yield product IC. The mother liquor is combined from the wash of the crude material and recrystallized from

EtOAc/Hcxane. 33 $ of 18 shows the following: 10 HPLC: 97.4:2.17 of the R,S to S,S isomers. 28.5 g of IC

shows the following: HPLC-95.7:3.7. The combined 18 and 1C is recrystallized from CHCI3 MeOM 10:1; pro-viding a product IF having a yield of 48.7 g of white crystal.
15 The mother liquor of the first aqueous wash is crys-
tallized (EtOAc/Heptane) to yield product ID of 21.4 g; HPLC: 71.56:25.52.
The mother liquor of lB and IC is combined and

recrystallized from CHCIt/MeOH/Heptane to yield 20 55.7 g white crystals of product 10.
ID is recrystallized from CHCI3/MeOH to yield the product lB.
All mother liquor is combined, concentrated then the

25 residue is dissolved in hot CHCI3/MeOH 10:1; put on a silica gel column; and eluted with EtOAc/Heurie
40:60. The material crystallized out on the column and the silica gel is extracted with CHCI3/MeOH and con-centrated. Recrystallization of the residue from 30 CHClfHeptane 3:1 yields 33.7 g of product II. The mother liquor of!! is recrystallized to yield 18.7
g of product 1K.

The mother liquor of 1K is crystallized to yield 6.3 g of product 1L.
35 II, 1K and 1L is combined and recrystallized from

CHCI3/Heptane to yield 48 g. The combined mother liquor of II, 1K, and IL is
concentrated to yield 31 g of IM.
The product IF provides the following data.
40

Anal. tF

m.p. 229-230’C.
Cak Found
C: 77.84 77.14
45 0: 6.02 6.45
N: 3.56 3.13

These data are consistent with the formula

50
F

55

Ph

Pb

OH

Ph

60 PliNIIOC

r’ph

65 EXAMPLE
162 g (0.206M) ofthe combined products IF, IG, lB and IL of Example I are suspended in 800 ml Me-thanol/THF (5:3). Cooled to 0 C. and added to 11.7 g

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11
sodium methoxide. The mixture is stirred until every-
thing is dissolved, then put in the freezer overnight: The reaction mixture is allowed to warm to room tempera-

ture, quenched with 15 ml HOAc, then concentrated in vacua at 40° C. to obtain expected product as follows:

10

Ph OH

ONCO2Me
15
PbNBC

This product is added to 500 ml H20 and extracted 20

twice with EtOAc (300 ml). The combined extracts are washed with saturated NaHCO3, brine, dried over an- hydrous magnesium sulfate, filtered and the solvent

evaporated. The residue is chromatographed on silica gel in EtOAc/Heptane (1:4) as eluent to yield 109 g 25 colorless oil which is recrystallized from Et20/Heptane to yield:
73.9 g first crop; white crystals
8.2 g second crop; white crystals.
The crystals provide the following data; 30 m.p. 125°-126° C., aD20=4.23° (1.17M, CH30H)

Caic. Found
C: 72.76 72.51
II: 6.30 6.23
N: 5.30 5.06

These data are consistent with the formula

F

Fb OH

NCO2MC

PbNHcO’5

EXAMPLE 3

12

Stirring is continued for four hours at 70° C. The reaction mixture is then quenched with 69 ml glacial acetic acid and allowed to warm to room temperature. The mixture is concentrated in vacua and the residue is

taken up in EtOAc, washed with water extensively, then saturated NH.sCl, NaIIC03 (saturated), and finally with brine. The organic layer is dried over anhydrous MgSO4, filtered and the solvent evaporated. The NMR of the reaction is consistent with starting material plus product in about equal amounts plus some material on the baseline ofthe TLC. The material ofthe baseline of the TLC is separated from starting material and the product is extracted by acid/base extraction. ’The or-ganic phase is dried and concentrated in vacua to yield 73 g. The NMR and TLC are consistent with the for-
mula

F

Ph OH 0 0

N -.-.- - OtBu

PhCO

EXAMPLE 4

35 73 g crude product of Example 3 is dissolved in 500
ml absolute THF and 120 ml triethyl borane is added, followed by 0.7 g t-butylcarboxylic acid. The mixture is stirred under a dry atmosphere for 10 minutes, cooled to
 78° C. and 70 nil methanol is added and followed by
40 4.5 g sodium borohydride. The mixture is again stirred at -78* C. for six hours. Then poured slowly into a 4:1:1 mixture of ice/30% H202/}120. This mixture is stirred overnight then allowed to warm to room tern-45 perature.
CHCI3 (400 in]) is added and the mixture is parti-tioned. The water layer is extracted again with CHCI3. The organic extracts are combined and washed exten-sively with H() until no peroxide could be found. The
50 organic layer is dried over MgSO., filtered and the
solvent is evaporated.
The residue is treated by flash chromatography on
silica gel, i.e. EtOAc/Hexane 1:3 to yield 51 g.
The product is dissolved in THF/McOH and added

55 to 100 nil in NaOH, then stirred for four hours at room 77 ml of diisopropylamine is dissolved in 250 ml THF temperature. The solution is concentrated at room tern- in a 2000 ml three-neck flask equipped with therrnome- perature to remove organic solvent, added to 100 ml
ter and dropping funnel. The reaction mixture is kept H20, and extracted with Et20 twice. The aqueous layer under nitrogen. The mixture is cooled to 42° C. and is acidified with IN HCI and extracted with EtOAc added to 200 ml 2.2M of n-butyl lithium (in Hexane) 60three times. The combined organic layers are washed dropwise over 20 minutes and stirred for 20 minutes

before adding dropwise 62 ml of t.butylacetate, dis-
solved in 200 ml THF (over about 30 minutes). This MgSOa, filtered, and the solvent evaporated. The resi-
mixture is stirred 30 minutes at 40° C., then 140 ml due is taken up in 2 liters oftoluene and heated toreflux
2.2M of n-butyl lithium is added over 20 minutes. When 65 using a Dean-Stark trap for 10 minutes.
addition is complete, 81 g of the product of Example 2 The reaction mixture is allowed to cool to room tern-
in 500 ml absolute THF is added as quickly as possible perature overnight. Reflux is repeated for 10 minutes
without allowing the temperature to rise above 40° C. and cooled for 24 hours.

51

.4.

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The procedure above is repeated. The reaction is left

at room temperature for the next 10 days, then concen- trated to yield 51 & of colorless foam.
This product is dissolved in minimum CRC13 and chromatographed on silica gel eluting with EtOAcf-Heptane (50:50) to yield 23 g in pure material. Chromatography on silica gel in CHCI3I2-propanol (98.5:15) yields 13.2 S.

Caic.
C: 73.31
H: 615
N: 5.16

EXAMPLE 5

Preparation of 2R-trans-5-(4-fluorophenyl)-2-(l-

methylethyl)-N,4-diphenyl-l-[2-tetrahydro4.hydroxy- 6-oxo-2N-pyran-2-yl)ethylj-IN/-pyrrole-3.carboxa-

inide

The product of Example 4 is recrystallized from EtOAcIHcxanc. Fraction I yields 8.20 g of 4A. The mother liquor yields 4.60 g of 413, HPLC of 4B shows 100% ofthe product to be the 1R.(R*R*)J isomer. 4A is recrystallized to yield 4.81 g of 4C. 4B is chroinato-graphed on silica gel in CHCI3/2.propanol to yield 4.18 g colorlessfoam of 4D showing ajI3+24.53’ (0.33% in CHCI3). 4C is recrystallized and the mother liquor of 4C is to yield 2.0 g.HPLC which indicates 100% of the k-trans isomer 2R-trans-5-(4-fiuorophenyl)-2-(l.. methy1ethy1).N,4-diphenyl.1.[2.tetrahydro_4bydroxy 6-oxo-2H-pyran-2-yl)ethyl)-IH-pyrrole-3-carboxamide.

EXAMPLE 6

Preparation of diastereomeric a-methylbenzylainides A solution of the racemate, trans-(–)-5-(4-fluoro-phenyl)-2-(I-methylethyl)-N,4-diphenyl-1-[2-setrahy-dro-4-hydroxy-6-oxo-2H-pyran.2-yI)ethyl].IH-pyrrole-3-carboxamide, (30 g, 55.5 ml) in (R)-(+)-a-methylben-zylamine (575 ml, 4.45 mol, 98% Aldrich) is stirred overnight at room temperature.
The resulting solution is then diluted with ether (2 1) and then washed exhaustively with 2M NC! (4x500

in]). water (2x500 ml) and brine (2x500 ml). The or- ganic extract is then dried over MgSO4, filtered and
concentrated in vacuo to yield 28.2 g ofthe diastereom-eric a-methylbenzylamidcs as a white solid; m.p. 174.0’-177’. The a-methylbenzylainides are separated by dissolving 1.5 g of the mixture in 1.5 ml of 98:1.9:0.1 CRCI3CH30H:NR$0H (1000 mg/in]) and injecting onto a preparative HPLC column (silica gel, 300 mmX4L4 mm ID.) by gastight syringe and eluting with the above solvent mixture. Fractions are collected by UV monitor. Diastereomer 1 elutes at 41 minutes. Diastereomer 2 elutes at 49 minutes. Center cut frac-tions are collected. This procedure is repeated three

times and the like fractions are combined and concen- trated. Examination of each by analytical HPLC indi-cates that diastereomer I is 99.84% pure and diastereo- mer 2 is 96.53% pure. Each isomer is taken on sepa-
rately to following Examples.

EXAMPLE 7

Preparation of 2R-trans-5.(4-fluorophenyl)-2-(1-

methylethyl)-N,4-diphenyl-I -[2-(tctrahydro-4-hydroxy- 6-oxo-2H-pyran-2-yl)ethyl].lH-pyrrole..3-carboxamide
To an ethanolic solution (50M) of diastereomer I of Example 6, [3R[3k*(R*),5R*]J.2(4fluorophenyl)

14
14163- dihydroxy-541 -methylethyl)-3-phenyl4-((phenylainino) carbonyl)-N.(1.phenylethyl-IH-pyr-role- 1-heptanainide, (bydroxy centers are both R) (1 g, 1.5 minol) is added IN NaOH (3.0 ml, 3 mmol). The 5 resulting solution is heated to reflux for 48 hours. The solution is cooled to room temperature and con-centrated in vacuo. The residue is resuspended in water and carefully acidified with 6N HCI. The resulting

acidic solution is extracted with ethyl acetate. The or- 10 gsnic extract is washed with water, brine, dried over
M8SO4, filtered and concentrated in vacuo. This resi-due is redissolved in toluene (lOC) ml) and heated to reflux with azeotropic removal of water forthree hours. This is cooled to room temperature and concentrated in
I vacuo to yield 1.2 g of a yellow semi-solid. Flash chro-matography on silica gel eluting with 40% EtOAc/- Hexane gives 0.42 g of a white solid which still contains impurities. This is rechromatographed to give 0.1 g of 20 essentially pure R,R, enannomer, 2R-trans-5-(4-fluoro-phenyl)-2-(l-metbylethyl)-N,4-diphenyl-I-[2-(tetrahy-dro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-IH-pyrrole-3-carboxamide, as a white foam. HPLC shows this ma-terial to be 94.6% chemically pure Ia]j,230.51% in 25 CHCI3=25.5. The peak at room temperature= 53.46 minutes is tentatively assigned to an unknown diastereo-mer resulting from the 2% (S)-(-)-a-methylbenzyla-mine present in the Aldrich a-methylbenzylaminc.

30 EXAMPLE 8
Preparation of 2S.trans-5-(4-fluorophenyl)-2-(l-methylethyl)-N,4-diphenyl-l-[2.(trtrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-]H-pyrrole-3-carboxamide-(S,S enantiotner of the compound prepared in Example 35 5

Carrying out the procedure described in Example 7
on diastereomer 2 afforded 0.6 g of a foamy solid which was flash chromatographed on silica gel. Elution with 50% EtOAc/Hexane gave 0.46 g of essentially pure 40 S,S, enantiomer 2S.trans-5.(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-142.(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2.yl)ethyl3-IH.-pyrrole-3-carboxamide, as a white foam. HPLC showed this material to be 97.83% chemically pure. [a]i=0.51% in 45 CHC13= -24.8%.

EXAMPLE 9

Hydrolysis of chemical lactone of formula II
To a room temperature, solution of the lactone in
50 TifF is added a solution ofsodium hydroxide in water. The mixture is stirred for two hours HPLC:99.6% (product); 0.34 to (starting lactone). The mixture is diluted with 3 L water, extracted with ethyl acetate (2X L) and acidified to pH >< 4 by addition of 37 ml of 55 5N hydrochloric acid. The aqueous layer is extracted with 2x1.5 L portions of ethyl acetate. The combined ethyl acetate extracts are washed with 2x 1 L of water, brine and dried, gave after filtration the ethyl acetate

60 solution of the required face-acid. This solution is used directly in the fraction of the N-methylglucamine salt. The ethyl acetate extracts from the brine-water were concentrated to give 15.5 g of an off-white solid.

EXAMPLE 10

65 Calcium Salt from Sodium Salt and/or Lactone

Dissolve one mole lactose (540.6 g) in S L of MeOH; after dissolution add I L H30. While stirring, add one

4
4.

5,273,995 15 16
equivalent NaOH and follow by HPLC until 2% or less -continued
lactone and methyl ester ofthe diolacid remains (cannot
use an excess of NaOH, because Ca(OH)2 will form an
addition of CaCl2). Charge NaOH as caustic (51.3 ml, 5 Ca 98 eq.) or as pellets (39.1 g, 0.98 eq.).
The above procedure is shown as follows:

o 10

0 _H’N,,Ph

II mw. 1155.4g 2

OH - 15 EXAMPLE 11
.98 eq. NaO}l
MeOR, Treatment of Ethyl Acetate Solution of Free-acid of
5:1 the Formula I with N-methylglucamine
To a solution of the free-acid of the formula I
(0.106M) in ethyl acetate (3 L) is added a solution of

H Ph 20 N-methylglucaminc (20.3 g, 0.106 m) in (1:1) water-ace- S tone (120 ml, 120 -ml) with vigorous stirring at room

temperature. Stirring is continued for 16 hours and the
II OH OH o hazy solution concentrated in vacuo to -.250 mp. Tolu-

EtOAc,

Hexane ene (1 L) is added and the mixture concentrated to a 25 white solid .100 g. The solid is dissolved in 1670 ml
Wash >F...<>..$?.:

acetone and filtered into a three-neck flask equipped
with a mechanical stirrer and thermostat controlled

thermometer. The flask and filter is washed with 115 ml Ph
30 (1:1) water-acetone and the clear solution is cooled
slowly. This provided a precipitate which is re-dis-
solved by heating back to 65° C. Addition of a further

Upon completion of hydrolysis, add 10 L H20, then 20 ml of water followed by the washing gives a crystal-
wash at least two times with a 1:1 mixture of EtOAc/- line product which was isolated by filtration. The solids
35 are washed with 1200 nil CH3CI and vacuum dried at
Hexane, Each wash should contain 10 L each of 255 to give a white solid. Analysis of this material
EtOAc/Hexane. If sodium salt is pure, add 15 L of indicates that it contains 4% amine as well as 0.4%

MeOH. If it is impure and/or contains color, add 100 g residual acetone and 0.67% water. Analytical results are
of 0-60 charcoal, stir for two hours and filter over noted as follows:

Melting point: 105-155° C. (decomposition) Analysis supercel. Wash with 15 L MeOH. Perform a wt/vol Expected: C=63.73; 11-6.95; N=5.57; F2.9.53. Anal- on the reaction mixture, by HPLC, to determine the ysis Found; C=62.10-,11-6.89; N-5.34; F2. C61.92; H-

exact amount of salt in solution. 7.02; Nr5.38; F2.

Dissolve I eq. or slight excess CaC122H20 (73.5 g) in 1120=0.47% (KF)
43 HPLC: MeOH, H20, THF (40; 550; 250) 20 L H20. Heat both reaction mixture and CaCl2 solu- Econosil: C18, 5 g, 25 CM
tion to 60° C. Add CaCl2 solution slowly, with high 256 mm: 1.0 ml/min.
agitation. After complete addition, cool slowly to 15° C. 81 mm.: 98.76%
and filter. Wash filter cake with 5 L HO. Dry at 50° C. Opt. Ret.: ib 10.33° (c= 1.00, MeOH)

Residual Solvents: Ia50 CH2CH=0.260/c
in vacuum oven. Titrations:
Can be recrystallized by dissolving in 4 L of EtOAc 11C104 (0.IN)r203.8%
(50° C.) filtering over supercel, washing with I L Bu4NOH (0.I14)=98.59c’
EtOAc, then charging 3 L of hexane to the 50° C. Other salts prepared in a manner analogous to those

processes appropriately selected from Examples 10 and
solution. 11 above may be the potassium salt, beminiagnesium
The above procedure is shown as follows: salt, hetnizinc salt or the 1-deoxy-2-(methylamino)-D-
glucitol complex of the compound of formula I.
I claim:

OH OH 0 60 1. (*,Ra2..(4fluorophenyl)J,3,&thydroxy..5.

(1-mcthylethy1)-3-phenyl-4-[(pheaylamino).carbonyfl- ONa’ IH-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluoro-
h eq. CaCl2.2H20 phenyl)-2.(l-methylethyl).N,4-diphenyl-l.[2-(tetrahy- H20 dro4-hydroxy-6-oxo-2}I-pyran-2-yl)ethyl]-IH-pyrrole-

65 3-carboxamide; or pharmaceutically acceptable salts

00 thereof. Ph 2. A compound of claim I which is 1R(R*Rs)].2(4.

fluorophenyl)-3-8-dibydroxy-5-(l-methylethyl)-3-phe.

2020
Bogota, D.C.,

Doctor:
Carlos Reinaldo Olarte Garcia
Apoderado

ASUNTO: RadicaciOn PCT No 06-21164
TrÆmite 011
Evento 379
Actuaciôn 440
Folios 026

Industria y Comercio ’
S P E R I N T E N D E N C I A

OficioN°: 1031

Con fundamento en lo previsto por el artIculo 43 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le comunica que la oposicion presentada por el doctor JosØ Luis Reyes Villamizar, en su calidad de apoderado de TecnoquImicas S.A., reUne los requisitos formales exigidos por la ley al momento de su presentaciOn.

En cumplimiento de lo dispuesto en Ia citada norma, se le concede el tØrmino de sesenta (60) dIas hÆbiles siguientesa la fecha de notificaciOn del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifiquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capItulo quinto del titulo primero d9.JaCircular Unica No 10 de 2001.

ALIX CARMENA CESPEDES DE VERGEL
Jefe de la Divjiôn de Nuevas Creaciones.

El anterior oficio fue notificado por fijaciôn en lista de fecha,________________

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10 Sede CAN: Ti. 40A No. 38-50 Conmutador: 3820840 Fax: 382 26 95. Linea 9800-910 165
Web: www.sic.gov.co e-mail: infosic.pov.co Bogota D.C. - Colombia

2020
Bogota, D.C.,

Doctor:
Carlos Reinaldo Olarte Garcia
Apoderado

ASUNTO: Radicación PCT NO 06-21164
TrÆmite 011
Evento 379
Actuación 440
Folios 014

t1 0*n"’?? -I
Industria y Comercio
S U P E R I N T E N D E N C I A

Oficio N°: 13: 3

Con fundamento en lo previsto por el articulo 43 de la Decision 486 de la ComisiOn de la Comunidad Andina, se le comunica que la oposicion presentada por la doctora Eliana Isaura Moreno BohOrquez, en su calidad de apoderada de Gynopharm S.A., reUne los requisitos formales exigidos por la ley al momento de su presentaciOn.

En cumplimiento de lo dispuesto en la citada norma, se le concede el tØrmino de sesenta (60) dias hÆbiles siguientes ala fecha de notificaciOn del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifiquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capItulo quinto del tItulo primero de la Circular Unica NO 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la Dbisión de Nuevas Creaciones.

El anterior oficio fue notificado por fijaciOn en lista de fecha

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10 Sede CAN: Ti. 40A No. 38-50 Conmutador: 3820840 Fax: 382 26 95. Linea 9800-910 165
Web: www.sic.gov.co e-mail: infosic.Qov.co Bogota D.C. -Colombia

2020
Bogota, D.C.,

Doctor:
Carlos Reinaldo Olarte Garcia
Apoderado

ASUNTO: RadicaciOn PCT NO 06-21164
TrÆmite 011
Evento 379
ActuaciOn 440
Folios 024

Industria y Comercio
SUPER NTE N DEN CIA

OficioN°:

Con fundamento en lo previsto por el articulo 43 de la Decision 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada pore) doctor JosØ Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano Lafrancol S.A., reüne los requisitos formales exigidos por la ley at momento de su presentaciôn.

En cumplimiento de lo dispuesto en la citada norma, se le concede el tØrmino de sesenta (60) dias hÆbilessiguientes a Ia fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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

ALIX CARIN’A CESPEDES DE VERGEL
Jefe de la,bivisiOn de Nuevas Creaciones.

El anterior oficio fue notificado por fijaciOn en lista de fecha

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7y 10 Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840 Fax: 382 26 95. Linea 9800-910 165
Web: www.sic.gov.co e-mail: infosic.gov.co Bogota D.C. - Colombia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

Bogota, D.C., 14, agosto, 2009

Apoderado: Carlos Reinaldo Olarte

ASUNTO RadicaciOn 06-21164
TrÆmite 002
Evento 001
ActuaciOn 430
Oficio
Folios

Patente de lnvención 0

Via PCT (fase nacional) 0
No Sol. Internacional
Fecha de Presentaciôn Internal

Cap.l [Ill Cap. II 0
PCT/1132004/00291 9
W02005/026116

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:

Documentos estudiados

DescripciOn: Folios: 33 a 48 como se radicO inicialmente.

Reivindicaciones: Folios: 49 a 51 Como se radicO inicialmente.

Dibuios: Folios 52 a 55 Como se radicO inicialmente

Oposiciones: LAFRANCOL S.A.; GYNOPHARM S.A.

Folios 92 a 214.
Prioridad: Folio 1: US 60/503.592, 1 7-sep-2003

Respuesta del solicitante No dio respuesta a ninguna de las dos oposiciones.

Objeto de la invención

TItulo de la solicitud: FORMAS CRISTALINAS DE ACIDO [RR*,R*)]2(4 FLUOROFENIL)3-DIHIDROXl-5-(1 -METI LETIL)-3-FENIL-4-[(FENILAMINO)- CARBONIL]-1 H-PIRROL-1-HEPTANOICO.

El objeto de la presente solicitud de patente de invención consiste en: P JH OH 0 Off
- Reivindicaciones 1: Un Æcidolibre de atorvastatina cristalino.
- Reivindicaciones 2-10: Un Æcido libre deatorvastatina cristalino A
- Reivindicacionesl 1-13: Un âcido libre de atorvastatina cristalino B.
- Reivindicacón 14 Una composición que comprende Æcdolibre atorvastatina
cristalino.
- Reivindicación 15: Un mØtodo de tratamiento.

La invenciôn se catalogô, segUn la Clasificaciôn Internacional de Patentes (IPC.): C07D207/34, A61 K31/40, A61 P03/06.

De la solicitud de Patente

Reivindicaciones (artIculo 30 D 486 de la C.A.N.)

- Las reivindicaciones 2 y 4 son textos exactamente iguales, por 10 tanto son redundantes y 10 cual no es aceptable en los capItulos reivindicatorios.

- Las reivindicaciones 12 y 14 son textos exactamente iguales, por lo tanto son
redundantes y 10 cual no es aceptable en los capitulos reivindicatorios.

Excepción a la patentabilidad (artIculo 20 D486 de ía CAN, literal d))

- La reivindicaciOn 15 reclama un mØtodo de tratamiento, por lo tanto estÆ bajoel
alcance del artIculo 20 D486 do la CAN, literal d), por lo tanto no es patentable.

AnÆlisis de la(s) Oposición(es): (artIculo 43 D. 486 de la CAN)

- La oposicion presentada por LAFRANCOL S.A, presenta los documentos patente
US4,681,893; US5,273,995.
- La oposiciOn presentada por GYNOPHARM S.A, presenta los documentos
US6,583,29 1; W002/43667; EP 0848705 [ES2 167587]; EP 0848704[ES2 166456]. En las multiples anterioridades y en los argumentos se sustenta que la aWastatina, es ampliamente conocida y es la molØcula inicial para su amplia variedad de sales y polimorfos con patentes, entonces la atorvastatina no es nueva y que su estado aislado de âcido libre es un sôlido, que por lo tanto puede existir de acuerdo con su ordenamiento interno, en forma cristalina o amorfa, sin que ello signifique que se estÆfrente a un compuesto o sustancia qulmica diferente, entonces las oposiciones estÆn cimentadascon el arte mªs prOximo, por lo tanto deben ser tenidas en cuenta para el examen de patentabilidad.

Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el Estado de la TØcnica es la fecha de presentaciOn de la solicitud prioritaria 17-septiembre-2003.

Teniendo en cuenta la fecha indicada se realizO la bUsqueda en las bases de datos a que la oficina tiene acceso del estado de Ia tØcnica, y los aportados en las oposiciones encontrÆndose los siguientes documentosmÆsrelevantes:

Fecha de

NO Documento TItulo publicación*
DI US6,583,295 Salts of HMG-COA reductase inhibitors 24-jun-2003
Hydrolysis of [R(R*,R*)]2(4 fluorophenyl)--dihydroxy-5-(1
D2 W002/43667 methylethyl)-3-phenyl-4-[(phenylamino) 06-j U n-2002
carbonyl]-I H-pyrrole-1 -heptanoic acid esters with calcium hydroxyde Forma cristalina de la sal hemicalsica del Æcido [R(R*,R*)]2(4fluorofenil)
D3 ES2 167548 ,6-dihidroxi-5-(I -metiletfl)-3-fenil-4- 24-jun-I 998
[(fenilamino) carbonil]-1 H-pirrol-1-heptanoico (atorvastatina)
Forma cristalina Ill de la sal hemicalsica del Æcido[R(R*,R*)]2(4
D4 ES2 166456 fluorofenil)-3,ö -d ihidroxi-5-(1 -metiletil)- 24-jun-I 998
3-fenil-4-[(fenilamino) carbonil]-I H-pirrol-I -heptanoico (atorvastatina) Trans-6-[2-(3- or 4-carboxamido-

substituted pirrol-1 -yl)alkyl]-4- D5 US4,681,893 21-jul-1987 hydroxypyran-2-one inhibitors of
colesterol synthsis
[R(R*, R*)]2(4fIuorophenyI)p,ö-dihydroxy-5-(1 -methylethyl)-3-phenyl-
D6 US5,273,995 4-[(phenylamino) carbonyl]-I H-pyrrole- 28-dic-224
1-heptanoic acid, its lactone form and
salt thereof
Proces for preparing calcium salt forms
D7 W003016317 27-feb-2003
of statines

AnÆlisis de patentabihdad(seg(in requisito) (articulo 14 D486)

Novedad (artIculo 16 D486)

La solicitud en estudio reclama:

WI

1-Un acido libre atorvastatina cristalino.
2-10 Un acido libre atorvastatina cristalino Forma A o uno de sus hidratos que tiene un patron de difracciOn de rayos X en polvo que contiene los valores 20 siguientes med idos utilizando radiaciôn CuKa:
11-13Un acido libre atorvastatina cristalino Forma B o uno de sus hidratos que tiene un patrOn de difracciOn de rayos X en polvo que contiene los valores 20 siguientes medidos utilizando radiaciOn CuKu.
Atorvastatina es el nombre comUn que se le asigno a el compuesto Æcido[RR*,R*)] 2-(4-fluorofenhl)-3,-dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1 - heptanoico.

- La anterioridad Dl (US6,583,295) especialmente en el resumen, columna 1, columna 6, ejemplos 22 y 23, describe la obtenciOn cristalización y recristalizaciOn del Æcido libre de atorvastatina, igualmente enseæa la cirstalizaciOn de sus derivados. En los ejemplos ejemplo 22 y 23 (Dl) se obtiene el Æcido puro de atorvastatina en cristales. Los procesos d aislar y purificaciOn de anticolesterolemicos es conocido en el estado de la tØcnica, estÆnincluidos las tØcnicas de extracciOn, cromatografla, lactonizaciôn, y mØtodos de cristalizaciôn (columna 1, Dl), Se puede ver que el compuesto Æcido[RR*, -metiletil)-3-fenit-4-[(fenUamino)-carbonil]-1 h-pirrol-1 -heptanoico, y cristalizado noes nuevo, esta molecula por su estructura qulmica, el nUmero de âtomos de carbono, hidrogeno y oxigeno que 10 componen, necesariamente es sOlido, no es un gas ni un liquido. De otra parte la manera como se purifica en Dl y se cristaliza. Es lo que se reclama en la presente solicitud con solamente tres datos de un patrOn de difracciOn de RX y se sabe que se pude realizar un difractograma de polvo orientado, para que un cristal tome valores que yo quiero o para que no tome valores que no deseo que aparezcan, orientando el equipo, y es necesario ademÆstener en cuenta que los difractogramas no son para identificar sustancias, solamente cristales.

- La anterioridad D2 (W002/43667) especialmente en pag. 1, 3er pÆrrafo,pag. 2, pag
6 Ultimo pÆrrafo, demuestran queel el compuesto Æcido
,6-dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenilamino)-carbonhl]-1 h-pirrol-1 -heptanoico, se conoce en estado puro aislado. Por Ic tanto la diferencia con la presente solicitud es que la anterioridad no reporta dates de difracciOn de Rayos X para los cristales obtenidos, porque los difractogramas no son para identificar sustancias.

- La anterioridad D3 (ES2167587) especialmente en resumen, pag. 2 pÆrrafos 3-5;
Pag 5, pg. 8-9, describe la obtenciOn prificaciOn del acido libre de atorvastania, mediante la Iactonicación y ademÆs aparece como se obtienen los hidratos de atorvastatina, donde se indica que debe hacerse bajo condiciones de cristalizaciôn controladas,el ªcido libre de atorvastatina. Los procesos de aislar el acido puro, a partir de la forma de atorvastatina (forma lactonica). Se puede ver que el compuesto Æcido -metiletil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1 -heptanoico, no es nuevo; esta molØcula por su estructura qulmica, el nümero de Ætomosde carbono, hidrogeno y oxigeno que to componen, necesariamente es sôlido. En esta anterioridad no aparecen los datos de patrones de difracciôn de RX, para el Æcidolibre pero se conoce que es un sôlido

cristatino.

- La anterioridad D4 (ES2 166456) especialmente en resumen, pag. 2 parrafos 3-5;
Pag 3, peniItimo pÆrrafo, pag. 7 renglones 33-35 y 52-58; pag 8, describe la obtención prificación del acido libre de atorvastatina, y ademÆsaparece la manera como se obtienen hidratos de atorvastatina, donde se indica que debe hacerse bajo condiciones de cristalizaciOn controladas, que pueden ser empIricas determinadas y solamente es posible proporcionar un mØtodo que se haya demostrado apropiado en la prÆctica. Se demuestra que et Æcido libre de atorvastatina no es nuevo, et compuesto âcido ,&dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1 -heptanoico, es una molecula del estado de la tØcnica que por su estructura quimica, el nümero de Ætomosde carbono, hidrogeno y oxigeno que to componen, necesariamente es sôtido. En esta anterioridad no aparecen los datos de patrones de difracciOn de RX, para el Æcidolibre.

- D5 (US4.681.893) especialmente en el resumen y columna 13, describe la
obtenciôn prificación del acido libre de atorvastania, se obtiene en estado sótido. Los procesos de aislar el acido puro, apartir de la forma de atorvastatina a travØs de la forma lactonica. Se puede ver que el compuesto Æcido
3,-dihidroxi-5-(1 -metitetil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1 -heptanoico. En esta anterioridad no aparecen los datos de patrones de difracción de RX, para el Æcidolibre.

-136 (US5,273,995) especialmente en resumen, colum. 1 pÆrrafo 1;colum. 2 Ultimo parrafo; ejemplo 1; reivindicaciones 1, 2, 11 y 12, describe la obtención prificación del acido libre de atorvastania, y la recristalizaciOn del acido libre. Entonces se puede

ver que el compuesto Æcido[RR*,R*)]2(4fluorofenil)p,ö-dihidroxi-5-(1 -metiletil)-3-feni1-4-[(fenilamino)-carboni1]-1 h-pirrol-1 -heptanoico, noes nuevo, como tampoco es nuevo que se conozca que tiene estado sôlido y cristalino. En esta anterioridad no aparecen los datos de patrones de difracciôn de RX, para el Æcido libre.

- D7(W003016317) entomb de la invenciOn, pag.2 renglones 15-22, pag. 3 renglon 15-18; pag. 4 renglones 15-20, se puede ver que el compuesto Æcido[RR*,R*)]2 (4-fluorofenil)-p,ö-dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1-heptanoico, no es nuevo, como tampoco es nuevo que se conozca que tiene estado sOlido, se conoce ampliamente en el estado

Nivel inventivo (artIculol8 D486 de la C.A.N.)

-Tal como estÆ la solicitud reclama dos formas polimOrficas y dos formas pseudopolimorficas denominadas hidratos y cualquier forma cristalina, de una sustancia del estado de la tØcnica [RR*, R*)]2(4fluorofenil)I3,-dihidroxi-5-(1 - metiletil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1 -heptanoico, se sabe por D1 -D5 que la sustancia ha sido cristalizada y recristalizada, mediante diferentes mØtodos, pero no se reportaron los patrones de difracciôn de Rayos X, en tØrminos de los angulos interlineares, determinados mediante la tØcnica de Difracciôn de Rayos X, tØcnica que permite poner de manifiesto sOlo una propiedad fisica del estado sólido que no ha sido reportada cuando se ha obtenido en forma cristalina en las anterioridades. Al reportarse los patrones de difracción de RX es sOlo una manera de elucidar cual fue la forma de cristalina espontanea que se obtuvo de acuerdo con las condiciones termodinâmicas en se desarrollo la cristalizaciOn.
Dentro de estas formas, de empaquetamiento o agrupaciOn de las molØculas de atorvastatina dentro de una ordenaciOn, no es producto del ingenio del hombre, ya cualquier persona normalmente versada en la materia sabe que para obtención de cristales o polimorfos se deben manipular los siguientes parÆmetros:
I) Manipulando adecuadamente los Indices de cristalizaciôn
ii) Naturaleza del solvente
iii) Temperatura
iv) Velocidad de enfriamiento
v) Agitacion
vi) Cantidad de solvente usado

vii) Pureza del solvente
AsI, si el formulador encuentra que el ªcido dihidroxi-5-(1-metiletil)-3-fenhl-4-[(fenilamino)-carbonhl]-1 h-pirrol-1 -heptanoico 0 cualquier fÆrmaco, cualquier propiedad mecÆnica obviamente la formularÆ como cristal; no es la primera vez que se obtiene un sOlido cristalino de Æcido [RR*, ,-dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenilamino)-carbonil]- lh-pirrol-1-heptanoico. Los otros factores que afectan la cristalizaciOn son elecciOn del solvente, temperatura y control de la presiOn para hacer mÆslenta o mÆsrÆpida lacristahzaciOn, para no esperar a que cristalice en condiciones ambientales, la elecciôn de la Optima temperatura y del tiempo de crecimiento de los cristales, son ensayos de prueba y error que siempre deben hacerse, pero cuyo resultado no es patentable, porque por recristalizaciones jamas se obtiene un compuesto diferente, siempre es la misma estructura qulmica y la misma actividad, para nuestro caso antibiOtico y no parece obtenerse una caracteristica nueva ni tampoco obtenida por el ingenio del "inventor." Para una persona versada en la materia, las enseæanzas de D1 -D5 individualmente tomadas, muestran que el Æcido[RR*,R*)]2(4.fIuorofeniI)43,& dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenhlamino)-carbonil]-1 h-pirrol-1 -heptanoico cristaliza y que ha recristalizado. Los controles de las condiciones termodinÆmicasde cristalizaciOn las sustancias es 10 llevaran a cristalizar de la manera mÆs estable aesas condiciones termodinÆmicascontroladas, o sea, se obtendrÆ un empaquetamiento molecular espontaneo se la sustancia, para esas condiciones, y para saber quØ clase de empaquetamiento se obtuvo, se realizan patrones de difracciOn de Rayos X, a la monocelda.
Los datos de los patrones de RX, de los cristales del Æcido [RR*,R*)J2(4 fluorofenil)-p,ö-dihidroxi-5-(1 -metiletil)-3-fenil-4-[(fenhlamino)-carbonil]-1 h-pirrol-1 - heptanoico de la presente solicitud no aporta nada que enrriquezca al acervo tecnolôgico. Es decir el reporte de unos datos de formas de empaquetamiento molecular del Æcido -metiletil)-3-fenil-4-[(fenilamino)-carbonil]-1 h-pirrol-1 -heptanoico con contenidos de retenciOn de humedad, que se diferencia de otro cristal por el patron de difracciOn de RX, que se logra de acuerdo al solvente recristalizar controlando las condiciones termodinÆmicasde temperatura, velocidad de enfriamiento, agitaciôn y en cuanto al solvente, cantidad de solvente usado y pureza del solvente; es evidente que esos datos de cristalistales no constituye un aporte a los

procesos de cristalizaciôn.
En cuanto a los datos de patrones de difracción de rayos X el mØtodo detecta un fenOmeno fisico, a travØs del cual se manifiesta la interacciOn fundamental de los RX con los cristales, que consiste en medir las intensidades de la mayor cantidad posible de haces difractados del espectro tridimensional de difracciOn, de tal manera que se puedan obtener de ellas los módulos de los factores de estructura, y de sus valores mediante algUn procedimiento de asignaciOn de fases a cada uno de estos factores, tambiØn permite reconstruir la distribuciôn electrônica en la celdilla elemental, cuyos mÆximos corresponderÆn a las posiciones atômicas y de esta manera obtener la informaciôn de la estructura atOmica dentro de la celdilla unidad, si importar la sustancia. Es decir el mØtodo permite una descripciOn del patron estructural de la red cristalina de manera detallada mediante la cuantificaciOn de una propiedad inherente al estado sOlido de los cristales, descripciOn que incluye desde las dimensiones de la unidad de celda, el tipo de reticulo y el sistema cristalino hasta la determinaciOn de los posibles grupos espaciales.

En este orden de ideas, si se reclama protecciOn para una misma estructura quimica que cuenta con una capacidad particular de cristalizaciOn, es decir una propiedad inherente a la naturaleza de las molØculas de atorvastatina, resulta ambiguo que at momento de reivindicar el hÆbito cristalinode la estructura, Øste se defina en tØrminos de una propiedad fisica, cuando en sintesis se pretende protecciôn para el mismo nUcleo quimico, ya que como se indica en la solicitud el intermediarlo para obtener las sales conocidas, y al momento de obtener las sales no se hace reacciOn con los cristales, debe estar completamente disgregado a nivel molecular, ya que las reacciones no se Ilevan a cabo entre cristales, la forma como se reivindica es para pedir la protecciOn sobre la molØcula que ya ah sido cristalizada, pero aprovechando que no se han reportado datos de patrones de difracciôn de RX. Es decir, qulmicamente se reclama el mismo Æcido libre de atorvastatina, solo que debido a su capacidad de estado sOlido, es capaz de cristalizar en formas particulares, determinadas Unica y exciusivamente por la naturaleza del compuesto y los cristales no son producto de un prediseæoingenioso de la actividad humana.

Reivindicaciones afectadas Requisito que afecta
Documento NO
1, 14,15 Novedad

Dl
2-13 Nivel inventivo

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D3
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D5
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D6
2-13 Nivel inventivo

1,14,15 Novedad
D7
2-13 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 60 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 denegarâ la patente.

Notifiquese el presente oficio,con6re a lo dispuesto en el numeral 5.2, literal e), del

capitulo quinto del tItulo p’de/la Circular Unica NO lOde 2001.

ALIX CARMENZA CEEDES DE VERGEL
Jefe de DivisiOn de N4’evas Creaciones

El anterior requerimiento fue notificado por fijaciOn en lista, de fecha

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eel

(54) Title: PROCESSES FOR PREPARING CALCIUM SALT FORMS OF STATINS

(57) Abstract. Processes for preparing a calcium salt of a stasis from an ester derivative or protected ester derivative of the stalin by using calcium hydroxide are provided. The ester or protected ester derivative is contacted with calcium hydroxide to obtain the calcium salt Preferred statist are rosixvastatin, pitavaslatin and atorvastalin, simvastatin and lovastatin. In processes beginning with
a protected satin ester derivative, the protecting group is hydrolyzed during salt formation by contact with calcium hydroxide, or is contacted with an acid catalyst followed by contact with calcium hydroxide.

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PROCESSES FOR PREPARING CALCIUM SALT FORMS OF STATINS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit ofprovisional application Serial Number 60/312,812, filed August 16,2001 and U.S. Patent Application Serial No. 10/037,412, filed October 24,2001, which claims the benefit ofprovisional application Serial Number 60/249,319, filed November 16, 2000, all ofwhich are incorporated herein by reference.

10 FIELD OF THE INVENTION

statins.

The present invention relates to processes for preparing calcium salt forms of

BACKGROUND OF THE INVENTION

The class of drugs called statins are currently the most therapeutically effective

drugs available for reducing low-density lipojrotein (LDL) particle concentration in the blood stream ofpatients at risk for cardiovascular disease and thus, statins are used in the treatment ofhercholesterolemia, hyperlipoproteinemia, and atherosclerosis. A high level ofLDL in the bloodstream has been linked to the formation of coronary lesions that

20 obstruct the flow ofblood and can rupture and promote thrombosis. Goodman and

Oilman, The Pharmacological Basis ofTherapeutics, page 879 (9th Ed. 1996).

Statins inhibit cholesterol biosynthesis in humans by competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A ("HMG-00A") reductase enzyme. HMG-CoA reductase catalyzes the conversion of HMG to mevalonate, which is the rate determining

25 step in the biosynthesis of cholesterol. Decreased production of cholesterol causes an

increase in the number ofLDL receptors and corresponding reduction in the concentration ofLDL particles in the bloodstream. Reduction in the LDL level in the bloodstream reduces the risk of coronary artery disease. J.A.M.A. 1984, 251, 351-74.

Currently available statins include lovastatin, simvastaxin, pravastatin, fluvastatin,

30 cerivastatin and atorvastatin. Lovastatin (disclosed in U.S. Pat. No. 4,231,938) and

simvastatrn (ZOCOR; disclosed in U.S. Pat. No. 4,444,784 and WO 00/53566) are administered in the lactone form. After absorption, the lactone ring is opened in the liver by chemical or enzymatic hydrolysis, and the active hydroxy acid is generated.

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Pravastatm (PRAVACHOL, disclosed in U.S. Pat. No. 4,346,227) is administered as the sodium salt. Fluvastatin (LESCOL; disclosed in U.S. Pat. No. 4,739,073) and cerivastatin (disclosed in U.S. Pat. No. 5,006,530 and 5,177,080), also administered as the sodium salt, are entirely synthetic compounds that are in part structurally distinct from the fungal derivatives ofthis class that contain a hexahydmnaphthalene ring. Atorvastatin and two new "superstatins," rosuvastatin and pitavastatin, are administered as calcium salts. The structural formulas ofthese statins are shown below.

COOH
oH

HO 0 HO

0

H, CH3 143
-x"’o
HOLL)
Srw,stU,

N

COON NHOH

F

C,,,,-,,,- F

ON
H’C’

0S ’,

F OH

OH

OH

09

20 Atorvastatin is the common chemical name for [R-(R’, R)]-2-(4.fluorophenyl). J3,&-dihydroxy-5-(lmethylethyl)-3.phenyl-4-[(pheny1amino)cati,ony1]lH.pyrrolel heptanoic acid. The free acid of atorvastatin is prone to lactonization. The systematic chemical name of atorvastatin lactone is (2R-trans)-5-(4-fluorophenyl)-2-(l-methylethyl)-

25 carboxamide. Atorvastatin and its corresponding racemic lactone are disclosed in U.S. Patent No. 4,681,893.

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The lactone form is disclosed in U.S. Patent No. 5,273,995. In Examples 4 and 5’
ofthe ’995 patent, the lactone is prepared by dissolving 1, 1 -dimethylethyl (R)-7-[2-(4-? fluorophenyl)-5-(1-methylethy1)-3-phenyl4heny1aino)carbonyl)-1H-pynol4-yl)5.. hydroxy-3..oxo-1-heptanoate in tetrahydrofliran and triethyl borane, followed by the
addition oft-butylcarboxylic acid. After cooling, methanol is added followed by sodium borohydride. The mixture is poured into an ice/hydrogen peroxide/water mixture. Trichloromethane is added and the mixture is partitioned. The organic layer is dried over magnesium sulfate, filtered, and the solvent is evaporated. The product is dissolved in tetrahydrofuran and methanol and added to a solution ofsodium hydroxide. The mixture
10 is concentrated to remove organic solvent, added to water, and extracted with diethyl
ether. The aqueous layer is acidified with hydrochloric acid and extracted with ethyl
acetate. The organic layer is dried with anhydrous magnesium sulfate, filtered, and the solvent evaporated. The residue is dissolved in toluene and concentrated. The product is recrystallized from ethyl acetate and hexane to produce the lactone.
15 The lactone can also be prepared according to the procedures disclosed in U.S. Patent No. 5,00,080. For instance, in Example 2, Method A, cis-2-(4-luomphenyl)-- dihydroxy-5-(l.methylethyl).3-phenyl-4-(phenylamino)carbony1lHpyrrole1heptanojc acid, methyl ester is treated with sodium hydroxide, and after dilution with water and separation, the remaining layer are washed with hexane and ethyl acetate followed by
20 concentrated hydrochloric acid solution. Upon separation, the upper layer is washed with
hydrochloric acid and concentrated. The residue is dissolved in toluene.
As disclosed in the ’080 patent, the lactone can also be prepared by mixing (–)-cis-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid (Example 2, Method B); (–)- (2a,4o,6) or (–)-(2a,40,613)-6-(2-aminoethyl)-2-phenyl-1,3-dioxane-4-acetic acid
25 (Example 2, Method C); (–)-cis-9-(2-aminoethyl)-6,10-dioxaspiro[4.5]decane-7-acetic
acid (Example 2, Method D); (–)-cis-(4-(2-aminoethyl)-1,5-dioxaspiro[5.5]undecane2-acetic acid (Example 2, Method E); or (a)-(2a,4a,6n) or (–)-(2ci,413,613)-6-(2-aminoethyl)-2-methyl-3,3-dioxane-4- acetic acid (Example 2, Method F and G) with (a)- 4-fluoro-cx-[2-methyl-1-oxopropyl]-y-oxo-N,P-diphenylbenzenebutaneamide in dimethyl
30 sulfoxide. After heating, the solution is poured into a mixture of diethyl ether and
saturated ammonium chloride in water. After separation, the organic layer is washed with water and sodium hydroxide. The aqueous layer is acidified with dilute hydrochloric acid

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and extracted with ethyl acetate, to which hydrochloric acid is added, and the solution is concentrated. The residue is dissolved in toluene.

Another method ofmaking the lactone, according to the ’080 patent, includes
mixing (–)-cislj-diniethylethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate
5 (Example 2, Method H); (i)(2cx,4a,6a) or (–)-(2cx,40,60)4,l-dimethyl-6-(2-
aminoethyl)-2-phenyl-1,3-dioxane4.acetate (Example 2, Method 1); or (t)cis-1,l-dimethylethyl (4-(2-aminoethyl)-1,5-dioxaspiro[5.5]undecane-2-acetate (Example 2,
Method J) with (–)4-fluoro-cs-[2methyl-1-oxopropyl]-y-oxo-Njl-diphenylbenzene butaneamide in heptane:toluene (9:1). After heating, the solution is poured into a mixture
10 oftetrahydrofliran and ammonium chloride in water. After separation, the organic layer is
washed with brine, followed by the addition ofhydrochloric acid. After stirring, sodium hydroxide is added to the organic layer. The reaction is stopped by adding a mixture of water and hexane. After separation, the aqueous layer is acidified with dilute hydrochloric acid, extracted with ethyl acetate, and concentrated. The residue is dissolved in toluene.
The lactone or the free acid may be used to prepare the pharmaceutically
acceptable calcium salt,
3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) trihydrate. In animal models, atorvastatin calcium salt has been shown to lower plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol
20 synthesis in the liver. Atorvastatin is marketed by PFIZER as the hemicalcium salt
trihydrate under the trade name LIPITOR, as 10,20,40 and 80 mg tablets. Atorvastatin hemicalcium salt has the following structure:

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Industria y Comercio
SUP E RI N TEND E NC IA

REPUBLICA DE COLOMBIA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 7 U:

Por la cual se niega una patente de invenciôn

Rad. PCT/06-21164

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO en ejercicio de sus facultades legales, en especial de las que se confirieron en el artIculo
3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "FORMAS CRISTALINAS DE ’ ACI DO [R(R*, R*)]2(4FLUOROFENlL)BETA, O-DIHIDROXI-5-(I-METILETIL)-3-FENIL-4-
[(FENILAMINO)-CARBONIL]-1 H-PIRROL-1-HEPTANOICO", que corresponde a la solicitud internacional PCT/1B2004/00291 9 de fecha 06 de septiembre del 2004, fue radicada en esta Superintendencia el 03 de marzo del 2006 bajo el nümero 06-021164 -00000-0000, para que se iniciara la fase nacional en virtud del Tratado de Cooperaciôn en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe Ilenar la solicitud y cumpildas las exigencias legales, se ordenó publicar el extracto, hablØndose presentado oposiciOn por parte de TecnoquImicas S.A., representado legalmente por el doctor JosØ Luis Reyes Villamizar y por parte de Gynopharm S.A., representado legalmente por la doctora Eliana Isaura Moreno Bohôrquez.

TERCERO: Que el articulo 45 de la Decision 486 de la ComisiOn de la Comunidad Andina establece que: "Si la oficina nacional competente encontrara que la invenciOn no es patentable o que no cumple con alguno de los requisitos establecidos en esta DecisiOn para í a concesiOn de (a patente, 10 notificarÆat solicitante. Este debera respondera la notificaciOn dentro del plazo de sesenta dIas contados a partir de la fecha de ía notificación. Este plazo podrÆser prorrogado por una so/a vez por un perlodo de treinta dias adicionales. (...) Si e/solicitante no respondiera a la notificaciOn dentro del plazo senalado, o si a pesar de ía respuesta subsistieran los impedimentos para ía concesiOn, la oficina nacional competente denegara la patente".

CUARTO: Que realizado el examen de fondo, se requiriO al solicitante en los tØrminos del articulo 45 de la DecisiOn 486 de la ComisiOn de la Comunidad Andina, para que presentara respuesta a las observaciones de carÆcter tØcnicovisibles a folios 256 a 268 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta DecisiOn para la concesiOn de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del mismo, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artIculo 45 de la DecisiOn 486.

Sede Centro: Carrara 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 5870000
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Bogota D.C. - Colombia

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

REPUBLICA DE COLOMBIA SUPERINTENDENCIA DE INDUSTRIA V COMERCIO

Rad. PCT/06-21164

RESOLUCION 4-

Por la cual se niega una patente de invenciOn

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invenciOn para la solicitud correspondiente a "FORMAS CRISTALINAS DE ACIDO
BETA, 0-DIHIDROXI-5-(1 -METILETIL)-3-FENIL-4-[(FENILAMINO)-CARBONIL]-1 H-PIRROL-1-HEPTANOICO", que entrO en fase nacional en virtud del Tratado de CooperaciOn en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución at doctor Carlos Reinaldo Olarte Garcia, en su calidad de apoderado de WARNER LAMBERT COMPANY LLC., a la doctora Eliana Isaura Moreno Bohórquez, apoderada de GYNOPHARM S.A. y al doctor JosØ Luis Reyes Villamizàr, apoderado de TECNOQUtMICAS S.A., sociedades opositoras, o a quienes hagan sus veces, entregÆndoles copia de la misma, advirtiØndoles que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, del cual podrªn hacer uso a) momento de la notiflcaciôn o dentro de los 5 dlas hÆbiles siguientesa ella.

NOTIFIQUESE V CUMPLASE
Dada en Bogota, D.C., a los 31 DJC. 20112

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

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GUS’ONES

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